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REVIEW ARTICLE

Infections in the older population: what do we know?

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Abstract
The incidence of infections increases with age and results in a higher risk of morbidity and mortality. This rise is not mainly related to chronological age per se but has been linked mostly to individual factors such as immunosenescence; the presence of comorbidities; the occurrence of geriatric syndromes such as poor nutrition, polypharmacy, and cognitive disorders; and the presence of functional impairment concomitant with environmental, healthcare-related and microbiological factors such as the increasing risk of multidrug-resistant microorganisms. The geriatric concept of frailty introduces a new approach for considering the risk of infection; this concept highlights the importance of functional status and is a more comprehensive and multicomponent approach that may help to reverse the vulnerability to stress. The aim of this article is to provide some typical hallmarks of infections among older adults in comparison to younger individuals. The main differences among the older population that are presented are an increased prevalence of infections and potential risk factors, a higher risk of carrying multidrug-resistant microorganisms, an increase in barriers to a prompt diagnosis related to atypical presentations and challenges with diagnostic tools, a higher risk of under- and over-diagnosis, a worse prognosis with a higher risk of acute and chronic complications and a particular need for better communication among all healthcare sectors as they are closely linked together.

Keywords Infections · Aged · Frail elderly · Signs and symptoms · Clinical presentation

Introduction

The world population is ageing as a result of an increase in life expectancy, which is leading to a global shift from acute to chronic diseases [1]. However, acute illnesses such as infections remain an important cause of morbidity and mortality [2]. There is growing evidence that the burden of infectious diseases is important, especially among older persons, as has been reported for bloodstream infections, urinary tract infections, pneumococcal disease, *Clostridium difficile* and multidrug-resistant microorganisms (MDRO) [3–7].

Geriatrics, a word first used in 1909 by the American Ignatz L. Nascher, the father of geriatric medicine, has become a new medical discipline in the last century and was developed in 1935 in England by the mother of geriatric medicine, Marjory Warren [8]. In 1984, Rubenstein showed that geriatric evaluation and management units may improve outcomes of frail elderly inpatients, such as functional status, the rate of nursing home (NH) admission, hospital readmission and survival [9]. Since that study, the discipline has expanded in many countries worldwide. While results regarding mortality are more conflicting, different meta-analyses have shown that comprehensive geriatric assessment (CGA) will improve functional status, improve cognition and physical function and reduce falls, resulting in a higher rate of patients living at home and a lower rate of persons admitted to hospitals or into NHs [10–12]. Concomitantly, the concept of frailty has emerged since the 2000s and is an important health issue, adding a new dynamic approach to the evaluation of ageing [13]. In this context, close collaborative programmes between geriatricians, internal medicine specialists, general practitioners, infectious disease specialists and microbiologists are important and may improve practices and patient-oriented results [14] (Fig. 1).

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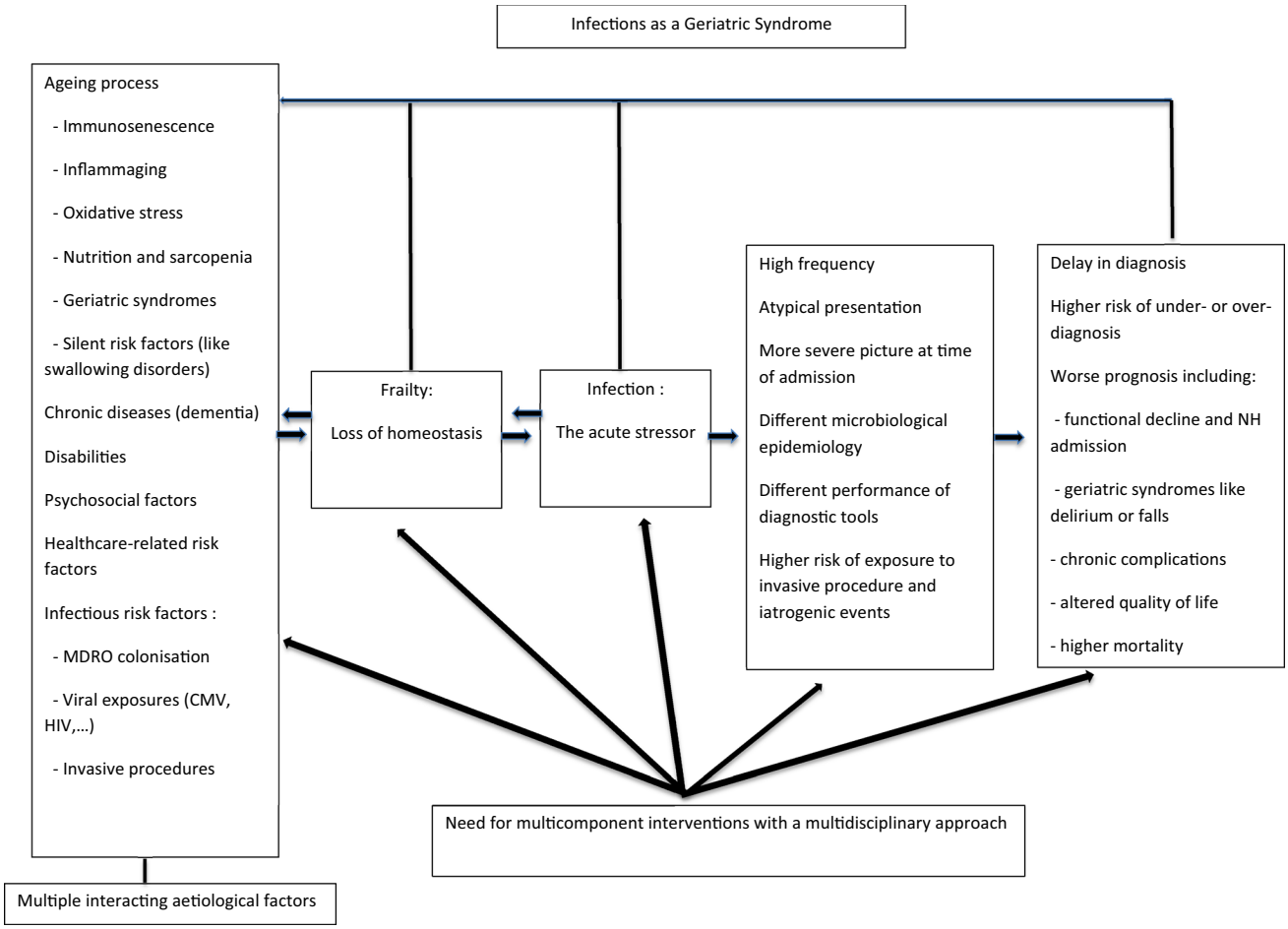

