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Infection in an aging population

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The global population is rapidly aging. Currently, 566 million people are ≥65 years old worldwide, with estimates of nearly 1.5 billion by 2050, particularly in developing countries. Infections constitute a third of mortality in people ≥65 years old. Moreover, lengthening life spans correlate with increased time in hospitals or long-term care facilities and exposure to drug-resistant pathogens. Indeed, the risk of nosocomial infections increases with age, independent of duration spent in healthcare facilities. In this review, we summarize our understanding of how the aging immune system relates to bacterial infections. We highlight the most prevalent infections affecting aging populations including pneumonia, urinary tract infections, and wound infections and make recommendations for future research into infection in aging populations.

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The aging immune system and bacterial infections

There are substantial changes in both innate and adaptive immunity with age (reviewed in [1•,2,3]). These changes are thought to contribute to the increased frequency of some infections among older individuals. With increasing age, leukocyte output from the bone marrow becomes biased towards myeloid cells at the expense of naïve lymphocytes [4]. This reduction of naïve T-cell output in combination with reduced output from the thymus due to thymic involution, and clonal expansion of T cells specific for chronic viral infections (e.g. CMV), is believed to reduce the capacity to respond to novel infections or vaccinations; however, there is conflicting data as to whether *de novo* immune responses are universally impaired in the elderly [5]. Similarly, changes in the B cell compartment alter *de novo* antibody responses and contribute to reduced responses to vaccines and infections [6]. For example, an inability to mount antibodies against *C. difficile* toxins appears to be a major reason for the increased susceptibility to infection in the elderly [7].

The innate immune response is similarly impaired in older individuals. Impaired neutrophil migration, extracellular trap formation and bactericidal mechanisms are believed to be a major contributor to infections and the slower wound healing observed in the elderly [8]. Similarly, changes in macrophage phagocytosis, anti-bacterial effector function and cytokine production contribute to the increased risk of infection with extracellular pathogens such as *Streptococcus pneumoniae* [9,10]. Changes in expression in antimicrobial peptides and pattern recognition receptors in the epithelial mucosa may influence the composition of the microbiome and influence the ability of mucosal pathogens to occupy their mucosal niche [11,12]. Additionally, physiological changes such as decreased nutritional status, swallowing difficulty (which increases the chance of microaspiration) and decreased mucociliary clearance predispose the older adult to infections. Lastly, immunosenescence and co-morbid conditions that occur with age (e.g. type 2 diabetes, dementia) and lifestyle factors such as residence in nursing homes have all been demonstrated to increase the risk of infectious disease in the elderly [13–15].

The physiological and immunological changes that occur with age also compound the presentation and diagnosis of infectious disease in the elderly. For example, fever is often much more muted and white blood cell counts may not increase as much as in younger adults which may cause infections to be missed [16]. Additionally, antibiotic treatment can be less effective because of the altered pharmokinetics that occur due to decreased renal function in older adults [17]. Consequently, the elderly are at both increased risk of developing bacterial infections but also more likely to misdiagnosed and their infections mismanaged.

Acute infections

Pneumonia

Lower respiratory tract infections (LRTIs, pneumonia) are the most common cause of infectious disease hospitalizations in older adults in the U.S. and are the 6th leading cause of death in the US, in which ~90% of the deaths occur in individuals who are ≥65 years old [16]. *Streptococcus pneumoniae* is the most common cause of LRTIs in all age groups, followed by respiratory viruses,

Haemophilus influenzae, Gram-negative bacilli, and *Staphylococcus aureus* (especially in nursing home settings) [18]. The elderly, and especially those with chronic inflammatory diseases, have a higher risk of developing pneumonia [19,20•]. This appears to be due to the fact that having higher than age-average levels of inflammatory cytokines in the circulation increases the risk of developing pneumonia [21]. Although a robust inflammatory response is generally protects against infections, in the elderly, high levels of circulating inflammatory cytokines during pneumonia are associated with more severe disease and higher mortality [22], a phenomenon which has been replicated in mouse models [9]. A single dose of the pneumococcal 23-valent polysaccharide vaccine is currently recommended at age 65 and is associated with protection against invasive pneumococcal disease (a relatively rare complication in the elderly), however, its protective effect against community-acquired pneumonia is less clear [23].

