



Infectious disease risk in the elderly

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There is little disagreement that infections in the elderly are more frequent and have higher morbidity and much higher mortality when compared with infections in younger adults. There is less agreement about the reasons for this increased risk. Infections that are more frequent or severe in the elderly are listed in Box 1 and include pneumonia, soft tissue infections, urinary tract infection, tuberculosis, some intra-abdominal infections, and some viral infections.

Some of the factors that contribute to the increased severity of infections in the elderly include the anatomical and physiological changes that occur with aging, impaired immune response, presence of co-existing diseases, increased therapeutic toxicity of certain drugs, increased hospitalization for other causes that lead to nosocomial exposure to drug-resistant pathogens, increased use of catheters, delays in diagnosis and initiation of therapy, and a relative lack of clinical trials in the elderly. These are discussed more fully below.

In this author's opinion, the most important factor that contributes to the increased severity of infections in the elderly are the large number of anatomical and physiological changes that occur with age. For example, aging is associated with impaired cilia movement. Most bacterial pneumonias result from micro-aspiration of upper airway bacteria and oral substances. Active cilia movement helps to clear these potential pathogens. Cilia movement declines with age (smoking can further damage this function) which would lead to increased number of micro-organisms in the lower respiratory tract, thereby enhancing the risks of bacterial pneumonia.

Older persons have an increased risk of benign prostatic hypertrophy. This leads to obstruction of urinary outflow and increased risks of urinary tract infections. Similarly, older women have a loss of peri-urethral host defenses because of the loss of tissue elasticity from decreased estrogen production starting

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Box 1. Infections that are more frequent or severe in older persons

Pneumonia
Bacterial
Viral (influenza)
Urinary tract infections
Sepsis
Skin and soft tissue infections
Intra-abdominal infections
Cholecystitis
Diverticulitis
Varicella zoster virus (shingles)

in middle age. These local changes also lead to increased peri-urethral bacterial colonization and increased risk urinary tract infections. Postmenopausal women also usually have increased residual urine volume following voiding; this is another factor that can lead to a potential reservoir for bacterial growth [1].

The normal changes of the skin with aging include atrophy, decreased elasticity, decreased blood flow (especially in persons with coexisting peripheral vascular disease or diabetes mellitus). Consequently, even mild, local trauma leads to tissue breakdown and increased risk of skin and soft tissue infections. It is not surprising that skin infections account for one third of all infections in some nursing homes [2]. Impaired mobility and prolonged bedrest significantly increase the chances for pressure sores; at least 10% of residents in long-term care facilities have these [3].

Another mechanical barrier that loses its function with aging is the ability to swallow correctly [4]. This may be related to the general decline in neuromuscular function. Impaired swallowing from neurovascular disease or a feeding tube, especially in hospitalized or institutionalized older persons, is more likely to result in aspiration of oropharyngeal secretions. Another contributing factor is the more frequent occurrence of adverse effects of sedating agents, especially long-acting benzodiazepenes. These agents would also increase the risk of aspiration. The impairment of cilia function from either age or smoking, and loss of the cough reflex, would further predispose this patient to an increased risk of bacterial pneumonia.

A variety of studies that date back through the previous century clearly demonstrated that a higher percentage of older persons demonstrated a lower febrile response to infections than younger persons. Approximately one third of seniors with serious infections do not mount a body temperature more than 98.6°F. This is true for such diverse infections as septicemia, pneumonia, tuberculosis, intra-abdominal infections, and urinary tract infections. For example, Finkelstein et al [5] studied 187 adults with community-acquired pneumococemia and found that those older than 65 years of age had an average

admission temperature of 100.8°F; 29% were afebrile or hypothermic. In comparison, subjects aged 20 to 49 years old had an average admission temperature of 102.5°F; only 9% were afebrile. Moreover, 44% of the older persons died, as compared with 14% of the younger adults.

