

A New Paradigm for Clinical Investigation of Infectious Syndromes in Older Adults: Assessing Functional Status as a Risk Factor and Outcome Measure

Kevin High¹, Suzanne Bradley², Mark Loeb³, Robert Palmer⁴, Vincent Quagliarello⁵, Thomas Yoshikawa⁶

ABSTRACT Adults aged 65 and over comprise the fastest growing segment of the U.S. population, and older adults experience greater morbidity and mortality due to infection than young adults. While this factor is well established, most clinical investigation of infectious diseases in the aged focuses on microbiology, and crude endpoints of clinical success such as cure rates or mortality, but often fails to assess functional status, a critical variable in geriatric care. Functional status can be evaluated as a risk factor for infectious disease or an outcome of interest following specific interventions utilizing well-validated instruments. This paper outlines the currently available data suggesting a link between infection, immunity and impaired functional status in the elderly, summarizes commonly employed instruments used to determine specific aspects of functional status, and provides recommendations for a new paradigm in which clinical trials of older adults include functional assessment. *J Am Geriatr Soc* 53:528–535, 2005.

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INTRODUCTION

The world is aging. Both industrialized and developing nations are experiencing a rapid growth in people aged

¹Department of Internal Medicine, Sections of Infectious Diseases and Hematology/Oncology, Wake Forest University Health Sciences, Winston Salem, NC ²VA Medical Center, Department of Internal Medicine, Division of Infectious Diseases, University of Michigan School of Medicine, Ann Arbor, MI ³Division of Infectious Diseases and Medical Microbiology, McMaster University and Hamilton Civic Hospitals, Hamilton, Ontario, Canada ⁴Section of Geriatric Medicine, Cleveland Clinic Foundation, Cleveland, OH ⁵Department of Internal Medicine, Infectious Diseases Section, Yale University School of Medicine, New Haven, CT ⁶Department of Internal Medicine, Charles R. Drew University of Medicine and Science, King-Drew Medical Center, Los Angeles, CA.

Contact Information for Corresponding Author: Medical Center Boulevard, Winston Salem, NC 27157-1042; Phone: 336-716-4584; Fax: 336-716-3825; Email: khigh@wfubmc.edu

65 years and older¹. Infection is common in older adults however, despite the recognition of infection as a serious health problem in the elderly^{2–4}, investigations of infectious syndromes in the aged often fail to address fundamental issues relevant to old and frail persons. Physical disability, cognitive and emotional impairment, quality of life, and social consequences critical to the older adult need to be included to fully assess the role these factors play in infection risk and outcome. Treatment studies in elderly patients may report on the usual parameters of clinical features, microbial etiologies, laboratory changes, radiological findings, clinical response, microbiological response, and mortality. While these parameters are important, they fail to indicate *what has happened to the patient*. A fundamental principle of geriatric research is inclusion of an assessment of the impact of disease on functional capacity and maintenance of independence. Does the patient return to the same level of function as before the infection? Can the patient still perform the basic functions of life such as dressing, eating, taking a bath, toileting, and walking? Did their cognitive function change during or after the infection? Has depression become clinically apparent and impacted the recovery of function? What were infectious and non-infectious complications, and did they differ from those seen in younger adults with the same infection? Was the length of hospital stay and cost of care higher than younger patients with a similar disease process? Was discharge to a place other than home (e.g. nursing home) required? These are many of the issues and questions that must be addressed in future infectious disease studies in older persons if we are truly to provide clinically meaningful data and information to clinicians, patients, and family caregivers.

This review briefly summarizes: the demography of aging, unique features of infection in an aging population, the underlying mechanisms of infection and inflammation that may alter functional status, commonly used instruments to measure functional status, and the current status of infectious diseases research with regard to functional assessment. A new governing paradigm for clinical studies that includes functional measures is suggested to answer the most clinically relevant questions in older adults with infection.

