

Sepsis in geriatric patients caused by bacteria of the order Enterobacterales

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Abstract

Introduction. Enterobacterales bacteria can cause severe sepsis in geriatric patients, which is associated with a number of risk factors, including antibiotic resistance. The problem is particularly clinically relevant in the context of increasing aging populations in developed countries. **Material and methods.** A literature review was conducted using online databases. The literature was searched for the review based on keywords. **Results.** Sepsis caused by Enterobacterales in older people, especially those over 75 years of age, remains a problem with a high incidence and, unfortunately, high mortality. The factors contributing to infection include, above all, previous use of antibiotics, the presence of invasive medical devices, and comorbidities such as diabetes or cardiovascular disease. Interestingly, the clinical picture in this group of patients is often atypical — symptoms may include falls, general weakness, or loss of appetite, which unfortunately can lead to delayed diagnosis. The most common sources of infection are the urinary tract and the respiratory system. Attention should also be paid to the growing number of multidrug-resistant strains, especially those producing ESBL and CRE, which significantly complicate treatment and worsen the prognosis. **Conclusions.** Sepsis caused by Enterobacterales in elderly patients is a clinical challenge due to its atypical course and problems associated with increasing antibiotic resistance. Early diagnosis, supported by clinical criteria such as SOFA or qSOFA, together with the rapid initiation of appropriately selected antibiotic therapy, is therefore very important. To improve treatment outcomes in this group of patients, not only prevention and efficient diagnosis are needed, but also sensible management of antibiotic resources. It can be said that without this, it will be difficult to achieve greater progress. *Geriatrics 2025;19:223-230. doi: 10.53139/G.20251928*

Keywords: sepsis, old age, Enterobacterales bacteria, geriatric patients

Introduction

Sepsis is defined as a syndrome involving physiological, pathological, and biochemical abnormalities caused by infection. In the fourth century B.C., Hippocrates first proposed the term “sepsis” as a process of decay or decomposition of organic matter [1]. The first definition of sepsis dates to 1992 and was the result of an agreement among world experts in the field of intensive care. Sepsis is defined as the systemic immune response syndrome (SIRS). The third redefinition of sepsis was made in 2016. Due to the already mentioned insufficient specificity of the existing (old) definition of sepsis, there was a need for a new definition that would be more specific than the previous one and allow easier recognition of sepsis in everyday clinical practice. It is based on the pathobiology and pathophysiology of the host’s response to infection, which is described as

“non-homeostatic.” The most important changes are the elimination of the terms “SIRS” and “severe sepsis.” Sepsis is now defined as a life-threatening organ failure caused by the host’s inappropriate response to infection. Organ failure is now considered if there is a change in sequential, sepsis-related organ failure assessment (SOFA), where two points or more are associated with a hospital mortality rate greater than 10%. Septic shock is defined as a subtype of sepsis, and is manifested by circulatory, cellular, and metabolic instability associated with a higher risk of death than sepsis itself [2,3].

Enterobacterales comprises multiple bacterial families, including the family Enterobacteriaceae that harbors the genera *Escherichia*, *Klebsiella*, and *Enterobacter*. *Escherichia coli* and *Klebsiella pneumoniae* are the most common causes of post-transplantation gram-negative bacteremia [4]. Members of this group inhabit a number

of different ecological niches and have been found in soil, water and in association with living organisms including plants, insects, animals and humans [5]. These infections are often endogenous and develop after the patient has been previously colonized with hospital strains, and the mortality rate from them, especially in intensive care unit patients, is quite high, up to 87% [6].

Material and methods

A literature review from 2002 to 2024 was conducted using the following online databases: PubMed, Google Scholar and Mendeley. The literature was searched for review based on the following keywords: sepsis, old age, Enterobacterales bacteria, geriatric patients.