Fig. 1 How infections fit within the conceptual framework of a geriatric syndrome as stated by Inouye SK in 2007 [138]

The aim of this narrative review is to describe different aspects of infections among old persons to improve the awareness of healthcare providers to the specificities of some aspects of clinical infections and to compare them to a younger population. In an attempt to narrow the focus, we do not address therapeutic aspects such as pharmacokinetic or dynamic changes with ageing. We used a similar design to a previous review article published in 2002, at a time when the concept of frailty was just emerging. References included in this review were identified by a Medline search of articles written in English or French since 1981 in the field of geriatric or infectious diseases and have been selected as relevant to or illustrative of the three authors' points of view [15]. The two main search terms used were "elderly" and "infection". A subset of criteria were cross-referenced with these and included: "epidemiology", "presentation", "microbiology", "frailty", "immune system", "geriatric syndromes", "pneumonia", "urinary tract infections", "asymptomatic urinary bacteriuria", "bloodstream infection", "endocarditis", "dementia", "herpes zoster", "procalcitonin", "multidrug-resistant microorganisms", "extended-spectrum beta-lactamase producing *Enterobacteriaceae*", "*Methicillin-resistant Staphylococcus aureus*", and "nursing homes". Additional clinical information, based on the clinical experience of the authors, is also provided to complement the relevant studies.

Epidemiology of infections in elderly people

The prevalence of infections increases with age [15]. This was shown in the community where the rate of urinary tract infections was increased by a factor of 2–20 with increasing age when compared to a younger population [16]. In a French survey performed in 46 hospitals, the risk of community-acquired bloodstream infections was more frequent in an old–old population compared to a young-old population, showing that old age among the older population is associated with an increased risk of infections [17]. This trend was also shown for nosocomial infections and within long-term care facilities (LTCF) [18]. For example, in a cross-sectional survey performed in a sample of nine geriatric centres

in Switzerland including 1919 patients, infection rates increased from 18% among male residents younger than 74 years to 22% among male residents older than 85 years [19]. In that study, age by itself was not an independent risk factor for infection. Other conditions, such as chronic bronchitis, swallowing disorders, nutritional problems, intravenous or urethral catheters and psycho-behavioural status, were all associated with an increased risk of infections. Infections are the main reason for hospital admission in the elderly and may lead to functional decline or the occurrence of geriatric syndromes such as falls, delirium or malnutrition. In the French "Arianne Study" performed by the Geriatrics Infectious Disease Observatory (ORIG) in 2001 in a large group of French hospitals (Charles-Foix Hospital Group; Ivry-sur-Seine, Paris), the prevalence of healthcare-associated infection (HAI) in geriatric sectors, including not only short-term acute care units but also intermediate and long-term care units, was 9.6%, which was 2% higher than in the general medical wards [20]. In that survey, the top five infections included the following, in order of frequency: urinary tract infection, respiratory tract infection, skin and soft tissue infection, surgical site infection and bacteraemia. In the Belgian National Nosocomial Infection Study performed in 2007 among 543 hospital units, the prevalence of HAI in geriatric wards was as high as 8.8%, which was 2.9% than in the general medical wards and 20% lower than in intensive care units [21]. In that prevalence survey, the mortality rate was higher in geriatric wards compared to surgical wards (18% and 5%, respectively), which was similar to the proportion of patients referred to an NH after hospital discharge from each ward (25% and 7%, respectively). More recently, the results from two Europe-wide point-prevalence surveys (PPSs) in 2016–2017 showed that 6.5% of patients in acute care hospitals and 3.9% of residents from LTCFs had at least one HAI [22].