DEMOGRAPHICS OF AN AGING WORLD

Through the early 20th century, the major causes of death in the United States were infectious diseases⁵, and life expectancy at birth was approximately 47 years⁶. The reduction of infectious deaths related to antiseptics, vaccinations, antibiotics, and public health measures has now increased life expectancies in many industrialized nations to over 75 years; an aging population is the result. While this change in demographic took a century in most of Europe, the U.S., Japan and Canada, the same transformation is now occurring in the developing world and will lead to a doubling of the population aged 65 and older in countries such as Brazil, China, and Thailand in about 25 years¹. As of 2000, an estimated 420 million persons were aged 65 years and older; this represents an increase of 9.5 million over the previous year. At least 31 countries have 2 million older citizens or more, and that number is to double by 2030 with the greatest increases in developing countries¹. Italy is the “oldest nation” with the greatest proportion of elderly (18%) in the population. The United States, with an elderly population of 13%, is not one of the top 25 oldest countries although by 2030, it is estimated that 20% of the US population will be aged 65 years or older^{1,7}. Most elderly persons will be women, representing 56% of adults \geq age 65, but women account for an increasing proportion of the oldest old (over age 85)⁷. The proportion of older adults who are members of a racial minority group is expected to increase from 11.3% to 16.5% over this time period⁷.

With increasing life expectancy, rates of chronic disease, disability, and health costs rise^{1,7}. It is estimated that 80% of adults aged 65 years and older have at least one chronic health condition and 50% will have at least two conditions⁷. In developed countries, costs for health care for older adults have been reported to be 3–5 times greater than for younger adults; \$12,100 (in 1997 dollars) for every adult aged 65 years and older⁷.

Multiple co-morbid conditions can contribute to a decline in function, an inability to live independently, and a need for long-term care. The percent of older adults receiving institutionalized care vary from society to society; rates for Northern Europe, North America, and Japan approach 6–9%. In the U.S., the life-time risk that a 65 year old will require some type of nursing home care is nearly 50%⁸. In 1997, most nursing home residents (75%) in the United States were women aged 85 years and older. In the last decade, costs to provide nursing home and home health care in the United States have doubled to a cost of \$132 billion⁷.

Fortunately, the future of older adults is not entirely a pessimistic one. Recent studies suggest that healthcare interventions can postpone or reverse disability in older adults and improve quality of life⁷. The challenge for the Infectious Diseases community is to provide interventions that not only treat the microorganism, but demonstrate a return of older adults to baseline or improved levels of function.

INFECTIONS IN THE ELDERLY: RISK FACTORS, CHARACTERISTICS, AND OUTCOMES

Compared to younger adults, elderly individuals have unique predispositions to infectious diseases as a result of multiple risk factors. First, impairments in innate and

adaptive immunity create risk for disease acquisition from specific infectious pathogens (e.g., *Listeria monocytogenes*, *Streptococcus pneumoniae*, *Mycobacteria tuberculosis* and varicella-zoster reactivation)⁹. Second, older adults have an increased prevalence of underlying co-morbid disease (e.g., diabetes, COPD, vascular disease) that foster risk for common community acquired disease including urinary tract infection, pneumonia, and soft tissue infection. Third, the increased prevalence of functional limitations with extremes of age (e.g., impaired swallowing and cough reflex), dwelling in crowded extended care facilities, and instrumentation with prosthetic devices (e.g., chronic bladder catheterization, implantable cardiac devices, artificial joints) leads to an increased risk for aspiration pneumonia, institutional-associated influenza and *Clostridium difficile* colitis, recurrent urinary tract infection, and prosthetic device infection¹⁰. The complexity of this population mandates that clinical research of infectious syndromes in older adults account for the multiple determinants of disease in the elderly^{11,12}.

Physicians must be cognizant of these unique predispositions to infection among elderly adults and seek early recognition, diagnosis, and therapy. A challenge for early diagnosis is the often subtle and unique presentation of infections in elderly adults. For example, basal body temperatures in older adults may be lower than the standard mean of 37°C (or 98.6°F)^{13,14}; in one study of elderly nursing home residents, a single temperature of 101°F had a sensitivity of only 40% among those with infection¹⁵. Furthermore, common infections like pneumonia and urinary tract infection are less likely to present with classically recognized features (e.g., cough and sputum production, or dysuria), and more commonly present with a change in cognitive function (e.g., confusion) or physical function (e.g., inability to perform activities of daily living)¹⁶. This altered presentation is fostered by underlying sensory deficits (e.g., hearing and vision impairment) and dementia in the elderly host. Impaired vasopressin responses with age lead to dehydration, hypernatremia, and azotemia when infection develops and also contribute to cognitive and functional decline¹⁷.

