

Gram-negative infections in frail patients

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SUMMARY

Introduction: Gram-negative infections (GNIs) are frequently encountered both in community and hospital settings. Frail patients, defined as elderly individuals with multiple comorbidities, are particularly vulnerable to them. The presentation and the course of GNIs differ in aged patients compared with younger ones, making their management a unique challenge. This review aimed to outline the essential elements of the presentation, diagnosis, and outcome of GNIs in frail individuals.

Methods: MEDLINE/PubMed library search was performed using the following terms: frail, frailty, elderly,

Gram-negative, infections, pneumonia, urinary tract infection, and bloodstream infection for the purpose of the review.

Conclusions: Elderly patients with multimorbidity represent a distinct population with relevant differences in GNIs presentation, diagnosis, and outcome. Several pitfalls should be avoided and appropriately addressed when facing GNIs in this group of patients. Future studies focusing on this population should be encouraged.

Keywords: Elderly, Gram-negative, infections, frail patients, comorbidities.

INTRODUCTION

Gram-negative infections (GNIs) remain a fearsome condition for most clinicians due to their high rates of both morbidity and mortality, alongside the increasing prevalence of multidrug-resistant Gram-negative bacteria (GNB) [1, 2]. Additionally, certain groups of patients are particularly prone to GNIs and their complications; elderly patients with multiple comorbidities are an especially at-risk group [3]. Such patients represent a heterogeneous population, oftentimes residing in community living situations, long-term-care facilities residents, and hospitals. Multiple studies highlighted the impact of infections on this population

[4, 5]. For instance, an Italian study found an overall infection rate of 11.8 per 1000 person-days in long-term-care facilities, with urinary and lower respiratory tract infections as the most frequently observed [6]. Most of these infections were caused by Gram-negative pathogens, elucidating the increasing role of these organisms in the elderly, with increasing concerns regarding Gram-negative bacteria resistance patterns [6, 7]. As longevity increases worldwide, infection rates also rise. For this reason, GNIs are expected to increase, creating further medical and social strain for patients and the community.

Different definitions of the term 'geriatric patient' exist; for the purpose of this review, we adopt the one of the European Union of Medical Specialists - Geriatric Medicine Section (UEMS-GMS), considering the frail individual as a patient with multimorbidities together with age more than 65 years or having more than 80 years [8, 9]. This article

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aims to present a general framework of this population's presentation, diagnosis, and prognosis of Gram-negative infections.

■ MATERIALS AND METHODS

A narrative review format was selected. For the purpose of the review, the search was done on the MEDLINE/PubMed library database using the following keywords: frail, frailty, elderly, Gram-negative, infections, pneumonia, urinary tract infection, and bloodstream infection. The search was restricted to reviews published between 1960 and 2023 and was limited to the English language.

■ PRESENTATION AND DIAGNOSIS OF GRAM-NEGATIVE INFECTIONS IN THE ELDERLY

Elderly patients are particularly prone to Gram-negative infections because of coexisting chronic or acute diseases that disrupt skin and mucosal barriers, impair clearance mechanisms, or compromise cellular responses to GN bacteria [10]. Infections in these patients are more frequent and severe and have peculiar features concerning microbial epidemiology, clinical presentation, laboratory results, treatment, and infection control [11]. These facts often result in diagnostical challenges for clinicians [12].

Concerning microbial epidemiology, infections may be caused by pathogens that differ among older patients from those affecting younger ones [13]. Indeed, several studies have shown a higher prevalence of Gram-negative bacterial infections in the elderly. This observation concerns, for example, urinary tract infections, bloodstream infections, and pneumonia [14-16].

Regarding the clinical presentation and the diagnosis of infections in elderly individuals, this is frequently hampered by the atypical presentation and lack of distinctive symptoms of infections, including fever or localised pain [17]. Because of the relatively poor prognosis of older patients with infections, a careful clinical assessment specific to this category should be performed [3]. From a general point of view, fever, the cardinal manifestation of infection, may be absent or of low grade in elderly patients, even when severe or life-threatening infections are implicated. The elderly tend

to have lower baseline temperatures; a normal febrile response in these patients may not reach traditional fever cut-offs, and the development of fever may be delayed up to 12 hours [18, 19]. Elderly patients with infections may also present atypical signs and symptoms, including acute confusion or delirium as dominant findings. They may also have a subacute course with symptoms of weakness, anorexia, weight loss, fall, urinary incontinence, or loss of physical functional capacity [13].

Furthermore, specific considerations apply to some infections. The main difficulties in diagnosing urinary tract infections (UTIs) in older adults are caused by an increased prevalence of asymptomatic bacteriuria and the frequent use of urinary catheters [12]. Indeed, clinical clues of UTIs are frequently absent in patients with indwelling urinary catheters [10]. Concerning pulmonary infections, signs and symptoms of pneumonia are difficult to interpret in the elderly with chronic bronchitis or other pulmonary diseases in which cough and sputum production are present [10]. Moreover, microbiological aetiology in elderly patients with pneumonia is difficult to obtain due to the inability to produce a good-quality respiratory sample. Another important concern is that older patients are less likely to present with classic radiologic findings of pneumonia, especially multilobar infiltrates.