This increasing prevalence of infection with age is related to different factors. The real impact of age is a controversial issue, and other contributing factors, which are more frequent with age, likely more strongly impact the risk compared to chronological age alone. For example, a limited impact of increasing age on the risk of *Clostridium difficile* was demonstrated after adjustment for acute conditions, frailty markers and prior healthcare utilization [23]. Age has been associated with age-related changes of the immune system, including alterations of the innate and adaptive immune system [24]. For example, modifications of the innate immune system include a decrease in the bactericidal activity of neutrophils and the phagocytic capacity of macrophages and an increase in pro-inflammatory cytokines such as IL_{-6}, IL_{-1beta}, IL_{-10} and TNF_{-alpha}. Those high levels of pro-inflammatory factors have led to the concept of "human inflammaging", a chronic subclinical inflammatory state [25]. Modifications of the adaptive immune system include a decrease in naïve T cells, a lower CD4/CD8 ratio, an increase in dysfunctional memory and effector T cells, a decrease in both the number of naïve B-cells and the diversity of the B cell repertoire with a lower antibody affinity, and an increase in auto-reactive antibodies. T-cell dysfunction is an important component of ageing of the immune system. Thymic involution is associated with a shrinking of the T-cell receptor (TCR) repertoire; a lower reservoir of antigen specificities, a reduction of regulatory T-cell diversity (Treg), and clonal expansion of memory T cells are all observed with ageing and will lead to an imbalanced immune response [26]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) increase with age, leading to the "oxidative stress theory" of ageing. Oxidative stress has been associated with chronic conditions such as cardiovascular diseases, diabetes, COPD, chronic kidney disease, dementia, frailty and sarcopenia [27]; all of these are risk factors for infections. Within the last 20 years, many data have demonstrated that viral or bacterial infection will trigger ROS or RNS production [28]. However, the negative association among oxidative stress, infection and ageing must be clarified. Recent data have shown a more complex and beneficial role of ROS in the regulation of cellular metabolism and development and the improvement of the lifespan [29]. As mentioned before, the ageing immune system is also associated with a low-grade non-specific pro-inflammatory state that has been linked to the occurrence of chronic conditions such as COPD, heart failure and dementia, all of which increase the risk of infection [27, 30–32]. Dementia, in particular, has been associated with a higher risk of low respiratory tract infection and subsequent increased mortality [33]. Additionally, geriatric syndromes such as malnutrition, incontinence, pressure sores, falls, delirium, polypharmacy, cognitive problems and functional impairment are all important reported risk factors of infection among old persons [34–38]. Other factors linked to a higher rate of infections with ageing include a higher risk for invasive diagnostic procedure or treatments, a higher risk of promiscuity among NH residents or within geriatric acute care units, potential low compliance with hygiene control measures by the staff, a low rate of vaccination among older persons or healthcare workers and a higher rate of medical transfer between healthcare sectors [39–41].

A major issue is the potential link between frailty and infection. A complete review of this central geriatric concept is not within the scope of this article as it has already been reviewed in previous publications [42]. However, a consensus exists about the following major aspects of the concept: frailty is a multicomponent condition associated with a multifactorial vulnerability to stress that leads to an increased risk of negative health outcomes, such as functional decline and the occurrence of other geriatric syndromes, including infections and mortality. In the context of pneumonia, for

example, frailty has been independently associated with do-not-resuscitate orders and different healthcare transitions, even after adjustment for sepsis and pneumonia severity [43]. This loss of homeostasis is related to a progressive decline of reserve capacity in response to aggressive factors. It is a dynamic process with potential reversibility that occurs in a progressive or acute way, and it must be distinguished from chronological age, disabilities or polypathology. Frailty includes not only physical aspects but also psychosocial and contextual factors. Its pathophysiology is complex and includes nutritional aspects, sarcopenia and inflammatory factors. A direct link between infection and frailty has not yet been extensively studied. Frailty was associated with an impairment of the trivalent inactivated influenza vaccine-induced antibody response [44]. An indirect link between chronic cytomegalovirus (CMV) infection, human immunodeficiency virus (HIV), ageing and frailty has been established in the literature [45]. These conditions are commonly associated with a low level of chronic inflammation and immune activation that may induce age-related diseases and frailty. While CMV infection is rare in immune-competent older adults, CMV induces a strong T-cell response in CMV-seropositive older adults or among HIV-infected patients and may accelerate the appearance of frailty and chronic diseases. Using the Fried criteria of frailty (unintentional weight loss, weak grip strength, exhaustion, slow walking speed and a low level of activity), in the Women's Health and Aging Study conducted among community-dwelling females, chronic CMV infection was associated with frailty, and the observed effect was enhanced by inflammation [46]. However, this association remains controversial, and in a recent Belgian observational study in individuals aged 80 and older (the BELFRAIL study), no association between frailty and anti-CMV Ig_G titres was found after full multivariate adjustment for other comorbidities [47]. In the HIV population, accelerated ageing related to immune exhaustion and accelerated immunosenescence has been described, leading to age-related comorbidities and an increased prevalence of frailty that will occur earlier than in the general population [48, 49]. Here, there is also a reciprocal relationship between the ageing process and the occurrence of infection. Epidemiological data and correlations between chronic conditions and atherosclerosis, progression of obstructive lung disease and dementia support the hypothesis that the beneficial effects of inflammation that are necessary to fight infection may cause damage to other host tissues, accelerating the ageing process [15].