The subtle presentation of infection in older adults can have adverse consequences both for under-recognition of disease, and for over-use of empiric antibiotics. Because it is often difficult to distinguish true infection, over use of antibiotics is common, particularly in long-term care where 25–75% of antibiotic use has been found to be ‘inappropriate’, and strict adherence to minimum criteria for initiating antibiotics should be practiced¹⁸.

When infection does occur, systemic impairment in immune function, underlying co-morbidity, baseline functional deficits, and delayed recognition make elderly adults more prone to adverse outcomes. Compared to younger adults, case series and cohort studies have shown increased morbidity or mortality for older adults with a variety of infections including community acquired pneumonia¹⁹, bacteremia²⁰, infective endocarditis²¹, and HIV (even after adjustment for CD4 count at diagnosis)²². The precise contribution of underlying host predisposition (i.e., underlying co-morbidity or functional impairment) versus disease severity (i.e., related to immune deficits or delayed therapy) is difficult to discern from current data.

UNDERLYING MECHANISMS LINKING INFECTION, INFLAMMATION, AGING AND DISABILITY

Chronic inflammatory conditions are often associated with high levels of circulating cytokines, such as TNF- α , that induce muscle wasting and disability regardless of age, but this relationship may take on special meaning for older adults. Epidemiologic data suggest an association between chronic inflammation and a variety of adverse outcomes in older adults including death^{23–25} and disability^{26–32}. Frailty, defined as a wasting syndrome accompanied by increased vulnerability to functional disability, morbidity and mortality³³ is theorized to be exacerbated by ‘trigger events’ that enhance inflammation and play a central role in the development of functional limitations in the elderly (Figure 1).

Although waning immune responses in aged adults likely contribute to their risk of infection, not all facets of immunity are equally affected and some aspects of the immune response (e.g. innate inflammatory responses) are actually enhanced or prolonged with age^{34–37}. In contrast to young adults, aged humans demonstrate inflammatory responses that are significantly prolonged after experimental administration of endotoxin³⁶ or natural infection with common organisms such as *S. pneumoniae*³⁵. Even syndromes typically felt to represent inconsequential ‘colonization’ in older adults, such as asymptomatic bacteriuria, can be associated with activation of inflammation as evidenced by higher levels of circulating inflammatory cytokines³⁸. Co-morbidities common in the aged may also be coupled with low-level inflammation and play an important role in disability. For example, mild depression is associated with an enhanced and prolonged inflammatory response after the relatively trivial stimulus of influenza vaccination in older adults³⁹. Together, these data suggest there is an inability to appropriately down-regulate inflammation after infectious events in older adults, especially those with co-morbidity, and many investigators consider aging itself to be an inflammatory state⁴⁰.

How might sub-acute or prolonged inflammation in older adults lead to disability? Aging is associated both with a loss of muscle mass termed sarcopenia (reduction in specific force) and a waning of contractile force of the muscle fibers that remain (reduction in absolute force)⁴¹. Both are linked to infection and inflammation (Figure 2), and loss of

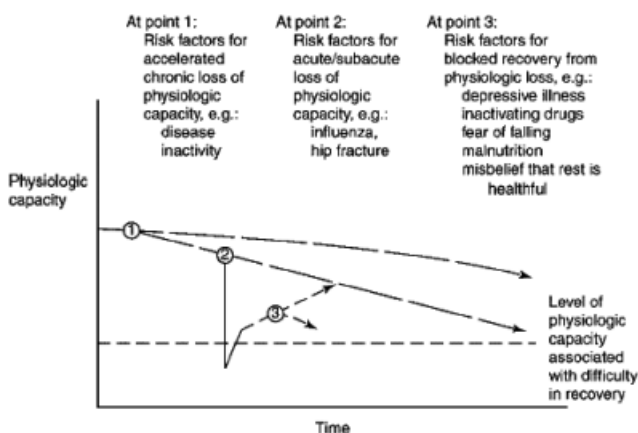


Figure 1. The role of trigger events in accelerating functional decline in older adults. Reprinted with permission from (32).