Urinary tract infections

Urinary tract infections (UTIs) are among the most common bacterial infections, affecting an estimated 60% of all women within their lifetime and become more frequent with age [24]. Uropathogenic *Escherichia coli* (UPEC) are associated with up to 80% of uncomplicated UTIs, defined as UTIs occurring in the absence of structural or functional UT abnormalities, catheterization, or pregnancy. Other species less commonly associated with uncomplicated UTIs include *Klebsiella pneumoniae* (6%), *Staphylococcus saprophyticus* (6%), Enterococci (5%), and *Proteus mirabilis* (1%) [25•]. While many of the same organisms that are associated with uncomplicated UTI in older populations are also seen in younger adults, the prevalence of these organisms shifts. In a study of UTI in a nursing home, UPEC accounted for only <50% of infections, whereas Enterococci (11%), *K. pneumoniae* (10%), *P. mirabilis* (10%), Viridans Streptococci (5%), and *Pseudomonas aeruginosa* (3.2%) numbers were higher [26]. Moreover, the spectrum of UPEC phylogroups associated with UTI in younger populations is enriched for virulent strains, whereas more than 50% of UPEC strains from elderly UTI are associated with commensal phylogroups [27]. Polymicrobial UTIs are also more common in older populations [28•], and polymicrobial UTIs are associated with increased disease severity [29,30]. Physical, hormonal, and immunological changes that occur throughout the lifespan are thought to increase the risk of UTI with age, however the mechanisms underlying the effects of these changes on UTI are not well understood. A well-characterized murine model for UTI was recently adapted to study the impact of age on UTI susceptibility [31]. Surprisingly, in contrast to the prediction that aged mice would be more susceptible to UTI, older mice were significantly less susceptible to UTI than younger animals, underscoring the need for better murine UTI models that recapitulate the epidemiology of UTI in humans. Murine models of surgically-induced menopause in young mice hold promise as decreased estrogen correlates with higher bacterial burden during UTI in this context [32••,33].

Skin and soft tissue infections

Skin, chronic wound, and soft tissue infections are very common; chronic wounds affect 6.5 million people in the U.S. alone [34]. Infected pressure ulcers (bedsores) are a frequent precursor to chronic wounds and are particularly frequent among aged populations in hospitals and nursing homes where impaired mobility and/or comorbidities such as diabetes and peripheral vascular disease are common [35,36]. Wound infections are commonly biofilm-associated and polymicrobial in nature, where *S. aureus*, *E. faecalis*, β-hemolytic streptococci, Gram-negative rods such as *P. aeruginosa*, and other anaerobes are common [37]. How these organisms interact within chronic wound biofilms is not well understood, and animal models of wound infection have been limited to monomicrobial infection in young animals.

Latent/reactivated chronic infections

Reactivation of latent infections, thought to be a consequence of immunosenescence, is common among aging and elderly populations. Varicella zoster virus (VSV), the causative agent of 'chicken pox' in children and young people, infects dorsal root ganglia and can remain dormant in those cells for decades. The majority of VSV reactivation occurs in individuals >50 years old, leading to often painful and debilitating herpes zoster (HZ, 'shingles') [38]. Complications such as ocular disease, bacterial superinfection, and meningitis occur in 10% of HZ cases, and HZ-associated mortality rates increase with age [39–41]. A live attenuated VSV vaccine significantly reduces HZ incidence and severity in older adults [42]. However, identifying mechanisms to prevent and/or treat the remainder of the HZ cases should be a priority given the debilitating nature of this disease (Table 1).

Mycobacterium tuberculosis infection is also characterized by an extended latent period during which the organism is sequestered within a granuloma, yet the organism persists in the asymptomatic due to its capacity to evade immune-mediated killing [43]. When the immune system is weakened or suppressed, due to HIV infection for example, *M. tuberculosis* can reactivate to cause a symptomatic and contagious infection [44]. Reactivated latent tuberculosis has been thought to be more common among the elderly, however, recent reports suggest that reactivation frequency may actually decrease with age [45,46]. If true, a complete understanding of the nature of immune suppression during HIV versus aging may shed light onto host mechanisms that control *M. tuberculosis* reactivation.

Table 1

Future challenges for a better understanding of infectious disease in aging populations

- Improve animal and cell-based model systems to accurately recapitulate the epidiomology and host response to infection observed in older individuals.
- Determine the mechanisms underlying reactivation of latent infections.
- Discover novel immunomodulatory therapies that work within the confines of the aging immune system.
- Understand the mechanisms by which co-morbidities and chronic inflammatory disease, which increase in prevalence with age, alter immunity to infectious organisms.
- Characterize the changing microbiome dynamics within the lung, urinary tract, skin and gastrointestinal tract associated with age.
- Understanding how polymicrobial interactions, either between microbiome members and pathogens or between co-infecting pathogens, impacts the severity and outcome of infection in older individuals.