Another issue is the frequent contribution of silent risk factors for infection with age. Age is associated with a high number of physiological changes in different organs that may contribute to infection. A complete organ-by-organ description has already been published in different review articles [50–54]. For example, swallowing is associated with physiological changes such as a loss of postural tonus, dental problems, a higher saliva viscosity, a loss of lingual proprioception, muscle and mucosal atrophy, slower swallowing with an increased time for alimentary bolus propulsion, a delayed pharyngeal phase and a higher risk of vallecular stasis [55]. All these factors may contribute to an increased risk of aspiration pneumonia with age [56]. The prevalence of dysphagia has been reported to be as high as 50% among elderly patients admitted to an acute geriatric ward for pneumonia, and it has been associated with poor outcomes such as prolonged hospital stays, higher rates of NH admission and intra-hospital or 30-day mortality [57]. Particularly in post-acute care units, moderate to severe dysphagia after extubation, which is frequently found after more than 7 days of mechanical ventilation, has been associated with an increased risk of recurrent pneumonia, re-intubation or mortality [58]. In clinical practice, direct observation by the nursing staff to detect warning signs of aspiration is not always sufficient. While direct signs such as cough during eating, dysphagia, reflux of food in the nose or food blockage are clearly signs of aspiration, caregivers must be aware of other less typical signs. For example, voice changes, respiratory congestion after a meal, refusing of eating, taking time for eating, repeated fever or weight loss of unknown origin, maintaining food in the mouth and clearing one's throat are all potential indirect signs of swallowing disorders that have to be checked by the nursing staff. To improve the detection of aspiration, the "water swallowing test" has been proposed as a screening test of Ref. [59]. This screening test has been proposed for frail patients, even those in palliative care units, by the French Society of Palliative Care and the French Society of Geriatrics and Gerontology [60]. When performed by qualified personnel, the "water swallowing test" allows the administrator to adapt the volume and viscosity slowly in accordance with clinical judgement criteria such as cough, voice changes and aspiration. Some authors have combined the test with oxygen saturation measurement to improve diagnostic accuracy [61]. In addition, a good inter-professional partnership in the clinical decision-making process will improve a prompt diagnosis and treatment, as shown within NH [62].

Another factor leading to an increased risk of infection is the higher risk of colonization by MDRO with age, which is an important issue in all healthcare sectors [63]. In many countries, methicillin-resistant *Staphylococcus aureus* (MRSA) and multi-drug resistant gram-negative bacteria (MDR-GNB), mostly extended-spectrum beta-lactamase producing *Enterobacteriaceae* (ESBLE), are the two major MDROs that contribute to clinical problems. Vancomycin-resistant *Enterococcus* (VRE) *is* less frequently responsible for infections or outbreaks or in specific settings, such as onco-haematological units. The prevalence of MDRO colonization amongst hospitalised patients has been evaluated

in geriatric evaluation and management units, and rates of MRSA and ESBLE carriage at the time of admission as high as 8% and 12%, respectively, were found in a Belgian PPS in 2011 [64]. In that study, age was a risk factor for MDRO carriage in a univariate analysis. However, the only remaining independent risk factor for MDRO carriage, for both ESBLE and MRSA, was a low level of functional status after adjustment in multivariate analysis. The contribution of functional status was also reported in previous studies [65, 66]. The level of autonomy is potentially a good surrogate marker of frailty as it results from the interaction between age, chronic disease-related disabilities, individual factors and contextual factors. Functionally disabled patients may share other potential risk factors for MDRO carriage, such as previous antibiotic consumption, chronic wounds, chronic catheter use, and multiple contacts with the healthcare system or potential reservoirs, such as a hospitals and NHs. In a recent systematic review, the prevalence of MDR-GNB among NH residents varied according to study location, and the proportion of MDR-GNB colonization ranged between 14% in NHs not in the United States to rates as high as 38% in NHs in the United States [67]. Extended-spectrum beta-lactamase producing *Escherichia coli* (ESBL-EC) is the most frequently isolated strain, followed by *Proteus spec.* and *Klebsiella spec.* MDRO colonization has been associated with negative outcomes [68, 69]. In a prospective 36-month cohort study in 23 Belgian NHs, survival estimates according to MRSA carriage status were reduced by a factor of 1,5 after multivariate adjustment, especially in frail demented patients [70].