The lack of a fever can contribute to higher morbidity and mortality by various mechanisms. First, fever is the cardinal sign of infection; its absence may lead the unsuspecting clinician into a failure in diagnosis and initiation of appropriate antimicrobial therapy. Next, fever is clearly an important host defense mechanism. Several animal models demonstrated that higher body temperatures are associated with enhanced survival from infection. For example, the classic studies by Kluger et al [6] showed that when lizards were placed in a terrarium which had different temperatures, infected animals tried to move to warmer environments to raise their body temperature. Lizards that were kept in higher temperatures, which then had higher body temperatures, had an enhanced chance of survival compared with those who were kept at lower temperatures. Fever may enhance host defense by augmentation of certain host defense mechanisms, such as polymorphonuclear leukocyte phagocytosis, antibody production, or cell-mediated immunity [7,8]. Higher temperatures may directly inhibit pathogen growth [7]. Fever may have an indirect response, such as lowering the amount of plasma iron that is necessary for bacterial growth [9]. Finally, lower body temperatures may be an epiphenomenon (ie, it is simply a biomarker for those destined to die).

The pathogenesis of a lower febrile response to infection in older persons is not understood. From a simple point of view this could result from either failure of the host to produce fever or enhanced temperature loss, such as through the skin. Studies on the febrile response of older rodents to certain pyrogens, such as tumor necrosis factor, interleukin-1, interleukin-6, and endotoxin, produced conflicting results [10]. Other studies demonstrated a failure of thermogenesis by brown adipose in aged rodents [10]. Brown adipose tissue is an important source of heat production and is also referred to as nonshivering thermogenesis, in rodents. Some of these studies may well be relevant to human disease but specific biological conformation is lacking.

Finally the well-known adage, “the older, the colder” may be relevant here. Baseline temperatures decline significantly with increasing age. Castle et al [11], in a study that involved nursing home residents, found that 47% of infected residents exhibited a temperature of less than 101°F. Many of these patients exhibited a substantial rise in body temperature above baseline ($\geq 2.4^\circ\text{F}$) but, because of their low baseline temperatures, had relatively unimpressive responses to infection in terms of their peak temperatures.

Clinicians should also be aware that when an older person presents with infection this is a potentially serious clinical finding [12]. Unlike in younger patients in whom relatively benign viral infections can be found, a study of 1200 ambulatory subjects demonstrated that older patients who presented to an outpatient setting with fever were more likely to have serious, bacterial infections. The death rate was 5% to 7% in subjects over age 60 years as compared with 0.2% in subjects aged 17 to 39 years.

The immune response consists of nonspecific (natural immunity) and specific immunity (cellular and humoral immunity). Older persons have well-described, age-related declines in these functions. Natural immunity does not require presensitization of the host and is effective shortly (within minutes to hours) following infection. Specific immunity requires longer to develop and requires repeated exposure to the pathogen, but is more potent.

Older persons have a clear *in vitro* decrease in polymorphonuclear leukocyte function [13]. There is impaired neutrophil migration and *in vitro* ingestion and killing. These *in vitro* findings do not have a clear clinical significance. Although there is a statistically significant decrease in these functions in the range of 10% to 30%, most experts agree that neutrophil function needs to decline by more than 90% before the risk of infection is increased. For example, a normal circulating granulocyte count is approximately 5000 cells/mL. Most studies did not show an increased risk of serious bacterial infections until the number of cells dropped lower than 500 cells/mL. Natural killer cells are another form of innate immunity. They are so named because they have the ability to recognize certain nonantibody-coated tumor or virus-infected cells and thereby effect cytolysis. They are also minimally impacted with age [14].

Mucutaneous tissues serve as mechanical barriers and a first line of defense against many pathogens. Mucous has many antimicrobial effects and though not well-studied, one clear age-related effect is the increased prevalence of xerostomia, which can also result from drug effects (eg, anticholinergic agents). One half of the body's antibody-producing cells and two thirds of the total immunoglobulins are present in the mucosal system. IgA is the predominant immunoglobulin; its function seems to be intact in older persons [15].

