

Sepsis in frail patient

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ABSTRACT

Frailty is defined as a clinical syndrome in which three or more of the following criteria are present: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity. Sepsis is defined as an inflammatory response to infection, with severe sepsis and septic shock being the most severe forms. The incidence of severe sepsis increases with older age and several studies have shown that there are many risk factors that predispose the elderly to a higher incidence of sepsis. Pre-existing co-morbidities such as cancer, diabetes, obesity, human immunodeficiency virus, and renal or pulmonary disease can cause sepsis, but other factors including poor lifestyle habits (*i.e.*, smoking, drug or alcohol abuse), malnutrition, and endocrine deficiencies, which are frequent in the elderly, may also predispose to severe infections. Other risk factors for sepsis include recurrent hospitalization, especially in the Intensive Care Unit, and nursing home residence, where interventions such as urinary catheterization or multiple drug use are quite frequent and many studies reported that people above 65 years of age are three times more likely to be admitted to hospital than those aged 16-64 years, and have a higher risk of prolonged hospital stays, institutionalization and death. Clinical evaluation of the frail patient with sepsis poses some challenges. The immune response becomes progressively less efficient with increasing age thereby causing an altered response to infection and it is important to know that the clinical evaluation of the so-called *fragile* patient with severe infection should take into account the sometimes unusual signs and symptoms that, if identified, can lead to early diagnosis. Laboratory diagnostics can also be of great help in this setting. The treatment of sepsis in the fragile patient can be *empirical* or based on microbiological culture. Moreover, *frail patient population* presents many clinical problems with numerous comorbidities, therefore anti-infective treatment is difficult, so the physician's armamentarium must include many antibiotic drugs, of which there are far more available for the treatment of sepsis caused by Gram-positive bacteria than for sepsis caused by Gram-negative ones or fungi.

Introduction

Frailty has always been considered synonymous with disability, comorbidity and other characteristics, but it may have a biological basis and be a distinct clinical syndrome.^{1,2} In fact, it is associated with advanced age and chronic, but non-specific disease, and there is no standardized definition or valid screening method for those who are truly frail.

Numerous geriatric interventions have been de-

veloped to improve clinical outcomes for frail older adults.³

People above 65 years of age are three times more likely to be admitted to hospital than those aged 16-64 years, and have a higher risk of prolonged hospital stays, institutionalization and death. However, older age alone is not a sensitive predictor of inpatient mortality.^{4,5}

An important study based on data from the Cardiovascular Health Study involving 5317 men and women aged 65 years or older, defined a series of distinctive traits for frailty.

There is growing consensus that markers of frailty should include low physical activity and age-associated declines in lean body mass, strength, endurance, balance, and walking performance, and that several of these signs must be present to constitute frailty.

Frailty is defined as a clinical syndrome in which three or more of the following criteria are present: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity.

These authors believe that there is also an intermediate frailty status, as indicated by the presence of only one or two of the criteria.¹

Therefore, advanced age alone is not a significant predictor of inpatient mortality, but some studies have shown that people over 65 years of age are three times

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more likely to be admitted to hospital than those aged 16-64 and that they occupy about two-thirds of acute hospital beds.^{4,5}

Sepsis is defined as an inflammatory response to infection, with severe sepsis and septic shock being the most severe forms.⁶ The incidence of severe sepsis increases with older age and several studies have shown that there are many risk factors that predispose the elderly to a higher incidence of sepsis.⁷

Pre-existing co-morbidities such as cancer, diabetes, obesity, human immunodeficiency virus, and renal or pulmonary disease can cause sepsis, but other factors including poor lifestyle habits (*i.e.*, smoking, drug or alcohol abuse), malnutrition, and endocrine deficiencies, which are frequent in the elderly, may also predispose to severe infections.⁸⁻¹¹

Other risk factors for sepsis include recurrent hospitalization, especially in the Intensive Care Unit, and nursing home residence, where interventions such as urinary catheterization or multiple drug use are quite frequent.⁷

Thus, the elderly are also at increased risk for colonization by Gram-negative multi-drug resistant organisms.¹²

Keeping the immune system of elderly and frail patients in mind is also quite important.

Their immune system is abnormal and there are functional impairments in both cell-mediated immunity and humoral immune responses. Memory cells have limited proliferative capacity in response to antigens, and B-cells and plasma cell populations also gradually decrease with aging.¹³

Moreover, frailty has also been associated with abnormalities in many physiological and biochemical systems. These include anemia, low albumin levels, elevated markers of inflammation, low levels of insulin-like growth factor-1 and dehydroepiandrosterone-sulfate, high hemoglobin A1c and micronutrient deficiencies.^{4,7}

All these factors predispose to infections and sepsis.