For all those contributing factors, a high number of publications have shown that, from an epidemiological point of view, the incidence and the contribution of infections and their negative health effects are the first important differences in older adults compared to young individuals. However, a progressive shift of the contribution of these factors may change over time. Recently, in Slovakia, a progressive shift in aetiology, complications and outcomes was shown when comparing two distinct periods (1984–1990 and 2007–2017). In that longitudinal study, better outcomes of infective endocarditis were linked to different treatment management, with a decreased risk of central nervous system embolization and an increased use of cardiac surgery leading to a subsequent lower attributable mortality [71].

Barriers to a prompt diagnosis

Atypical presentation of infections: the example of pneumonia

Pneumonia is the second most frequent type of infection in older adults but remains the first cause of infection-related mortality [72]. Like many other geriatric syndromes, an atypical presentation is a central hallmark of pneumonia among old persons. This will lead to a delayed accurate diagnosis and admission to hospital with a more severe clinical picture, contributing to a poorer prognosis.

Fever is less frequent, present in only 30–60% of older adults with pneumonia, while unexplained falls and functional decline are more frequently present [73]. Fever is more frequently associated with bacterial infection. A robust fever response over 38.5 °C has been prospectively associated with a lower mortality rate among surgical patients with bloodstream infections (13% versus 28% mortality, respectively) [74]. The blunted febrile response in older persons is often observed in frail individuals who live in NHs, where the diagnosis of fever is more challenging [75, 76]. Baseline body temperature declines with age, especially in this frail subpopulation, leading to the phrase "the older, the colder" [77]. The criteria for defining fever in the frail population were recently reviewed and include a single oral temperature over 37.8 °C, an increase of 1.1 °C over the baseline temperature or a repeated oral temperature over 37.2 °C [77]. Data regarding fever frequency are sometimes controversial. In a prospectively collected database on the presentation of infection in 4308 patients in a single tertiary medical centre, no difference in fever values as a presenting sign of infection was found between older patients and younger adults [78]. However, presenting signs such as septic shock, acute renal failure, a higher median leukocyte count and altered consciousness were more common in older adults [78]. As the included patients were selected at the time of hospital admission, selection bias may partially explain this finding. In a more recent study examining the clinical presentation of *Staphylococcus aureus* bacteraemia, in contrast with the previous study, fever was less prevalent at the time of admission (39% in those over 65 years versus 29% in those under 65 years), while here, a higher rate of septic shock and leukocytosis was reported [79]. A disproportionate severity at the time of presentation with an increased incidence of sepsis with age was also shown in a large observational longitudinal study in acute care hospitals in the United States [80]. Age was an independent risk factor for early death, and survivors were at a greater risk of NH admission. Aside from age and the factors mentioned in the section on epidemiology, the type of infection (pneumonia for example) and causal agent (gram-negative agents) along with their propensity for causing sepsis contribute to this more severe presentation at the time of hospital admission. In addition, changes in the physiological response in cases of sepsis, such as heart rate or blood pressure, suggest a reduced response in subjects above 65 years of age and are also associated with an increased risk of death [81].

Direct respiratory symptoms are less prevalent [82]. The three major signs "fever, dyspnoea and cough" are present

in less than 50% of older adults with pneumonia [73]. While many symptoms are less prevalent, an increase in the respiratory rate is a good and sensitive indicator of pneumonia (but with a low specificity); respiratory rate measurement equipment may allow early detection of pneumonia in hospitalised bedridden patients [83]. The higher risk for distant-organ dysfunction may contribute to the presence of non-respiratory symptoms such as edema, delirium and falls. Finally, a lower specificity of clinical auscultation reduces the ability of a good clinical differential diagnosis.

In addition, in the example of pneumonia, the atypical presentation, was in some cases a controversial issue, as was the case for pyogenic vertebral osteomyelitis where no differences in terms of low back pain, fever, or neurological signs were found in an older comparative group [84]. Another point is the risk of increasing the probability of a wrong diagnosis in some circumstances, as was shown for delirium in the case of a suspected urinary tract infection [85]. A recent literature review has shown that non-specific symptoms, such as delirium, are a common reason to suspect a urinary tract infection despite the presence of many other potential causes, particularly within NHs [85]. They concluded that evidence is insufficient to accurately define the association as "delirium-urinary tract infection" due to poor case definitions and inadequate control of confounding factors.