Regarding bloodstream infections (BSI), signs or symptoms are vague, and none appear to be critical in terms of specificity. Older patients with BSI have fewer symptoms in the early stages of the disease [16]. However, four clinical parameters are significantly associated with BSI in an elderly patient: rapid onset of fever, the presence of fever, new onset altered general state, and clinical signs related to the source of the infection [11]. Given that the prognosis for GNIs seems to be more severe in the elderly, it appears essential to detect this disease rapidly, also taking advantage of laboratory findings. It is worth noting that classical laboratory markers of infection, such as C-reactive protein (CRP) or leukocyte counts, have reduced sensitivity and specificity in elderly patients [20]. This observation was associated with the so-called 'immunosenescence', reflecting an inadequate immune response [21]. Interestingly, in elderly patients, the diagnostic accuracy of procalcitonin (PCT) for sepsis and infections without sepsis is

higher than that of CRP and leukocyte counts [22]. Considering this, PCT may represent a valuable tool for differentiating infective from non-infective conditions.

The abovementioned atypical clinical characteristics may delay diagnosis and early treatment in elderly patients, contributing to the significant morbidity and mortality of infection.

■ RISK FACTORS AND OUTCOME

Risk factors for GNI can be divided into modifiable and non-modifiable. Indeed, the most significant non-modifiable risk factor is age. Several studies reported higher in-hospital and 1-year mortality rates in patients aged ≥ 65 with Gram-negative BSIs than in younger patients [23–25]. Also, patients aged ≥ 65 are more likely to present organ failure, septic shock, and longer hospital stays [26]. Older patients who survive infections tend to have more severe clinical sequelae, including a higher tendency to reinfections, a decline of cognitive functions, and a worsening of their baseline health status [11].

Nevertheless, age is not the only factor associated with lower survival; other age-related factors, including a higher prevalence of malignancies, haematological disorders, chronic illnesses, disability, anatomical changes, malnutrition, and immunaging, have all been associated to worse outcomes, with most studies focusing on Gram-negative BSIs [27–29]. In addition, specific age-related changes in the immune response lead to an increased susceptibility to infections, including a decline of T-lymphocytes in terms of number and function, a decreased production of antibodies by B-lymphocytes, and an impaired macrophages' activation ability [30]. To sum up, all these elements have been thought to have a role in reduced cell-related immunity and increased susceptibility to infections.

Also, the source of infection represents a significant factor that influences the prognosis of Gram-negative infections. Respiratory and abdominal infections are associated with higher mortality than urinary tract infections (UTIs) [27, 28]. In particular, respiratory tract infections may exacerbate other chronic illnesses, such as chronic obstructive pulmonary disease, increasing the risk of acute respiratory failure [30, 31].

Furthermore, clinicians may also experience chal-

lenges when treating frail patients due to pharmacokinetic and pharmacodynamic considerations. Indeed, some physiological modifications in the elderly can alter antibiotics' pharmacology and toxicity. Reduced body mass, liquid volume changes, and impaired renal and hepatic drug clearance have all been linked, for instance, to reduced body distribution of beta-lactams and increased nephrotoxicity [32].

Modifiable risk factors are those for which preventive measures can be implemented. In elderly patients, atypical clinical and laboratory features of infective status have been associated with delayed diagnosis and treatment, both recognised as risk factors for mortality [30, 33]. Another major issue is the emergence of an increasing number of MDR strains of Gram-negative bacteria (GNB), especially ESBL-producing and carbapenem-resistant *Enterobacteriales* [34]. It is reported that MDR-GNB infections are associated with longer hospital stays and long-term complications, especially in older people [35]. For instance, MDR Gram-negative BSIs have been linked to more frequent inappropriate or ineffective antibiotic therapy, with a leading role of inadequate initial antibiotic therapy as a predictive factor of mortality [36]. Side effects of antibiotics are more frequent and more severe due to chronic comorbidities and multiple treatments, which should continually be assessed to avoid drug interactions [11, 37]. Specific attention should be paid to Antibiotic Stewardship programs to monitor the side effects and antibiotic interactions in the elderly population.

Another modifiable element to consider is the increased use of medical devices among elderly patients. The mortality risk is higher for medical devices-related infections; for instance, catheter-related bloodstream infections (CRBSIs) and catheter urinary tract-related bloodstream infections (CAUT-BSIs). Indeed, central venous and indwelling urinary catheters play a key role in the onset of bloodstream infections in aged hospitalised patients [36]. Regarding CRBSIs, although Gram-positive bacteria more frequently cause device-related BSI (CRBSIs), elderly patients present a higher rate of GN-BSI [11]. Concerning urinary tract-related bloodstream infections (UT-BSIs), an indwelling urinary catheter is one of the main risk factors for developing bloodstream infections associated with sepsis and MDR-GN aetiology [15]. Patients with indwelling and vascular catheters are fre-

quently institutionalised in long-term care facilities or prone to prolonged hospitalisations, both being risk factors for MDR-GN infections and associated with comorbidities and worse underlying health status.

■ CONCLUSIONS

Frail patients are particularly vulnerable to Gram-negative infections. Age, the presence of age-related comorbidities, the consequences of institutionalisation, and the frequent use of medical devices all account for the atypical clinical and laboratory presentation of GNIs in this population. This peculiarity may lead carers to a delay in diagnosis and treatment, resulting in a worsened prognosis. These patients should indeed be considered a special population. Clinicians should approach them accordingly with a high index of suspicion and careful global assessment. Moreover, the increasing worldwide prevalence of multidrug-resistant GN pathogens represents a substantial threat due to their pattern of reduced susceptibility to antibiotics and device-related infections. The number of elderly patients with multiple comorbidities is expected to increase. Specific measures should therefore be implemented, including appropriate stewardship considerations for at-risk patients and dedicated frailty teams. Future studies focusing on the implication of ageing on GNIs should be encouraged to improve diagnosis, treatment and outcomes.

Conflict of interest

The authors declare no conflict of interest.

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