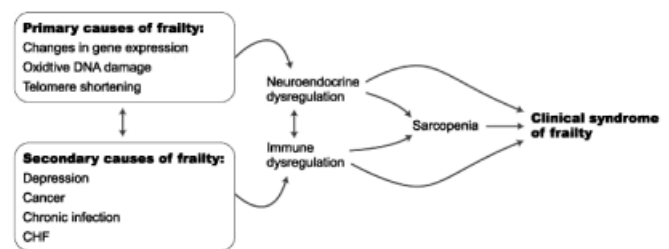


Figure 2. Hypothesized relationship between infection/inflammation and other risk factors that leads to sarcopenia and frailty. Reprinted from (81) with permission.

muscle strength is a robust, independent predictor of falls, disability, and mortality in older adults (reviewed in ref²⁶). Inflammation is a direct cause of sarcopenia^{42–47} via cytokine-induced muscle cell dropout without regeneration of muscle fibers during the phase of convalescence. ‘Notch’ pathways that modulate self-renewal in a variety of tissues^{48,49} may be markedly impaired with age and play a prominent role in this failure⁵⁰. Similarly, inflammation may contribute to age-related declines of absolute contractile force via pathways mediated by insulin-like growth factor-1 (IGF-1). IGF-1 strongly enhances both muscle regeneration⁵¹ and muscle contractility via excitation-contraction coupling⁴¹, but IGF-1 expression and activity are blunted by inflammation. Even transient elevations in TNF- α can inhibit IGF-1-mediated signaling over long periods of time^{52,53}.

Taken together, the data summarized above suggests:¹ there are strong epidemiologic links between infection, inflammation, reduced muscle mass and disability in older adults;² biologically plausible pathways support a causal link, and³ interventions to prevent infection (‘trigger events’) or speed recovery from infectious illnesses and thereby blunt the inflammatory response in older adults have the potential to positively impact functional status.

EVALUATING FUNCTIONAL STATUS IN PATIENTS AND CLINICAL TRIALS

Functional status is defined in terms of basic and instrumental activities of daily living (BADL, IADL). BADL include the ability to independently bathe, dress, groom, eat, transfer from bed to chair, toilet and maintain continence. The more complex IADL tasks include the patient’s ability to independently take medications, handle finances, perform household tasks, shop, use public transportation, and use a telephone. Loss of independence in the performance of BADL and IADL may occur during or after an infectious illness in older adults.⁵⁴

Prognostic importance

Functional status has prognostic importance that is not always captured by measures of disease severity, co-morbidity, or diagnosis. In studies of hospitalized elderly patients, dependence in the performance of BADL is an independent predictor of mortality, nursing home placement, length of stay, and costs of medical care^{55,56}. Nosocomial infection and severe functional impairment are stronger predictors of mortality than age alone in hospitalized patients,⁵⁷ and in nursing home patients, baseline performance of BADL is

the major determinant of survival following pneumonia⁵⁸. These observations underscore the importance of including measures of functional status when evaluating outcomes of infectious disease therapies.

Measures of Functional Status

While many instruments to define functional status are available, we will specifically focus on those validated for study in older adults. Reliable instruments or scales are administered as self-reports, questionnaires or performance-based measures⁵⁹. Global instruments capture functional status and items of health-related quality of life. The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) includes eight subscales: physical functioning (with 10 items), bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, vitality (energy/fatigue), and general health perceptions⁶⁰. A modified SF-36 eases scoring (www.rand.org/health/surveys/sf36item/). The index of ADL and the physical self-maintenance scale for BADL are widely used for clinical and research purposes when greater specificity of individual BADL and IADL items is desired (for example, when using ADL items as predictor or outcome variables)^{61,62}. The IADL scales are generally more sensitive than BADL to change over time^{62,63}. The BADL and IADL scales are often adapted for use as self or proxy-reports. In rehabilitation studies the Barthel Index,⁶⁴ and its derivative Functional Independence Measure,⁶⁵ are sensitive and commonly used instruments with good scaling (wide range of values) properties.