Clinical evaluation and diagnosis

Clinical evaluation of the frail patient with sepsis poses some challenges.

We know that the immune response becomes progressively less efficient with increasing age thereby causing an altered response to infection.¹³

It is well known that older patients, particularly those with comorbidities, may be affected by severe infections without presenting any of the typical symptoms, such as fever, which may be absent in 30-50% of cases.^{14,15} This is mainly due to alterations in the thermoregulatory mechanisms: the presence of shivering and vasoconstriction may be observed, while hypothalamic regulation and thermogenesis are altered in old age.¹⁶

Among the less specific symptoms, we may observe weakness, malaise, delirium, confusion, loss of appetite, urinary incontinence or falls to the ground, any of which may be the only indicators of an underlying infection.¹⁷

Laboratory markers of inflammation may also be minimally altered, often leading to a delay in administering appropriate therapy.¹⁷

Generally speaking, elderly patients with severe infections, unlike younger subjects, are not able to accurately relay their symptoms, thus requiring us to resort to clinical tools in order to classify the patient.

Therefore, in the presence of a suspected infection, laboratory tests are of great importance.

Blood samples must be collected for blood cultures, urine samples for urine cultures and for the antigenic search for *Streptococcus pneumoniae* and *Legionella pneumophila* when we suspect, or find evidence of, pulmonary infection.¹⁷

In the presence of a possible invasive fungal infection, particularly *Candida* [*e.g.*, in patients with some evidence of colonization and carriers of central venous catheters (CVC) undergoing total parenteral nutrition and/or recent major surgery], it may be useful to evaluate for the antigen β -d-glucan serum marker.¹⁷

Rectal swabs should be collected from patients in nursing-home residences or who have recently been hospitalized in order to rule out colonization by multi-resistant enterobacteria. The results of the swab would be useful for establishing the most appropriate antibiotic therapy.¹⁸

In case of diarrhea, the search for *Clostridium difficile* toxin should always be performed in institutionalized patients.¹⁹ The collection of sputum for culture tests is of limited value, although sometimes it may be of help.¹⁷ Low albumin and high C-reactive protein values were found to be independent risk factors for mortality in the elderly.^{4,7}

Radiological exams may be abnormal in frail patients with pneumonia or may be non-specific, given also the possible presence of pre-existing or underlying conditions such as heart failure. The appearance of wheezing alone may be a sign of sepsis, even in the absence of radiological evidence of pneumonia.²⁰

It follows that the clinical evaluation of the so-called *fragile* patient with severe infection should take into account the sometimes-unusual signs and symptoms that, if identified, can lead to early diagnosis. Laboratory diagnostics can also be of great help in this setting.

The treatment of sepsis in the fragile patient

We usually consider the *frail patient population* to be made up of a very large number of patients. This population presents many clinical problems with nu-

merous comorbidities, therefore anti-infective treatment is difficult.^{1,21,22}

However, since the beginning of the 21st century one of the main problems in case of bacteremia and sepsis is the increase in Gram-negative bacterial infections. Mortality ranges from 12 to 38% and depends on the timeliness and correctness of antibiotic therapy, as is the case for other etiologic agents.²³ Bacteremia and septic shock by Gram-negative bacteria must be managed from the therapeutic point of view before achieving potential microbiological isolation.^{24,25}

In recent years, issues related to Gram-negative infections have become critical in all larger hospitals. Moreover, an increasing percentage of Gram-negative organisms have become resistant to many antibiotics and treatment has become very difficult.^{25,26}

The American National Healthcare Safety Network (NHSN) recently issued a report on resistance in Gram-negative infections (2009-2010) involving 27,766 patients with sepsis: i) *Acinetobacter baumannii* has a 67% resistance rate to carbapenems; ii) *Klebsiella pneumoniae* has a 13% resistance rate to carbapenems (although in 2015, in Italy it was actually between 25-40%); iii) *Escherichia coli* has a 42% resistance rate to fluoroquinolones; iv) *Pseudomonas aeruginosa* has a 31% resistance rate to fluoroquinolones and a 26% resistance rate to cephalosporins and to 3rd and 4th generation carbapenems.

