Perspective: Aging and Infectious Diseases: Past, Present, and Future

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As we enter into the 21st century, infectious disease specialists will be managing a greater number and proportion of patients with infections who are ≥65 years old. Much has been learned about aging, host resistance, and infections over the past 15 years. However, if we are to meet the challenge of the complex issues of geriatric infectious diseases, infectious disease clinicians, teachers, and researchers must assume a more proactive role in clinical care, training, education, and research on problems and issues confronting the aging population.

In 1982, Dr. Paul Beeson, a pioneer in the field of infectious diseases and then editor of the Journal of the American Geriatrics Society; was kind enough to invite me to write my perspective on the new and emerging problem of geriatric infectious diseases (GID) [1]. Now 15 years later, I am pleased and privileged to provide a brief overview of the field of GID during the period 1982–1997, as well as give my perspectives on the future direction of aging and infectious diseases.

Past

As early as the late 19th and beginning of the 20th century, the interrelationship of aging, immunity, and infections was recognized by Elie Metchnikoff, the discoverer of cellular immunity. Metchnikoff developed the first theory of aging based on infection and immune dysregulation [2]. He reasoned that certain intestinal microbes were responsible for chronic toxin production, and these toxins activated macrophages to attack the body’s own tissue (i.e., a form of autoimmunity). Metchnikoff advocated replacing the indigenous intestinal microflora with lactobacilli, which would inhibit toxin-producing organisms and thus retard the aging process [2]. A temporary but fervent popularity of fermented milk products, particularly yogurt, in Europe was an outcome of Metchnikoff’s theory of aging.

However, there was a paucity of scientific data on the associations of aging, host resistance and defenses, and GID until late 1960s and early 1970s. With an awareness of a rapidly growing number of elderly persons and an increase in life expectancy of people from developed countries, research in gerontology (study of aging) and geriatrics (care of the elderly), including gerontoimmunology and GID, began to flourish. Such investigations indicated that aging was definitely associated with immune senescence (now more commonly termed immune dysregulation) [3–6] and, most likely, explained the clinical observations of higher prevalence, morbidity, and mortality of certain infections in the elderly (table 1) and the poorer responses to vaccination with old age [7–15]. However, despite this wealth of new information up to the early 1980s, much remained to be understood about the impact of aging on risk, etiology and severity of infections, the underlying pathogenetic mechanisms of immune dysregulation, differences in clinical manifestations of infection with age, and how aging affects antimicrobial therapy.

Present

Over the past 15 years, a substantial amount of information has been accumulated about gerontoimmunology, GID, and geropharmacology. It is clear now that aging has its greatest impact on cell-mediated immunity, with a lesser but substantial effect on humoral immune function [16–18]. Cytokine synthesis or activity (e.g., interleukin-1 [IL-1], IL-2, IL-6) or cytokine receptors may be adversely affected by age. The pathogenetic mechanisms of these abnormalities are being elucidated, with evidence indicating defects in mRNA expression as well as signal transduction [19–21]. More recently, preliminary data suggest that cytokine antagonists (IL-1 receptor antagonist and soluble tumor necrosis factor [TNF]) are elevated in plasma of healthy elderly compared with healthy younger adults. The increase in cytokine antagonists results in reduced production of IL-2, which decreases T cell proliferation [22]. When elderly patients with urinary tract infections were examined, their levels of cytokine antagonists were substantially higher than those in the healthy elderly, suggesting that inappropriate or subclinical infections in the latter group might account for immune suppression [22].

The data on the association of aging with macrophage and neutrophil function are less clear. Studies on the impact of old age on macrophage integrity have been limited [23]. Recently, in a mouse study, there was an increase in the number of bone marrow macrophages but a decrease in generation of TNF, either spontaneously or when activated by granulocyte-macrophage colony-stimulating factor, in old mice compared with
The etiology, clinical manifestations, therapy, and prognosis of pneumonia in elderly patients may be quite different in comparison with younger adults [39, 40]. With increasing age and frailty, there is an increase in the rate of pharyngeal colonization with gram-negative bacilli [41, 42]. Hence, it is not surprising that there is a high prevalence of gram-negative bacillary pneumonia in both community-dwelling elders and nursing home residents. Antimicrobial therapy should be adjusted accordingly. The mortality from pneumonia is considerably higher in older patients than in younger counterparts (see table 1).

With the exception of persons with human immunodeficiency virus (HIV) infection, the elderly are at greatest risk for contracting tuberculosis [43, 44]. Mortality from tuberculosis also increases with age. Drug-resistant tuberculosis is less of a problem in the elderly (except in those coming from areas with endemic drug-resistant mycobacteria), and thus most older patients with this infection can be treated with isoniazid and rifampin for 9 months, rather than the four-drug regimen advocated by the American Thoracic Society and Centers for Disease Control and Prevention [45].