Performance-based measures of physical function

Performance-based measures of gait, balance and mobility obtain information that is complementary to self-reports and ADL scales. A Short Physical Performance Battery that includes an assessment of standing balance, a timed 8-foot walk and a timed test of five repetitions of rising from a chair and sitting down, was shown in a cohort study to predict disability in ADL and mobility⁶⁶. The Timed Up and Go test is a simple measure of the patient's gait speed: the patient is timed while rising from a chair, walking 10 feet, turning and returning to sit in the chair.⁶⁷ The more comprehensive Performance Oriented Balance and Mobility Assessment rates the patient's gait initiation, turns, step length and height, step symmetry and continuity, path deviation, and trunk sway.⁶⁸ The Physical Performance Test assesses performance of eight tasks that simulate ADL.⁶⁹

Measuring Cognitive Functioning

Cognitive impairment is common in elderly patients, adversely affects functional status, and is most often due to dementia or delirium. Infectious diseases are among the most common causes of delirium. Cognitive function is assessed through use of questionnaires including ADL items, and brief tests of mental status.⁵⁹ The Mini-Mental State Examination is a 30-item instrument that screens several cognitive domains and is most useful in non-hospitalized patients.⁷⁰ The Short Portable Mental Status Questionnaire, a 10-item instrument, is a practical instrument for use in hospitalized patients.⁷¹ The Confusion Assessment

Method is used to diagnose delirium in studies of hospitalized patients. It assesses patients for an acute change in mental status and fluctuating course, inattention, disorganized thinking and altered level of consciousness.⁷²

Measuring Depression

Depressive symptoms are predictive of functional decline and increased risk of mortality. The short-form Geriatric Depression Scale is a 15-item scale that can be completed as a self-report or through interview of patients with normal cognition.⁷³ The Center for Epidemiologic Studies Depression scale contains 20-items and is used in studies of depression in community-based samples. (www.chcr.brown.edu/pcoc/cesdscale.pdf)

Functional status in Long-term Care Residents

In institutional long-term care the federally mandated Minimum Data Set (MDS) provides patient data including demographic characteristics, dementia severity, co-morbidity, and measures of physical disability. ADL summary scales derived from the MDS can be used in health services research.⁷⁴

Co-morbidity measures

Many measures of co-morbidity exist and are used to adjust for the effects of chronic disease on outcomes of therapy. The Charlson co-morbidity index, which weights chronic diseases with a point score, is widely used in studies of ambulatory and hospitalized elderly patients⁷⁵, and can be adapted to use for infectious diseases research.

Overall recommendations for measuring functional status

Recommended functional assessment measures are summarized in Table 1. Specific tools are selected based on study goals. For example, general instruments provide breadth of information that is most useful in community based studies or large populations whereas more specific measures such as ADL items are useful in hospitalized or long-term care patients.

EXISTING LITERATURE ON FUNCTIONAL STATUS AND RESPIRATORY TRACT INFECTION IN OLDER ADULTS

Because the elderly frequently have multiple risk factors for disease acquisition or poor outcomes, a multivariable model is best suited to studying infectious episodes in older adults^{11,12}. However, adequately designed clinical research regarding the relationship between functional status and infection in older adults is limited. The majority of the literature, not surprisingly, focuses on respiratory infections, one of the greatest threats to the health of older adults⁷⁶, and a brief review of the data are presented here as an example of the current literature. In addition, nearly all studies have been performed in long-term care residents raising several issues regarding power to detect a difference and generalizability.

Studies can be broadly categorized into one of two groups, the assessment of functional status: 1) as a risk factor for infection, or 2) as an outcome after an infectious episode. Relatively few studies exist in the former category,

Table 1. Some Recommended Measures of Functional Status. (Measures for which the range of scores is marked with an * indicate higher score = better functional status. Unmarked ranges indicate higher score = worse functional status)