Results

Epidemiology

Sepsis, defined as life-threatening organ dysfunction caused by dysregulated host response to infection, contributes to 11 million deaths annually, representing one-fifth of all causes of death [7]. A meta-analysis incorporating 27 studies from seven high-income countries showed that the incidence rate and case fatality ratio of severe sepsis were 270 per 100000 person-years and 26%, respectively (Sepsis-2 definition). The latest data from the 2017 Global Burden of Diseases, Injuries and Risk Factor Study showed that 48.9 million incident cases of sepsis and 11.0 million sepsis-related deaths were reported globally in 2017, with the highest age-standardised incidence and mortality of sepsis occurring in areas with the lowest socio-demographic index. The global burden of sepsis is larger than previously estimated and may continue to be great because of a prolonged life expectancy and an ageing population. In 2017, the World Health Organization and World Health Assembly recognised sepsis as a global health priority, and adopted a resolution to improve the prevention, diagnosis and management of sepsis [8]. Similar findings of increased incidence of sepsis, with the mean age of patients with severe sepsis being around 60 years, have been reported in studies from the eastern part of the world. Mortality rates associated with severe sepsis also increase with increasing age, with the highest mortality in old elderly (patients more than 85 years of age). There is a dearth of data regarding the outcome of elderly patients with sepsis and septic shock. A few studies which have been conducted in this specific patient population and have shown that severe sepsis and septic shock are common in elderly patients and these patients have an increased

mortality as compared to their younger counterparts [9]. Sepsis also appears to be the most common reason older adults are admitted to an intensive care unit (ICU). In a prospective cohort study of older adults with a mean age of 75 years, approximately 64% of older adults admitted to an ICU met the definition of sepsis [10].

Risk factors

Enterobacterales sepsis is a major challenge in the elderly patient population. Determinants of its occurrence are divided into: healthcare-related factors, patient-specific factors, and infection-related elements. Understanding these factors is key to developing strategies to improve patient outcomes.

1. Healthcare-related factors

- Prior antibiotic exposure

History of carbapenem use significantly increases the risk of carbapenem-resistant Enterobacterales (CRE) infections, often leading to adverse clinical outcomes [11-13].

- Invasive medical devices

Drainage tubes and urinary catheters facilitate pathogen transmission and are associated with a higher risk of iatrogenic infections (HAIs), especially with prolonged use, increasing the chance of CRE infections [14,15].

- ICU stay

Intensive care unit admission is associated with exposure to invasive procedures, broad-spectrum antibiotics and resistant pathogens, which contributes to the development of sepsis [12,13,16].

- Ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP), especially caused by resistant strains of Enterobacterales, correlates with higher mortality and prolonged ICU stay [13,16,17].

2. Patient-related factors

- Age-related immune decline

Immunosenescence reduces both innate and adaptive responses, which increases susceptibility to severe infections, including sepsis [14,18,19].

- Comorbidities

Chronic conditions such as diabetes, cardiovascular disease and renal failure not only increase the risk of sepsis, but also increase the risk of sepsis. [14,20,21].

- Weakness

Reduced physiological reserves in elderly patients increase the risk of sepsis mortality [16,17].

- Polypharmacy

Multidrug therapy promotes interactions, organ dysfunction and increases the risk of infection, complicating sepsis treatment [14,19].

3. Factors related to infection

- Virulence of pathogens

Enterobacterales, particularly carbapenem-resistant Enterobacteriaceae, have multiple virulence determinants, such as carbapenemases, that enable antibiotic resistance and bypass host defense mechanisms [12,13,22].

- Multi-drug resistance

Infection caused by multi-drug resistant bacteria (MDR-E) limits therapeutic options, which is associated with higher mortality and longer hospital stays [14,15,17].

- Sepsis severity

SOFA and QSOFA indices serve as prognostic tools; higher scores are associated with more severe sepsis, organ failure and death [13,16,22].

- Immune response and inflammation

Immunosenescence and chronic low-grade inflammation influence a deregulated inflammatory response during sepsis, leading to tissue damage [18,23].

- Monocyte and T-cell dysfunction

Contributes to impaired function of key immune cells, which compromises the body's ability to fight [21,23].

Table I. Key risk factors contributing to Enterobacterales sepsis in geriatric patients

Category of factors	Description
Healthcare-related factors	Prior exposure to carbapenems increases the risk of CRE infections [11-13]
Patient-related factors	Age-related immune decline (immunosenescence) impairs the immune response. [14,18,19]
Infection-related factors	Multidrug resistance among Enterobacterales complicates treatment and worsens clinical outcomes. [14,15,17]

Variability of symptoms and sequence of onset of symptoms

Sepsis, particularly in the context of Enterobacterales, poses significant challenges in the geriatric population due to impaired physiologic reserves, the presence of comorbidities and atypical clinical manifestations. This section provides a detailed examination of the variability of symptoms, the chronological sequence of their onset, and a comprehensive clinical presentation of sepsis in this demographic group.