The aging microbiome and susceptibility to infection

Changes in the gut microbiota with age and increased susceptibility to *Clostridium difficile* infection

The microbiota of the infant gut is variable and unstable as colonization is established. The microbiota of the adult gut is fairly stable but is influenced by diet, lifestyle and infection. The gut microbiota of the healthy elderly is less well studied but appears to be stable within an individual, though highly variable between individuals, and contains a more diverse range of species than young adults [47]. In the elderly, changes the levels of specific genera or species (e.g. *Prevotella*) and the ratio of *Bacteroidetes:Firmicutes* have been reported [48••,49]. Additionally, metagenomic analyses indicated that there are fewer butyrate or short chain fatty acid-producing bacteria in the elderly, which may contribute to increased intestinal permeability, immunological and nutritional defects [47]. In residents of long-term care homes that are the most frail and unwell, the microbiota shifts dramatically and this appears to correlate with diet, frailty, physical function, co-morbidities and inflammation [48••]. Since the microbial dysbiosis that occurs after repeated or intensive antibiotic use is such a strong risk factor for *C. difficile* infection, it has been proposed that this age-related microbial dysbiosis may explain why the elderly are at much higher risk of acquiring *C. difficile* infections [7]. Mechanistic evidence of the role of microbial dysbiosis is required since factors such as medications (i.e. proton pump inhibitors), increased antibiotic use, longer and more frequent stays in hospital, and living in long-term care homes are also risk factors for *C. difficile* infection [50,51••,52].

The respiratory tract microbiome and susceptibility to colonization and infection with *S. pneumoniae*

Nasopharyngeal colonization (defined as asymptomatic and transient occupancy by *S. pneumoniae*) is a pre-requisite for pneumonia or invasive pneumococcal disease. In children, colonization by *S. pneumoniae* occurs frequently and is generally asymptomatic; however, when colonization is not appropriately controlled, dissemination from the nasopharynx may result in pneumonia, meningitis or septicaemia [53]. In adults, colonization is less frequent and of shorter duration due to adequate immune control, and consequently, disease is rare [54]. Few studies have addressed the dynamics of carriage in the elderly; however, it appears that as in adults, carriage rates are low [55]. The combination of low colonization rates and high incidence of pneumonia implies that colonization may be brief and proceed swiftly to infection. In support of this theory, peaks of invasive pneumococcal disease in the elderly occur during winter holidays when contact with grandchildren, the major reservoir for *S. pneumoniae*, is presumed to occur [56].

Inter-species and intra-species competition between *S. pneumoniae* and members of the microbiota of the upper respiratory tract (URT) contribute to the ability of *S. pneumoniae* to establish colonization [57,58]. Thus, age-related changes in the composition of the upper respiratory tract microbiota could influence the ability of *S. pneumoniae* to establish colonization or be permissive to infection. Although inter-species interactions, especially between *S. aureus* and *H. influenzae*, have been shown to influence pneumococcal carriage in children, this has been less well documented in adults [59]. Instead, it has been shown that adults who had more diverse nasal microbiota with a lower number of dominant species such as Corynebacterium were more likely to be natural *S. pneumoniae* carriers and more likely to become experimentally colonized by the pneumococcus [60]. Thus, the composition of the URT microbiome in youth and young adulthood contributes to the ability of *S. pneumoniae* to establish colonization and, ultimately, infection. Our study of nursing home elderly found that the microbiome of the nares had more diverse species and a lower percentage of protective Corynebacterium [55], which mimics the colonization permissive phenotype of the previous study [60]. The oropharyngeal microbiome can also harbour *S. pneumoniae* and has been shown to change with age [61,62]. One study has demonstrated the oropharyngeal microbiomes of older adults with *S. pneumoniae* pneumonia is different in its composition of anaerobes and certain keystone species; however, it is not clear if this contributes to or results from pneumonia [62]. Further studies need to be performed to determine whether the changing composition of the aging microbiome contributes to the risk of infections that originate from the airways.

Future directions

Acute bacterial infections in the elderly are more costly due to longer hospital stays and difficulties in managing infections in the context of co-morbidities; however, the economic and social consequences of these infections go beyond acute treatment. For example, acquiring a bacterial pneumonia in mid- or late-life often exacerbates or accelerates sub-clinical or existing chronic inflammatory conditions such as cardiovascular disease or dementia and can be the harbinger of declining health and decreased quality of life [19,20•]. Similarly, acute infections are associated with accelerating the progression of cognitive decline [63••]. Thus there is considerable urgency to develop novel preventative and therapeutic measures to ensure that older adults maintain their health and independence for as long as possible. In order to accomplish this, better animal models that account for the constraints of the aging immune response and the chronic inflammatory conditions and co-morbidities that accompany aging are required. The etiology of infections in the aged are often polymicrobial in nature but how this impairs host defense or complicates diagnosis and antimicrobial therapy is not well understood. As the global population ages at unprecedented rates, and as antibiotic-resistant bacteria are increasingly prevalent, a complete understanding of microbial pathogenesis in older individuals will be essential for improved diagnostics and therapeutics among this growing patient population.

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