Diagnostic tools that are more challenging

Considering the example of pneumonia, microbiological data are more frequently lacking because of the difficulty accessing microbiological samples such as sputum or blood cultures from patients or healthcare workers with a negative attitude. However, it was recently reported that sputum samples have an added value to the community-acquired pneumonia diagnosis in the elderly, regardless of whether they are high- or low-quality samples [86]. In that context, no microbiological agents were found in 40–50% of the cases. However, some studies have reported that older persons have a higher diversity of causal agents with a higher proportion of gram-negative bacteria (GNB), such as *Escherichia coli*, *Klebsiella spec*., *Proteus spec*., *Enterobacter spec* [87]. This higher representation of GNB in the epidemiology of infection in the oldest old has also been found for community and nosocomial-associated bloodstream infection in the elderly population [17]. However, *Streptococcus pneumoniae* remains the leading bacterial agent responsible for pneumonia [88]. The production of beta-lactamases increases with age, leading to a more common use of broad-spectrum antibiotics. *Mycoplasma pneumoniae* is rarely found, while *Chlamydia pneumoniae* is more frequent [72]. In some countries such as China, high prevalence rates of tuberculosis among old frail underweight males have been reported in a rural context [89]. Finally, as mentioned before, a greater risk of aspiration pneumonia, including anaerobic or polymicrobiological agents, is frequently encountered in the oldest old, particularly among NH residents or frail hospitalised older adults.

Radiological abnormalities are also different in older adults compared to younger adults [90]. Interpretation of radiological abnormalities is more difficult, and many radiographic changes in the chest have been described in the elderly, such as calcification of the cartilage rings of the trachea and main bronchi, calcification of the costal cartilage, a poor degree of calcification of the ribs and vertebral bodies, and an unfolded aorta [91]. Access to a chest X-ray is important to improve diagnostic accuracy and subsequent prognosis evaluation and to improve differential diagnoses, such as heart failure, pleuresia, pulmonary embolism or tumour. No correlation with microbiological results was found. A delay in the appearance of the radiological infiltrate is frequently observed in the clinical context due, in part, to the dehydration frequently present at the time of admission. A lower disappearance of infiltrates is also more frequent, concomitant with a longer time to recovery [82]. More recently, high-resolution computed tomography has been used as a useful adjunct to conventional radiography to improve diagnostic accuracy, better define the infiltrate pattern and exclude other potential diagnoses [92].

The use of biomarkers may be helpful in improving diagnosis. In a meta-analysis published in 2017, adding C-Reactive Protein (CRP) measurement to the classical clinical diagnostic work-up for suspected pneumonia in the community improved the discrimination and risk stratification of patients [93]. However, it left a group of patients classified as intermediate risk; clinical decision-making remains challenging in this group. In a palliative care setting, CRP performance was sufficient for detecting infections at the time of admission. In that study, the change observed in serial CRP measurements was a valid prognostic indicator, as is the case in many other settings [94]. The use of other biomarkers, such as procalcitonin (PCT), remains a controversial issue for detecting infection in older adults. PCT has been used to define prognosis. In a single-centre study, PCT was effective in predicting ICU admissions but not effective in predicting death in elderly patients with sepsis [95]. While it's use as a prognostic tool, similar to CRP, was also associated with prognosis in other clinical conditions such as community-acquired pneumonia, its usefulness as a diagnostic tool remains a controversial issue [96]. A previous work in a Swiss geriatric teaching hospital has shown that PCT was associated with infection in elderly patients at the time of admission, but this association disappeared after full multivariate adjustment [97]. Despite a high reported specificity, sensitivity was low. A systematic review published in 2012 showed that in the hospital context or in the

emergency department, the sensitivity of this biomarker varies between 24 and 97%, while the specificity varies between 20 and 100% [98]. The authors highlight the difficulty in interpreting these data because of the different settings, cut-offs and outcomes used in the published studies. The added value to clinical judgement also remains an open question. In another systematic review, using sepsis as a model, PCT had an insufficient accuracy; it was good for use in rule-out scenarios but insufficient for use as a rule-in diagnostic tool, as is the case in young adults [99]. Using systemic inflammatory response syndrome as an outcome in the emergency department, PCT had a better accuracy among persons over 75 years compared to persons 65–74 years old [100]. Other remaining questions are how to improve the diagnostic accuracy, compared to CRP, and whether adding other biomarkers such as albumin may improve the diagnostic properties [96, 101]. A final issue is the link between frailty and PCT levels. In a retrospective study published in 2018, PCT levels were associated with the frailty condition in non-infected patients, while surprisingly, this association was not found in frail patients with pneumonia [102].