Age-related defects are most apparent in T-cell mediated immune processes and are discussed more fully elsewhere in this issue. These include decreased proliferative response to mitogens, decreased production and response to important cytokines such as interleukin-2, impaired cell-mediated cytotoxicity, and lower delayed type hypersensitivity. Although it is convenient to ascribe these changes to the increased risk of infections in older persons, they have thus far only been proven to be important for the excess in certain viral diseases, such as influenza or varicella zoster infection and tuberculosis. There is also a clear, age-related increased risk of progression of human immunodeficiency virus [16]. Whether this, too, is due to impaired immune response remains to be determined.

Older persons have impaired and enhanced serum antibody responses. They demonstrate a moderate decrease in antibody response, especially to T-dependent antigens. This is likely to explain the lower antibody response to some vaccines in older persons. They also have an increased risk of paraproteins, that result in such hematological diseases as multiple myeloma and monoclonal gammopathy of unknown significance [17]. Further, older persons have a higher rate of autoantibodies, such as rheumatoid factor.

A patient who presents with multiple infections and whether this individual requires an immunological work-up is a common clinical scenario. In general, these types of work-ups are unrewarding, especially in older persons. First,

essentially all congenital causes of immunodeficiency present by young adulthood. Second, profound immune dysfunction is rarely the cause of increased infections in older persons. The one exception to this is human immunodeficiency virus infection. Current data show that approximately 11% of all newly reported cases of HIV in the United States occur in persons over 50 years of age [16]; HIV-antibody testing is warranted in an individual with opportunistic infections (eg, *Pneumocystis carinii* pneumonia) regardless of his or her age. Third, most of the commonly available, clinical, immunological tests (Box 2) are too insensitive to detect the subtle, age-related immunological changes.

The next factor that leads to increased severity of infections in older persons is the increased prevalence of coexisting diseases; infections can cause these diseases to decompensate. For example, the increased myocardial oxygen demand from infection may not be able to be met by the failing heart, leading to further decompensation of myocardial contractility and further cardiac decompensation. The concept of frailty, which is usually used for the very old, is related to the presence of comorbid diseases. Frailty is identified by extreme old age, multiple comorbid diseases, and disability [18]. For the nongeriatrician, it is perhaps easiest to characterize older persons as having a disability when there is dependency of one or more activities of daily living or instrumental activities of daily living. ADLs are bathing, dressing, toileting, transfers (from bed to chair), continence, and feeding. IADLs are using the telephone, shopping, cooking, housekeeping, laundry, transportation, taking medications, and money management.

The next area of concern is increased therapeutic toxicity from some commonly-used antimicrobial agents. This is especially common with aminoglycosides [19]. These drugs have higher renal and eighth cranial nerve toxicity. Once daily administration may circumvent this concern [20]. Another adverse outcome of the use of broad-spectrum antimicrobial agents is the occurrence of *Clostridium difficile*-associated diarrhea. This disease usually occurs after the institution of a broad spectrum antimicrobial agent; there is a clear age-related increase in its occurrence [21]. The age-related increase in the occurrence of *C difficile* may reflect changes in local immunity, aspects of cellular immunity, or changes in intestinal physiology.

Hospitalization is more frequent in older persons. Further, infections are very common in nursing homes; more than 1.5 million infections occur annually in

Box 2. Immune function tests

Human immunodeficiency virus antibody
Complete blood count with differential
Quantitative measurement of antibodies (IgG, IgM, IgA)
Delayed-type hypersensitivity skin testing
Pre- and postimmunization antibody titers (eg, tetanus)

long-term care facilities. It was estimated that 45% of seniors will require long-term care at some time during their life [22]. Infection is a leading cause of transfer to an acute care facility. Much of this increased incidence may be the result of the common occurrence of chronic diseases and other debility in these patients. These patients also have loss of mechanical barriers through conditions such as pressure ulcers and feeding tubes. Epidemics of infections occur, including respiratory illnesses by influenza and other diseases and enteric diseases caused by *Clostridium difficile*, *Shigella*, *Salmonella*, and other viral illnesses. Older persons who reside in nursing homes or are admitted to hospitals have a higher rate of oropharyngeal colonization with gram-negative bacteria [23]. These bacteria are not necessarily more pathogenic than other organisms; however, they are more difficult to treat. Other nosocomial pathogens, such as methicillin-resistant *Staphylococcus aureus* and vanomycin-resistant *Enterococcus*, are also major players.