UTI is the most common bacterial infection in older adults, and in contrast to younger adults, in whom UTI is a disease primarily of sexually active women, UTI occurs frequently in both elderly women and men [46, 47]. However, the vast majority of UTIs in the elderly are asymptomatic [48, 49]. Nevertheless, asymptomatic UTI is a true infection—as evidenced by a host inflammatory response (pyuria or presence of urinary cytokines) [50]. Despite this evidence, antimicrobial therapy is not recommended for the majority of elders with asymptomatic UTI [51]. Short-course (e.g., 3 days) treatment is not recommended for older patients with symptomatic UTI; a standard 7–14 days of therapy is suggested [47].

Infections in long-term care facilities (LTCFs) such as a nursing home (now called nursing facility) is an important domain of GID. Pneumonia, UTI, and skin and soft tissue infections (“pus”) constitute ~75% of infectious diseases in LTCFs [52, 53]. Tuberculosis in LTCFs is a serious medical and public health problem and accounts for nearly 20% of all cases of this infection in the elderly [54, 55]. Methicillin-resistant Staphylococcus aureus has been a major problem in LTCFs [56, 57], and more recently, clinicians are reporting that vancomycin-resistant enterococci have begun to emerge in LTCFs [58].

Much has been learned about the appropriate selection and dosing of antimicrobial agents from numerous pharmacologic studies and clinical trials [59]. For most serious infections in elderly patients, ß-lactam antibiotics should be considered as first-line therapy because of their efficacy, favorable pharmacokinetics (high serum levels, infrequent dosing), lack of need for measuring serum concentrations, and safety [60].

Immunizations with tetanus toxoid, influenza, and pneumococcal vaccines are recommended for elderly persons [61]. The incidence of tetanus, which is relatively low in the United States, has been declining in part because of widespread use of tetanus toxoid immunizations [52]. Although the incidence of influenza is lower in the elderly than in younger age groups, the elderly have a higher rate of mortality from influenza than do younger persons [64, 65]. Mortality from influenza is highest in the very elderly, those with chronic pulmonary or cardiac disease, and those with immunosuppression [66]. Influenza vaccine is recommended for persons 65 years and older. Influenza vaccine is also recommended for persons 6 months to 65 years of age at high risk for complications from influenza [66]. Influenza vaccine against the variants of the A and B viruses is recommended for all pregnant women and for household and child-care contacts of pregnant women [67].

Table 1. Important geriatric infectious diseases and their relative mortality rates.

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<thead>
<tr>
<th>Infections</th>
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NOTE. NA = comparative data not available.

* No. indicates multiplier factor (e.g., 3 times greater).
1 For renal infection.
2 Excluding human immunodeficiency virus–infected younger adults.

young mice [24]. However, whether aging adversely influences microbicidal activities of macrophages is unknown. Similarly, there is a lack of consensus—despite numerous studies—on whether the neutrophils of older adults function normally against microbial infection [25–30]. Investigations have shown specific or isolated defects along the pathway of neutrophil function (e.g., chemotaxis, phagocytosis, microbicidal events), but it is unproven whether these findings translate into clinically relevant abnormalities.

The clinical manifestations of diseases in the elderly may be altered (i.e., atypical, nonspecific, absent). These alterations may be due to aging or associated underlying diseases. Aged patients with infection may fail to exhibit a febrile response [31]. Animal investigations suggest that one potential explanation for depressed temperature responses with age is altered responses to pyrogenic cytokines (IL-1, IL-6, TNF) [32–34]. However, it is also clear that some frail elderly may elicit a robust temperature elevation when infected, but the temperature fails to reach the criterion for “fever” (e.g., 38°C); these elders have a lower-than-normal baseline core body temperature [35]. Consequently, it has been recommended that a rise in body temperature in elderly persons (e.g., 2°F or 1°C) in the appropriate clinical setting be one criterion for fever [36].

Cognitive impairment, primarily as delirium or acute confusional state, is a very common mode of presentation of elderly patients with infections [37]. Conversely, infections are often the most frequent causes of delirium in elders. The absence of symptoms in the presence of active infection is not unusual in older persons harboring an infectious disease, such as asymptomatic urinary tract infection (UTI) [38].

Because of growing interest in GID, there is a substantial number of clinical studies of a variety of infectious diseases in the geriatric population. Some of the salient findings from this large volume of literature will be briefly summarized.