1. Typical and Atypical Symptoms of Sepsis in Geriatric Patients

Typical Symptoms

- Fever: despite being a common symptom, it may be absent in as many as 20% of elderly patients affected by sepsis [24].
- Tachypnoe and tachycardia: represent common symptoms of systemic inflammatory responses [25,26].
- Difficulty breathing: often associated with respiratory infections, a common source of sepsis in the elderly [27,28].
- Hypotension: a significant drop in blood pressure that can lead to septic shock [29,30].

Atypical symptoms

- Mayhem or altered mental status: represents one of the most common atypical presentations, complicating the early diagnosis of sepsis [24-26].
- Falls or weakness: These symptoms are often inappropriately identified as indicators of underlying sepsis [24,25].
- Loss of appetite and malaise: these nonspecific symptoms can be mistakenly attributed to alternative conditions such as weakness or age-related changes [24,26].
- Dehydration and decreased activities of daily living (ADLs): subtle indicators that can mark the early onset of sepsis [24,26].

2. Sequence of symptom onset in geriatric sepsis

Once typical and atypical symptoms are identified, it is important to understand their chronological occurrence, which can help in faster diagnosis and treatment.

2.1. Initial phase

- Non-specific symptoms: malaise, loss of appetite and generalized weakness are usually the initial signs [24,26].
- Subtle changes in mental status: delirium or confusion may manifest early, potentially preceding the appearance of other systemic indicators [24,25].

2.2. Progression to systemic inflammation

- Fever or hypothermia: although fever is more commonly seen, hypothermia may also occur, especially in patients of advanced age or debilitation [24,25].
- Tachycardia and tachypnea: represent early indicators of systemic inflammatory response syndrome (SIRS) [25,27].

2.3. Organ dysfunction

- Respiratory failure: breathing difficulties may worsen to acute respiratory failure, requiring mechanical ventilation [29,30].
- Renal dysfunction: acute kidney injury often occurs as a complication, commonly associated with sepsis-induced hypoperfusion [27,32].
- Cardiovascular instability: hypotension potentially ending in septic shock may occur [29,30].

2.4. Late phase

- Multiple organ failure: this is a critical and life-threatening complication that significantly increases mortality among the geriatric population [29,30].
- Immunosuppression: elderly patients may be subject to a paradoxical state of immune suppression after the initial superinflammatory response, thus complicating recovery [24,29].

3. Full clinical presentation of sepsis in geriatric patients

3.1. Vital signs and physical examination

- Vital sign abnormalities: tachycardia, tachypnea, hypotension, and fever or hypothermia are common clinical signs [25,27].
- Physical examination findings:
 - Respiratory: the presence of crackles, wheezing or weakened breath sounds may signify pneumonia, which is a common etiologic factor in sepsis [27,28].
 - Cardiovascular: jugular venous distension along with peripheral edema may be observed in patients experiencing fluid overload [29,30].
 - Neurologic: mental status changes, which can range from mild confusion to comatose state, are characteristic of sepsis in the elderly [24,25].

3.2. Laboratory findings and biomarkers

- Inflammatory markers: elevated white blood cell count, C-reactive protein (CRP), and procalcitonin (PCT) are often documented [27, 28].
- Markers of organ dysfunction.
- Kidney: elevated serum creatinine and blood urea nitrogen (BUN) levels indicate renal dysfunction [27,31].
- Liver: hyperbilirubinemia along with elevated liver enzymes can manifest in severe cases [29,30].
- Coagulation: disseminated intravascular coagulation (DIC) is a potential complication [29,30].

3.3. Source of infection

- The predominant sources of sepsis in geriatric patients include:
 - Urinary tract infections (UTIs): these account for about 60% of recorded cases [27,31].
 - Respiratory tract infections: pneumonia is a common driver of sepsis among the elderly [27,28].

Table II. Comparison of typical and atypical symptoms of sepsis in geriatric patients

Type of symptoms	Description	Literature cited
Typical	Fever, tachycardia, tachypnea, hypotension, and difficulty breathing	[25,27]
Atypical	Mayhem, falls, weakness, malaise, loss of appetite, and decreased ability to perform activities of daily living (ADLs)	[25,26]

- Skin and soft tissue infections: although less common, these infections can rapidly worsen in people with weakened immune systems [29,30].

4. Clinical diagnosis

The diagnostic process begins with a thorough physical examination of the patient. Typical signs of sepsis include fever, tachycardia, tachypnoea, hypotension and leukocytosis. The Sequential Organ Failure Assessment (SOFA) and qSOFA (quick SOFA) scales are helpful in diagnosing multiple organ dysfunction. Although the qSOFA should not be used as the sole diagnostic tool, it can help identify patients at increased risk of severe disease [32].