Domain	Measure	Example/Comment	Range of Scores
Health-related quality of life	Short-form 36 (SF-36)	Community based study of a chronic infection and treatment (for example, osteomyelitis, endocarditis)	0–100*
Basic activities of daily living (ADL)	Index of ADL; physical functioning subscale of SF-36	Predictors and outcomes of nosocomial pneumonia in nursing home patients	ADL: 0–6*; SF-36: 0–100*
Instrumental ADL (IADL)	Lawton IADL; OARS (Older American Resources and Services) IADL	Follow-up of patients after hospitalization for abdominal wound infection	0–7*
Mobility	Timed Up and Go Test Short Physical Performance Battery (SPPB)	Study of physical limitations after systemic infection; the SPPB for community based prospective studies to define quality of life after treatment of infections	TUG: 0–30 seconds; SPPB: 0–12*
Cognition	Mini-Mental State Examination (MMSE); Short Portable Mental Status Questionnaire (SPMSQ)	Cognitive function in patients with delirium secondary to infection	MMSE: 0–30*; SPMSQ: 0–10
Delirium	Confusion Assessment Method	Incidence of delirium associated with acute infections	0–4
Depression	15-item Geriatric Depression Scale	Study of neuropsychiatric effects of chronic infection	0–15
Long-term Care Residents	Minimum Data Set (MDS)	ADL summary scales can be derived from the MDS	0–10*
Co-morbidity	Charlson Co-morbidity Index	Assigns points for underlying co-morbidities and allows adjustment for their effects	0– \geq 5

but one prospective cohort study, among 475 residents of 5 nursing homes, demonstrated that immobility (defined in the study as dependency in bathing, dressing, transferring, going to the toilet, continence, and feeding) was an independent risk factor for lower respiratory tract infection⁷⁷.

Both prospective and retrospective studies have addressed functional status as an outcome after infection with mixed results. For example, a prospective study in a Veteran's Affairs facility examined the clinical course of patients with pneumonia. The majority of patients who survived did not show a significant reduction in functional status, as measured by an ADL score every 3 months for one year⁵⁸. This was likely due to a floor effect (limited ability to detect a decline due to limits of the scale itself despite true declines in function), since the median ADL score before infection was 17 (of a possible 18). This study did demonstrate an association between worse functional status and increased mortality. In contrast, in a retrospective cohort study designed to assess predictors of mortality in 378 nursing home residents with pneumonia, poor functional status (ADL score > 14) was not associated with risk of death⁷⁸.

A prospective cohort study of 781 episodes of lower respiratory infection in 1044 LTC residents revealed an incidence of functional status decline of 29%, defined as a 3-point increase on the Minimum Data Set (MDS) activities of

daily living (ADL) long form scale⁷⁴. In multivariable modeling, variables associated with functional decline included both decline in self-performance of toilet use in the 24 hours prior to evaluation and baseline ADL score. Addition of treatment variables to the model showed that initial hospitalization was also associated with ADL decline. Residents with decline in functional status at 30 days were less likely to recover to their baseline status at 90 days.

In a retrospective cohort study set in an academic long-term care facility, 16 of 65 (25%) residents hospitalized had worsening functional status at 2 months while 47 of 243 (19%) residents had worsening function (defined by increased dependency) after pneumonia⁷⁹. No comparison was done however with residents who did not have pneumonia. A prospective study that did compare nursing home residents with pneumonia vs. those without⁷⁷ demonstrated residents with pneumonia or other lower respiratory infections were no more likely to have a deterioration in functional status than in those in whom infection did not develop. The rate of functional decline was actually greater prior to the infection than after for residents with pneumonia. A possible explanation might again be a floor effect; declines in function may not be detectable in previously impaired hosts using the instruments employed.

In a retrospective study of 116 nursing home residents who developed influenza-like illness were compared to 127