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States, significantly increases with age, largely due to inadequate immunizations (including booster doses). Although the rates of influenza in the elderly are not especially high, the majority of influenza-related deaths (75%) occur in this population [61]. There is not a unanimity of opinion on the efficacy of the pneumococcal vaccine in elderly persons [62, 63]. Nevertheless, the prevailing opinion and recommendation are to administer the vaccine to all persons ≥65 years old.

**Future**

As we move into the next millennium, infectious disease specialists can expect to see a greater number of elderly patients in their clinical practice. With the aging of the “baby boomers,” it is projected that the current number of ~33 million Americans ≥65 years old will double by the year 2030 [64].

What are the important GID problems and issues that will confront us in the immediate future, as well as the next 25–30 years? What is the best strategy to address these issues?

Because of space limitation it is not feasible to provide a complete list of important issues in aging and infectious diseases. The following are a few areas of concern in GID that need further investigation and resolution:

- Determine the quantitative impacts of immune dysregulation on the susceptibility to and recovery from infectious diseases, that is, how much influence does aging really have on the risk and outcome to infections?
- Elucidate more precise definitions of subcellular and molecular mechanisms causing immune dysregulation in order to develop potential therapeutic interventions.
- Develop a simple, accurate, noninvasive, and inexpensive method to determine the microbial etiology of pneumonia in the elderly (currently <20% of elderly pneumonia cases have a specific etiologic diagnosis).
- Define the pathogenetic mechanisms of chronic asymptomatic bacteriuria in noncatheterized older adults (which would then lead to potential intervention strategies).
- Find innovative methods and techniques that prevent, reduce, or eliminate microbial (primarily bacterial and yeast) colonization of chronic bladder catheters on a long-term basis.
- Investigate newer approaches of intervention that reduce the mortality and morbidity of gram-negative bacillary sepsis in elderly patients.
- Establish more sensitive and specific as well as simple, rapid, and inexpensive methods to screen for tuberculosis. (The tuberculin skin test in the elderly is subject to high rates of false-negative reactions.)
- Clarify the role of or necessity for prophylactic antibiotics for elderly persons who have prosthetic devices, especially joint prosthesis, or undergo dental or other invasive procedures.
- Develop strategies that will improve the efficacy of both influenza and pneumococcal vaccines in the elderly (e.g., immune modulators).

How do we best address these and other GID problems? Although there has been a rapidly developing interest and increase in number of trainees entering the field of gerontology and geriatrics, there remains a critical shortage of academic geriatricians [65]. Furthermore, the majority of academic geriatricians lack the skills and training in immunology and infectious diseases to pursue these complex GID problems. I believe the time has come for infectious disease clinicians, educators, and researchers, as well as infectious disease professional organizations, to take a more proactive role in addressing and solving many of the issues in GID. Several potential pathways and approaches to achieve this objective include the following:

- Adult infectious disease fellowship training programs should have a curriculum emphasizing the biology of aging (especially immune changes with aging), geriatric pharmacology, and unique aspects of infections in the elderly (epidemiology, clinical manifestations, diagnostic approach, treatment, prognosis, and prevention).
- Continuing medical education courses and conferences on infectious diseases should regularly include topics addressing the special problems of GID.
- The Infectious Diseases Society of America should consider having a special category of “Aging” for abstract presentation at its annual scientific meeting (much like the national meeting of the American Federation for Medical Research).
- Journals oriented exclusively to infectious diseases should feature a section regularly devoted to infectious disease issues and problems of the elderly (some journals have already assumed this practice). Research papers focusing on aging and host resistance or host response to infections as well as GID should be actively solicited by infectious disease journals. Infectious disease textbooks should have a special chapter on aging and infectious diseases.
- Funding agencies for infectious disease and infectious disease–related research (e.g., National Institute for Allergy and Infectious Diseases) should allocate specific dollars for basic, clinical, epidemiologic, and health services research focused on basic mechanisms of diseases and host resistance with aging; diagnosis, treatment and prevention of infections in the elderly; innovative approaches to improving administration and outcome of antimicrobial therapy in frail, sick elderly; models of delivery of infectious disease care in older people; and methods to improve the efficacy of vaccines in elderly persons.

Infectious disease specialists have always successfully met infectious disease challenges that threatened the health and public health of our society (e.g., toxic shock syndrome, legionnaire’s disease). We are now in the midst of our yet biggest challenge, HIV infection. However, over the next quarter century, the problems of aging and infections will be equally if not more daunting than those of HIV infections. I hope that we, as infectious disease specialists, will face our newest challenge and seize the opportunity to become major contributors to the health and well-being of the largest segment of our population, the aging adult.
References