5. Microbiological Diagnosis

The gold standard for microbiological diagnosis of sepsis is to collect samples for culture before starting antibiotic therapy, as long as this does not significantly delay the introduction of treatment. At least two blood samples should be taken from different catheters. For patients with vascular catheters inserted for more than 48 hours, it is advisable to take samples also from these sites. In addition, material for microbiological testing should be collected from any potential source of infection, such as urine, feces or wound material, according to procedures that minimize the risk of sample contamination [32,34].

Each culture should be analyzed in both aerobic and anaerobic cultures. The use of MacConkey agar medium allows assessment of the lactose fermentation capacity of the microorganisms under study. The indole assay can be useful in identifying the presence of tryptophanase, which is positive for *Escherichia coli*, for example. Gram staining in direct preparation helps to quickly determine whether the microorganism is gram-positive or gram-negative. Antimicrobial susceptibility testing and interpretation of the antibiogram are essential for effective therapy selection [32,34].

6. Imaging and laboratory studies

Imaging studies are crucial in identifying large foci of infection, the rapid localization and removal of which are priorities in the treatment of sepsis. Laboratory tests, although not specific for sepsis, help assess organ function and the severity of inflammation. Important parameters include arterial blood gasometry, lactate levels (elevated levels >2 mmol/L indicate tissue hypoperfusion), renal and liver function parameters and hemostatic indices, blood count (including leukocyte count),

CRP, procalcitonin and IL-6 are helpful in assessing the degree of inflammation.

Procalcitonin, especially a decrease in its concentration, can be helpful in assessing the effectiveness of antibiotic therapy and in deciding whether to shorten it. At the same time, it should not be a determinant as to the inclusion of antibiotic therapy. Determination of procalcitonin can only complete the overall clinical assessment [32].

7. Treatment

According to the Surviving Sepsis Campaign recommendations, treatment of sepsis and septic shock should be initiated immediately after their diagnosis—preferably within the first hour—because these are immediately life-threatening conditions. Postponing the implementation of antibiotic therapy significantly worsens the prognosis [32]. The primary point of treatment of sepsis is to remove the source of infection, e.g. removal of the vascular catheter [32,34].

Treatment of sepsis with Enterobacterales etiology includes all basic therapeutic measures, such as fluid resuscitation and maintenance of adequate hemodynamic status of the patient. Crucial to patient survival, however, remains the proper choice of antibiotic therapy [32].

8. Empiric antibiotic therapy

The first-line treatment is broad-spectrum empiric antibiotic therapy, which covers the most common pathogens associated with the potential source of infection and ensuring adequate penetration of the drug into the focus of infection. The choice of therapy should also take into account the current epidemiological situation and the presence of resistant strains, including beta-lactamase-producing bacteria (e.g. ESBL, AmpC).

For Enterobacterales, possible therapeutic options include carbapenems, beta-lactams, beta-lactam inhibitors, fluoroquinolones, aminoglycosides, sulfamethoxazole/trimethoprim.

Empirical treatment most often includes: – carbapenems (e.g., meropenem, imipenem), especially in cases of suspected resistance to cephalosporins. Carbapenems are the traditional first-line treatment one of the most effective options for controlling infections with *Enterobacter* etiology. Despite high efficacy, there is growing resistance to this group of antibiotics. – IV-generation cephalosporins (e.g., cefepime) effective against bacteria producing AmpC beta-lactamases, provided there is no ESBL.

Beta-lactams with beta-lactamase inhibitors (e.g., piperacillin/tazobactam), especially in cases where there is no suspected ESBL-type beta-lactamase production [34,35].

9. Targeted treatment

De-escalation of therapy is the next step of treatment, which involves adjusting antibiotic therapy according to the result of the antibiogram with the determination of drug susceptibility of the microorganism- selection of treatment targeted. Enterobacterales are pathogens that pose a therapeutic challenge due to Third-generation cephalosporins (e.g., cefotaxime, ceftriaxone) and fourth-generation cephalosporins are ineffective in the presence of ESBL. Their use may contribute to the development of multidrug-resistant infections. The use of third-generation cephalosporins is not recommended in severe infections with *Enterobacter cloacae* and *Enterobacter aerogenes* [34].