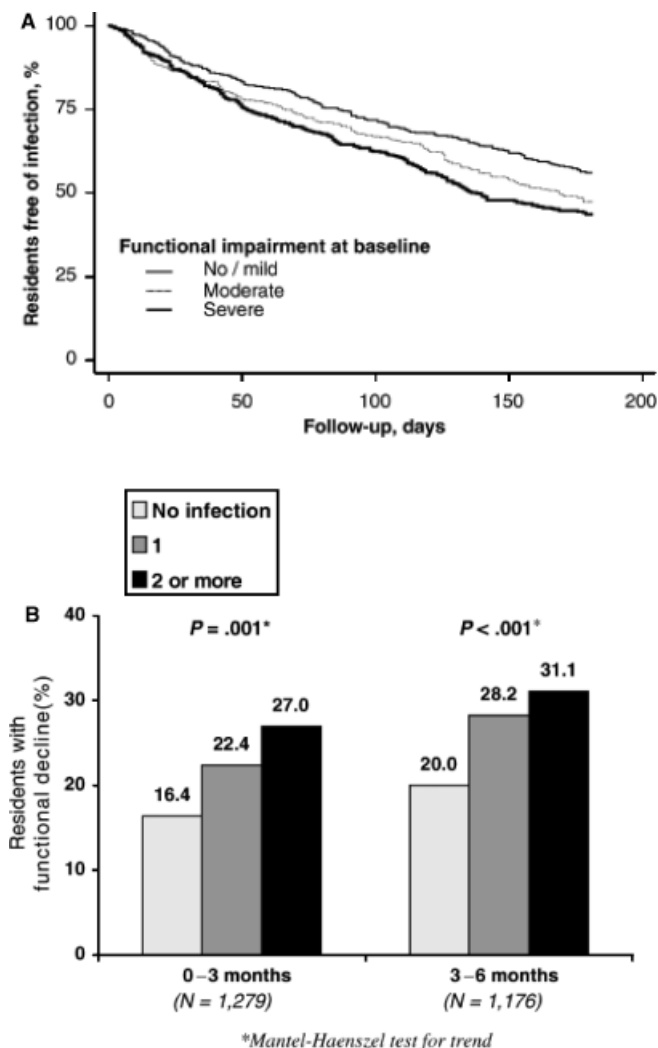


Figure 3. (A) Risk of infection over six months in Long-Term Care residents stratified by baseline functional status (Reprinted from (80) with permission). (B) Risk of functional decline following 0, 1 or ≥ 2 infections over six months in Long-Term Care residents (Reprinted from (80) with permission).

residents randomly selected residents without influenza illness⁸⁰. Significantly more cases (25%) than control subjects (16%) experienced a decline in functional status⁸⁰.

Finally, one large, prospective trial examined functional status both as a risk factor and outcome variable in older adults, and suggests there is a strong interaction between these two factors⁸¹. Functional status was assessed in LTC residents age 65 and older ($n = 1324$) at baseline, 3 months and 6 months. Baseline moderate impairment of functional status (defined as an ADL score of 2-4) or severe impairment (ADL score >4) were independent risk factors for infection (Figure 3A). Further, while functional decline occurred on average for all study subjects, the decline was more rapid in those that experienced an infectious episode, and the “change in slope” toward a more rapid loss of function was temporally associated with a “trigger episode” of infection. Further, there was a dose-response with an increased risk of functional decline as the number of infectious episodes increased from 0 \rightarrow 1 \rightarrow 2 or more (Figure 3B).

As indicated above, the major focus on functional status has been in the long-term care setting. To our knowledge, there are no large studies evaluating functional status longitudinally in older adults treated in the community for infection or admitted with infections from the community to acute care hospitals. Furthermore, there is a paucity of information about the effect of choice, timing or duration of anti-infective agents on functional status, and very limited data on physical therapy, nutritional supplements or other interventions to reduce disability during or after an episode of infection. Clearly, more research needs to be performed in this area, and studies must be designed to answer the questions of importance in caring for older adults.

CONCLUSIONS/RECOMMENDATIONS

1. The population of aged adults is growing rapidly, and infectious diseases in the elderly present specific challenges for clinical investigation. Age itself is not a surrogate marker for issues in geriatrics and should not be considered an adequate assessment of functional status, cognitive capacity, co-morbidity or frailty.
2. Numerous studies indicate that infections and other illnesses adversely impact the functional status of older adults. Mechanistic data support a relationship between infection/inflammation and age-associated functional decline.
3. Research of infectious syndromes in the elderly should include not only well-accepted clinical and microbiologic parameters, but measures of functional status, cognitive integrity, psychological burden, quality of life and discharge placement needs. This may be facilitated by multi-disciplinary teams of researchers with both Infectious Diseases and Geriatrics experience and expertise.
4. Functional parameters can be assessed by well validated instruments and should be evaluated both as risk factors and outcomes of interest. The quality of clinical research in older adults depends on inclusion of these parameters when investigating infectious syndromes, and should be encouraged by journal editors, scientific program reviewers, and regulatory agencies in order to provide meaningful information for clinicians who care for the growing population of older adults.

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