Ethical and financial considerations are another unique aspect of infections in nursing homes. For example, a nursing home patient with a relatively short life expectancy may be better cared for in a familiar environment rather than being transferred to an acute care setting with further decline in cognitive function. These issues are best addressed by having a living will completed when the patients are admitted to nursing home, rather than in an emergency situation. Some nursing homes do not provide the same level of skilled nursing that is available in an acute care hospital. Therefore, relatively common treatments, such as supplemental oxygen, intravenous therapy, and respiratory therapy and availability of rapid laboratory examinations cannot be assured.

Infection control is another consideration in caring for nursing home residents. Employees need to be screened for communicable diseases such as tuberculosis. Annual flu shots for employees and residents should be encouraged, and strict hand washing should be a routine part of health care. A recent study on the efficacy of flu shots in chronic care facilities suggested that the most effective way to decrease mortality was to inoculate the employees rather than the residents [24].

Delays in diagnosis and initiation of therapy also lead to the increased severity of infections in older persons. This is likely the result of the relatively atypical presentation of infection in this patient population. As discussed earlier, several studies consistently demonstrated that significant number of elders have a blunted febrile response to infection. Patients with infections may therefore present with a normal body temperature. They may also present with relatively nonspecific findings, such as an unexplained change in functional status, tachypnea, nausea, vomiting, loss of appetite, falls, incontinence, or change in mental status. Finally, it may more difficult to obtain appropriate clinical specimens in some older persons. Older persons with pneumonia and other respiratory infections frequently have a lack of sputum production; also, mental status changes may lead to a difficulty in cooperating in the collection of these specimens. Additionally, as discussed earlier, many nursing homes lack the facilities for the timely turnover of routine laboratory tests.

The last important reason for the enhanced severity of infections in older persons is the lack of clinical trials. Just as pediatricians frequently state that children are not small adults, geriatricians can also state that seniors are not simply old adults. Many common, therapeutic trials routinely exclude persons over the age of 65 in the treatment of infectious diseases and other general medical problems. Clinicians need to be cognizant of this fact when trying to apply evidence-based medicine to different clinical conditions.

Principles of antimicrobial therapy

Unique challenges are involved in treating infections in older persons. Because of the lack of typical signs and symptoms with many infections, clinicians must consider the possibility of an infectious process whenever an older person presents with a change in functional capacity that cannot be explained readily by another cause. Other signs and symptoms that should suggest the possibility of an infection include tachypnea, loss of appetite, nausea, vomiting, falls, incontinence, and altered mental status. After an infectious disease seems to be a primary consideration, the clinician must quickly determine the most likely source, expeditiously pursue any diagnostic tests, and initiate therapy. Because empiric therapy is usually indicated, broad-spectrum antimicrobial therapy is usually chosen. For most cases, this would be a third generation cephalosporin, β -lactam/ β -lactamase inhibitor, or a fluoroquinolone. These drugs are recommended because of their relative broad-spectrum activity, lack of common adverse effects, few clinically-significant drug interactions, and availability of parenteral and oral preparations of the drugs.

Several principles should be followed for subsequent therapies. When microbiological data indicate a specific pathogen, a change to a more narrow-spectrum agent is appropriate. This will decrease the chances of an adverse outcome such as antibiotic-associated diarrhea. Noninfectious causes for changes in functional status, such as pulmonary embolus or decompensation of other organ function—heart failure, electrolyte imbalance, renal dysfunction, or uncontrolled diabetes mellitus, should be considered. It is not uncommon for an older person to respond more slowly to therapy. When the patient becomes clinically stable it is prudent change to change to an oral agent. Finally, despite one's best efforts, it is not uncommon for an older person to not return to his premorbid level of function. In this case, early consultation with a case manager is needed to identify appropriate placement.

References

- [1] Kunin C. Detection, prevention, and management of urinary tract infections. Philadelphia: Lea & Febiger; 1987.
- [2] Magaziner J, Tenney J, DeForge B, et al. Prevalence and characteristics of nursing home-acquired infections in the aged. *J Am Geriatr Soc* 1991;39:1071–8.