In the treatment of sepsis, we may consider an empirical preparatory treatment rather than targeted treatment in case of bacterial culture isolation. Taking into account only frail patients with severe sepsis or septic shock who have risk factors for *Pseudomonas aeruginosa*, or inpatients in hospitals where the resistance level as a percentage of Gram-negative bacteria is between 20-25%,²³ the proposed scheme includes aminoglycoside + one of the following: cefepime 2 g every 8 h or ceftazidime 2 g every 8 h or piperacillin - tazobactam 4.5 g every 6 h or meropenem 1 g every 8 h.²³⁻²⁶

A separate chapter is warranted for panresistant Gram-negative sepsis such as *K. pneumoniae*-producing carbapenemase (KPC). Nowadays, this is a problem in our hospitals, especially in frail, elderly patients who are hospitalized at length and undergo multiple courses of antibiotics, in particular carbapenem, or who are colonized by KPC. Approximately 20% of patients who are colonized by these bacteria suffer from severe sepsis, and mortality amounts to about 50%.^{27,28}

Several reports claim the superiority of a combination therapy in these cases, and treatment usually consists of the following scheme: colistin 9,000,000 U loading dose followed by 4.5 million U every 12 h intravenously (iv) + tigecycline 200 mg loading dose followed by 100 mg every 12 h or fosfomycin 4-6 g every 6-8 h or meropenem 2 g every 6 h if MICs are at least ≤ 32 or aminoglycoside.

Antibiotic therapy should be reconsidered on the basis of new resistances that are developing: in some areas, KPC resistance to colistin may be as high as 30%. The physician's armamentarium must include many antibiotic drugs, of which there are far more available for the treatment of sepsis caused by Gram-positive bacteria than for sepsis caused by Gram-negative ones.

Furthermore, infections caused by CVCs or vascular devices are frequently related to problems such as osteomyelitis from soft tissue infection and endocarditis.^{24,25,27-31}

Treatment of severe sepsis by Gram-positive bacteria in the fragile patient should be evaluated based on the patient's additional risk factors and comorbidities and on the ecosystem of the hospital where they are being treated in relation to the percentage of methicillin-resistant *Staphylococcus aureus* that is present.

A proposal for therapy might be: vancomycin 30 mg/kg iv (usually 2 g continuous infusion) or teicoplanin 10-12 mg/kg/day iv administered once these molecules benefit from an initial loading dose. A good choice is also the association of a glycopeptide with a single daily dose of rifampicin 15 mg/kg/day iv.

But in some types of sepsis, such as the ones caused by CVCs, or in organ involvement (lung or soft tissue), several other options are available, such as: daptomycin 8-10 mg/kg/day iv administered in one single administration or linezolid 1.200 mg iv in continuous infusion.

If microbiological findings reveal a methicillin-sensitive *S. aureus*, then the choice could fall on: oxacillin 2 g iv every 6 h.³⁰⁻³⁴

We have divided the therapeutic proposals for the treatment of sepsis regardless of whether etiology is Gram-positive or Gram-negative. Nonetheless, empirical approach therapy still remains valid when the causative agent is uncertain; in this case the recommendation is to associate: piperacillin-tazobactam 4.5 g \times 3 iv (or continuous infusion) or meropenem 1 g \times 3 iv + amikacin 15-20 mg/kg/day iv administered once + glycopeptide or daptomycin.^{27,28,35,36}

In addition, it must be kept in mind that the frail patient is also susceptible to a certain frequency of sepsis caused by invasive fungal infections (IFI).

In recent Italian case studies, about 60% of patients with candidemia had been admitted to Internal Medicine Departments, thus confirming that sepsis targets the fragile patient.³⁷ Even in this case, correct timing of the beginning of therapy is critical to outcome. Delaying the start of treatment beyond 96 h may result in a 40% to 50% mortality rate. Even among IFIs, we have observed a change in the relationship between *Candida albicans/non albicans*, thus, the recommendation for the empirical-rational therapy (which can also make use of the evaluation score rather than biochemical mark-

ers) is the following: echinocandin, caspofungin starting dose of 70 mg/day iv then 50 mg iv/day or micafungin 100 mg iv once/day or anidulafungin 2×100 mg iv starting dose then 100 mg iv dosing.

If the antifungal sensitivity test indicates sensitivity to fluconazole, it may be subsequently administered at a dose of 800 mg iv instead of echinocandin.³⁸⁻⁴²

Standardizing the timing of antibiotic therapy or antimycotic administration in the case of sepsis, especially in frail patients, is absolutely impossible. It is necessary to consider clinical and biochemical parameters and safety of therapy, and the therapeutic intervention should be tailored to the individual patient.

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