Bacteria that produce ESBLs (Extended Spectrum Beta-Lactamases) – effective treatment is carbapenems (e.g. meropenem, imipenem); – when carbapenems are unavailable, alternative treatment is fosfomicin or tigecycline; [34] Enterobacterales producing AmpC beta-lactamases carbapenems are the best treatment option; – alternatives such as piperacillin/tazobactam and cefepime show efficacy in trials [36,37,38], but IDSA (Infectious Diseases Society of America) [35] does not recommend their use in patients with severe infections. Resistance to carbapenems (CRE)-includes polymyxins, tigecycline, fosfomicin and carbapenems. In this case, the best therapeutic option is combination treatment [34,35], polymyxin (e.g., colistin) with the addition of carbapenems, tigecycline, fosfomicin, aminoglycosides-in the absence of colistin resistance; – tigecycline or a combination of two carbapenems, in the case of resistance to colistin; Dual carbapenem therapy-one molecule acts as “trap” for carbapenemase. their ability to acquire resistance to numerous classes of antibiotics. Once the patient’s condition improves, oral OST- Oral Sequential therapy can be considered: fluoroquinolones or trimethoprim/sulfamethoxazole, if the strain is susceptible [33,34].

10. Prophylaxis

WHO identifies two main lines of prophylaxis: preventing the spread of microorganisms and infections, and preventing infections from developing into sepsis [36]. The Surviving Sepsis Campaign elaborates

on these tenets, emphasizing that routine observation of critically ill patients with suspected infections for bacteremia – in order to quickly implement treatment – is crucial. In addition, it is recommended that medical units have programs that include screening for carrier or microbial infection [33]. It is also important to stress the importance of limiting the use of medical equipment to only those cases where it is necessary for the patient, and avoiding inappropriate use of antibiotics – which is important in preventing the development of multidrug-resistant strains [36].

Discussion

Atypical sepsis symptoms in elderly patients

In an article by Astrid L Wester, in a study she presented, older age groups were more likely to present atypical symptoms ($p < 0.001$), worsened general health ($p = 0.029$) and higher in-hospital mortality ($p < 0.001$) [39].

Empiric antibiotic therapy in patients ≥ 75 years of age

In the article by Albane Roseau-Vincenti, in the study she presented, empiric antibiotic treatment was considered appropriate in 86% of patients ($n = 360/418$). In-hospital mortality was 12.7% ($n = 62$) and was related to the severity of infection (OR 3.17, 95% CI 1.75-5.75), while urinary tract infections were protective (OR 0.34, 95% CI 0.19-0.60) [40].

Enterobacterales resistance in the elderly

In Caroline Hyernard’s article, elderly patients are at particular risk for infections caused by multidrug-resistant strains of Enterobacterales, including ESBL and CRE. Risk factors include immunosenescence, polypharmacotherapy and frequent hospitalizations [41].

Risk factors for mortality in sepsis in the elderly

In an article by Ignacio Martin-Loeches, multivariate analysis found that in patients aged ≥ 80 years, age (aOR 1.1; 95% CI 1.1-1.2; $p < 0.04$), modified APACHE II score (aOR 1.1; 95% CI 1.1-1.1; $p \leq 0.001$) and compliance with sepsis resuscitation package (6 h) as recommended by the SSC (aOR 0.214; 95% CI 0.1-0.9; $p < 0.05$) were independent risk factors associated with in-hospital mortality [42].

Impact of sepsis on outcomes in geriatric patients

In an article by Wan Gadzlina Wan Muhd Shukeri, compared to a younger group, older patients had higher

ICU mortality (26.7% vs. 11.6%; $p < 0.0001$) and in-hospital mortality (46.7% vs. 17.1%; $p < 0.0001$) [43].

Empirical therapy

Empirical therapy according to D. Dzierzanowska's book for gram-negative bacilli in a decubitus infection should use gentamicin or another active antibiotic against gram-negative bacilli. In addition, an antifungal drug should be considered especially when the patient is on parenteral nutrition or at risk [44].

Conclusion

Sepsis in geriatric patients attributed to Enterobacterales represents a multifaceted condition associated with significant morbidity and mortality. The atypical clinical presentation, which can include symptoms such as delirium, falls and absence of fever, poses significant diagnostic challenges. Prompt diagnosis and specifically

tailored therapeutic strategies are essential to improve outcomes in this susceptible population. Clinicians are encouraged to maintain a heightened level of suspicion and use clinical criteria such as SIRS, SOFA and QSOFA to identify sepsis early and initiate appropriate therapeutic interventions.

Conflict of interest

None

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