- [3] Brandeis G, Morris J, Nash D, et al. The epidemiology and natural history of pressure ulcers in elderly nursing home residents. *JAMA* 1990;264:2905–9.
- [4] Feldman RS, Kapur KK, Alman JE, et al. Aging and mastication: changes in performance and in the swallowing threshold with natural dentition. *J Am Geriatr Soc* 1980;28:97–103.
- [5] Finkelstein M, Petkun W, Freedman M, et al. Pneumococcal bacteremia in adults: age-dependent differences in presentation and in outcome. *J Am Geriatr Soc* 1983;31:19–27.
- [6] Kluger M, Ringer D, Anver M. Fever and survival. *Science* 1975;188:166–8.
- [7] Bennett I, Nicastrì A. Fever as a mechanism of resistance. *Bacteriol Rev* 1960;24:16–34.
- [8] Hanson D, Murphy P, Silicano R, et al. The effect of temperature on the activation of thymocytes by interleukins I and II. *J Immunol* 1983;130:216–21.
- [9] Kampschmidt R, Pulliam L. Effect of human monocyte pyrogen on plasma iron, plasma zinc, and blood neutrophils in rabbits and rats. *Proc Soc Exp Biol Med* 1978;158:32–5.
- [10] Bender B, Scarpace P. Fever in the elderly. In: Mackowiak P, editor. *Fever: basic mechanisms and management*. Philadelphia: Lippincott-Raven; 1997. p. 363–73.
- [11] Castle SC, Norman DC, Yeh M, et al. Fever response in elderly nursing home residents: are the older truly colder? *J Am Geriatr Soc* 1991;39:853–7.
- [12] Keating III HJ, Klimek JJ, Levine DS, et al. Effect of aging on the clinical significance of fever in ambulatory adult patients. *J Am Geriatr Soc* 1984;32:282–7.
- [13] Nagel JE, Han K, Coon PJ, et al. Age differences in phagocytosis by polymorphonuclear leukocytes measured by flow cytometry. *J Leukoc Biol* 1986;39:399–407.
- [14] Bender BS, Chrest FJ, Adler WH. Phenotypic expression of natural killer cell associated membrane antigens and cytolytic function of peripheral blood cells from different aged humans. *J Clin Lab Immunol* 1986;21:31–6.
- [15] Waldman RH, Bergmann KC, Stone J, et al. Age-dependent antibody response in mice and humans following oral influenza immunization. *J Clin Immunol* 1987;7:327–32.
- [16] Bender BS. HIV and aging as a model for immunosenescence. *J Gerontol A Biol Sci Med Sci* 1997;52:M261–3.
- [17] Kyle RA. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. *Eur J Haematol Suppl* 1989;51:70–5.
- [18] Fried L. Frailty. In: Hazzard W, Bierman E, Blass J, et al, editors. *Principles of geriatric medicine and gerontology*. New York: McGraw-Hill Inc.; 1994. p. 1149–56.
- [19] Moore RD, Smith CR, Lipsky JJ, et al. Risk factors for nephrotoxicity in patients treated with aminoglycosides. *Ann Intern Med* 1984;100:352–7.
- [20] Prins JM, Buller HR, Kuijper EJ, et al. Once versus thrice daily gentamicin in patients with serious infections. *Lancet* 1993;341:335–9.
- [21] Aronsson B, Mollby R, Nord CE. Antimicrobial agents and *Clostridium difficile* in acute enteric disease: epidemiological data from Sweden, 1980–1982. *J Infect Dis* 1985;151:476–81.
- [22] Kemper P, Murtaugh CM. Lifetime use of nursing home care. *N Engl J Med* 1991;324:595–600.
- [23] Nicolle LE, McLeod J, McIntyre M, et al. Significance of pharyngeal colonization with aerobic gram-negative bacilli in elderly institutionalized men. *Age Ageing* 1986;15:47–52.
- [24] Carman WF, Elder AG, Wallace LA, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. *Lancet* 2000;355:93–7.