A higher risk of under- or over-diagnosis

As mentioned before, due to an atypical presentation, old persons are at higher risk of under-diagnosis of some infections such as aspiration pneumonia. However, over-diagnosis also remains an important clinical problem. Asymptomatic bacteriuria has been reported to be highly prevalent in females (19%) and males (6%) over 65 years in the community and can reach rates as high as 47% in females and 30% in males in LTCFs [103, 104]. In a Cochrane Database Systematic Review, It has been shown that the treatment of asymptomatic bacteriuria, compared to no treatment, will not prevent a new symptomatic urinary tract infection, new complications or mortality but will increase the risk of adverse events and antibiotic resistance [105]. Risk factors for antimicrobial overuse include fever in the absence of an alternative source, altered mental status, and leukocytosis [106]. In a retrospective audit in rehabilitation units for persons over 65 years old, asymptomatic bacteriuria or catheter-associated asymptomatic bacteriuria were present in more than 50% of the bacteriuria episodes [107]. However, unnecessary treatment accounted for 55% of all antibiotic treatment-days received, showing that there is room for improvement in efforts to better target patients. In the European Surveillance of Antimicrobial Consumption in NH Subproject, even though results varied substantially across countries, antibiotics were most frequently used for the prevention of urinary tract infection, showing that uroprophylaxis is a potential target for quality improvement [108]. The use of a decision algorithm to determine the scenarios in which urine cultures should be ordered and the conditions for starting antibiotic treatments have been associated with a reduction in urinary analyses and antimicrobial use [109]. In practice, multidisciplinary collaborative programmes have shown that weekly rounds with all staff members, including geriatricians, microbiologists, infection diseases specialists and clinical pharmacists, will reduce and improve antibiotic use within acute geriatric wards [14]. Furthermore, a close collaboration with the microbiological department will not only improve the quality of care and reduce costs but will indirectly improve patient survival by alerting clinicians earlier [110].

Prognosis of infection

Acute and chronic complications

Infection has been associated with a higher risk of acute and chronic complications. In clinical practice, it is frequently a reason for falls, poor nutrition or delirium. A threefold increase in the probability of death has been reported in some studies in the oldest old [111]. This trend may be related to several contributing factors, including a longer delay in the diagnosis and the start of adequate therapy, a decrease in host resistance related to reducing physiological reserve capacity and chronic underlying diseases, a poor tolerance of invasive diagnostic or therapeutic approaches with an increased risk of severe adverse drug reactions, a delayed or poor response to antibiotic therapy and a greater risk of HAIs implicating MDROs.

From a geriatric point of view, functional decline is a major partially reversible negative outcome that is frequently encountered during infection and an important target for multidisciplinary team intervention in acute geriatric wards or LTCFs. The reciprocal relationship between functional impairment and infection was nicely shown in a Swiss study in Lausanne where NH residents with severe functional impairment at baseline had a hazard ratio for infection during the 6-month period of follow-up of 1.46 (95% CI 1.22–1.75) compared to residents with no or mild functional impairment [112]. In contrast, the rate of functional decline among the residents presenting with two or more episodes of infection during the six-month period was also higher compared to that among residents without infections (31% and 20%, respectively).

Chronic complications are also more frequent, as is the case for herpes zoster (HZ) reactivation [113]. The lifetime risk HZ is 20–35%, with a progressive increase with age linked to a progressive decline in cellular-mediated immunity during ageing [114]. The HZ incidence increases with age by a factor of 2–3 such that the annual incidence for adults aged 20–40 years is 2–4 new cases/1000 person-years, while the incidence for old persons over 65 years may rise

to 6-10/1000 person-years [114]. Other risk factors include haematological malignancies, solid tissue tumours, organ transplantation, HIV, inflammatory diseases, surgery, traumatic and genetic factors such as female sex and white race [115]. HZ has been associated with negative outcomes, such as a higher rate of mortality, as was reported in a systematic review from 12 European studies [116]. Healthcare utilization, such as outpatient visits, emergency room admission or NH admissions, has been reported to be higher in the older group [117]. Hospitalization for HZ was reported with a threefold increase in incidence rate when comparing a group aged 70–79 years and a group aged over 80 years in Sweden [118]. In addition to pain and discomfort, HZ may lead to problems in performing usual activities and self-care, reductions in mobility and experiences of anxiety or depression, all reported 90–180 days after the rash onset [119]. Postherpetic neuralgia (PHN), which is induced by HZ neuronal damage, is a common complication of HZ [113]. PHN neuralgia lasts from several weeks to several years and significantly affects physical and psychosocial well-being [120]. Age is a risk factor for HZ progression to PHN, increased pain severity before and during HZ events, an increased extent of the rash and ophthalmic or trigeminal involvement [121]. As the risk of PHN (defined as pain lasting more than 30 days) in the general population is 6.5%, it may affect 11.7% of persons aged over 55 years and 14% of those aged over 80 years [122, 123]. Partial protection by a single regimen with the live attenuated HZ vaccine was demonstrated for an average of 5 years after vaccination in the 50 years to 79 age group; the vaccine efficacy against HZ was 51% and the vaccine efficacy against PHN was 67%. However, due to the progressive decline of efficacy with time and in some age groups, the age for starting reimbursement varies by country and ranges between 50 and 70 years. More recently, a two-dose regimen of an adjuvanted varicella-zoster virus subunit vaccine among older persons between 50 and 70 years old led to more than 90% vaccine efficacy without significant variation among age groups [124, 125].

Prognostic tools

Prognostic tools that have been used in clinical practice to improve the detection of patients at risk for pneumonia have included predictors related to age. The inclusion of new geriatric variables such as delirium has been shown to improve the diagnostic performance of the tools. The CURB-65, a five-item scoring system, includes respiratory rate, blood pressure level, blood urea nitrogen level, age over 65 years and a new onset of confusion [126]. It was shown that mortality increased from less than 3% for a score of less than 2/6 to nearly 30% for a score above 4/6. This demonstrates that age and some geriatric syndromes, such as delirium, independently affect the prognosis of infections. The performance of CURB-65 was recently questioned in the oldest old patients with pneumonia [127]. Its predictive ability was recently extended to acute respiratory infections [128]. In clinical practice, integrating a broader range of prognostic tools may help the clinician to guide triage and treatment decisions [128]. Other tools have been recently developed in specific settings. The Frail-Nursing Home Tool was developed to better define the prognosis of pneumonia among NH residents and included the following characteristics: fatigue, resistance, ambulation, incontinence or illness, loss of weight, nutritional approach, and needing help with dressing [129]. This tool has shown good properties for predicting outcomes and may be useful in helping clinicians develop an adequate care plan.

Prevention of infections: the importance of links between medical sectors

The burden of HAI and antibiotic resistance in LTCFs has been widely documented since 2006 in different European countries [130]. Since the alarming study conducted by Rooney et al. where the prevalence of ESBL-EC was as high as 40% in a large sample of LTCFs in Dublin, additional PPSs have been published to document epidemiological data within NHs [131–133]. This high rate in the surrounding area of Dublin was related to the spread of the so-called ST131 epidemic strains of *Escherichia coli* O25b. In Belgium, a PPS within 60 NHs in 2011 showed a weighted prevalence of 6.2% for ESBLE carriage and 12.2% for MRSA carriage among the 2610 screened NH residents [132]. More recently, with a similar design, a new PPS showed an increase of ESBLE carriage (weighted prevalence of 11.3%) with a slight decrease to 9% for MRSA carriage in the same country [133]. In the 2011 study, a comparison of the enzyme distribution and prevalence data from the adjacent hospitals and the included NHs showed a clear relationship between the epidemiological data in those two sectors, which has been called a "revolving door" in the literature [134]. In 2010, the European Centre for Disease Prevention and Control started a PPS of HAI and antimicrobial use in European LTCFs, derived from the HAI in LTCFs projects (HALT). These PPSs provide important information on antimicrobial use within LTCFs and help to identify targets for improvements to promote appropriate antibiotic use [135]. All of these data serve to alert clinicians to the need for improved hygiene control procedures and antibiotic use, especially in older persons. While the first study identified that there was room for improvement in a large number NHs within the participating countries, a recent positive trend of key antibiotic-related quality indicators has been obtained in some European countries [136, 137].

The ESBLE spread is a very good example of the need to collaborate between different sectors because of the complexity of interacting ecosystems. Reducing antibiotic pressure, reducing cross-transmission (not only among household contacts or foreign travellers but also among healthcare providers), identifying specific actions against some successful strains, and reducing individual and collective risk factors for MDRO carriage, are all important issues. Efforts must also include actions in the environment (soil, sewage, waste water), in the food chain and the animal world (pets and wildlife). Better communication among the community, hospitals and NHs will contribute to better control of the MDRO spread and help to reduce the risk of infections.

Key messages

We conclude that infections share common characteristics with other geriatric syndromes and fit within the criteria published in 2007 by Inouye et al. [JAMA 55:780–791, 2007]. These conclusions are highlighted in Fig. 1. As it is a frequent condition in elderly populations, infection may be a stressor that will induce a higher risk of negative geriatric outcomes such as functional decline, the occurrence of other geriatric syndromes, premature NH admission, re-hospitalization and mortality. The presentation of infection in elderly populations is atypical, leading to a risk of under-diagnosis. The physiopathology is complex, but a loss of homeostasis is a central phenomenon that will reveal frailty. Risk factors of infection are common with other geriatric syndromes, such as disabilities, dementia, low physical activity, sarcopenia, and poor nutrition. The relationship among inflammaging, immunosenescence, oxidative stress, functional status, and chronic conditions is complex and interrelated. Compared to a younger population, the epidemiology, potential risk factors, risk related to MDRO carriage, mode of presentation, performance of diagnostic tools and prognosis are all different in the elderly population. A more comprehensive approach is necessary to prevent frailty. We emphasise the need to improve communication between healthcare sectors and the community because of important links that are particularly relevant in older persons.

Compliance with ethical standards

Conflict of interest All authors declare that they have no significant competing financial, professional, or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

Statement of human and animals rights As it is a narrative review based on published data, no additional ethical approval is provided.

Informed consent Informed consent was obtained from all individual participants included in the studies reported in this review.

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