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

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Adults aged ≥65 years comprise the fastest-growing segment of the United States population, and older adults experience greater morbidity and mortality due to infection than do young adults. Although age is well established as a risk factor for infection, most clinical investigations of infectious diseases in older adults focus on microbiology and on crude end points of clinical success, such as cure rates or death; however, they often fail to assess functional status, which is a critical variable in geriatric care. Functional status can be evaluated either as a risk factor for infectious disease or as an outcome of interest after specific interventions using well-validated instruments. This article outlines the currently available data that suggest an association between infection, immunity, and impaired functional status in elderly individuals, summarizes the instruments commonly used to determine specific aspects of functional status, and provides recommendations for a new paradigm in which clinical trials that involve older adults include assessment of functional status.

Both industrialized and developing nations are experiencing a rapid growth in the number of people aged ≥65 years [1]. Despite the recognition of infection as a serious health problem among elderly adults [2–4], investigations of infectious syndromes in older individuals often fail to address fundamental issues that are relevant to old and frail persons. Treatment studies that involve elderly patients typically report information on clinical features, microbial etiologies, changes in laboratory values, radiological findings, clinical response, microbiological response, and mortality. Although 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 (i.e., does the patient still perform the basic functions of life, such as dressing, eating, bathing, toileting, and walking)? Did the cognitive function of the patient change during or after the infection? Has depression become clinically apparent, and has it affected the recovery of function? What were the infectious and noninfectious complications noted, and did they differ from the complications seen in younger adults with the same infection? Were the length of hospitalization and the cost of care higher for older patients than for younger patients with a similar disease process? Was discharge to a place other than home (e.g., to a nursing home) required? A new governing paradigm for clinical studies that includes functional measures is needed to answer the most clinically relevant questions regarding older adults with infection.

DEMOGRAPHICS OF AN AGING POPULATION WORLDWIDE

Through the early 20th century, infectious diseases were the major cause of death in the United States, and life expectancy...
at birth was ~47 years [5]. The reduction (as a result of antiseptic, vaccinations, antibiotics, and public health measures) in the number of infectious disease-associated deaths has increased life expectancy to >75 years in many industrialized nations; an aging population is the result. In most of Europe, the United States, Japan, and Canada, this change in demographics has taken a century to occur. The same transformation is occurring in the developing world and will lead to a doubling of the population aged ≥65 years in such countries as Brazil, China, and Thailand in ~25 years [1]. At least 31 countries have ≥2 million older citizens, and that number is to expected to double by 2030, with the greatest increases expected to occur in developing countries [1]. Italy is considered to be the “oldest nation,” because it has the greatest proportion of elderly individuals (18%) in its population. The United States (proportion of elderly individuals in its population, 13%) is not one of the top 25 oldest nations, although, by 2030, it is estimated that 20% of the US population will be aged ≥65 years [1, 6]. In the United States, women comprise 56% of adults aged ≥65 years, but they account for an increasing proportion of the oldest old adults (i.e., adults >85 years of age) [6]. The proportion of older adults in the United States who are members of a racial minority group is expected to increase from 11.3% to 16.5% by 2030 [6].

With increasing life expectancy, rates of chronic disease, disability, and health costs rise [1, 6]. It is estimated that 80% of adults aged ≥65 years have ≥1 chronic health condition and that 50% will have ≥2 chronic health conditions [6]. In developed countries, the health care costs for older adults have been reported to be 3–5 times greater than those for younger adults: $12,100 (in 1997 US dollars) for every adult aged ≥65 years [6].

Comorbid conditions can contribute to a decline in function, an inability to live independently, and a need for long-term care. The percentage of older adults who receive institutionalized care varies from society to society; rates for northern Europe, North America, and Japan approach 6%–9%. In the United States, the lifetime risk that a 65-year-old adult will require some type of nursing home care is nearly 50% [7]. In 1997, most nursing home residents (75%) in the United States were women aged ≥85 years. In the past decade, costs of providing nursing home care and home health care in the United States have doubled to a cost of $132 billion [6].

The future of older adults is not entirely pessimistic. Health care interventions can postpone or reverse disability in older adults and can improve quality of life [6]. The challenge for the infectious diseases community is to provide interventions that not only treat the microorganism but also demonstrate for older adults a return to baseline or improved levels of function.

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

Compared with younger adults, elderly adults have unique predispositions to infectious diseases as a result of multiple risk factors. First, impairments in innate and adaptive immunity create a risk for acquisition of disease due to specific infectious pathogens (e.g., Listeria monocytogenes, Streptococcus pneumoniae, Mycobacterium tuberculosis, and varicella-zoster virus reactivation) [8]. Second, older adults have an increased prevalence of comorbid disease (e.g., diabetes, chronic obstructive pulmonary disease, and vascular disease) that fosters a risk for common community-acquired disease, including urinary tract infection, pneumonia, and soft-tissue infection. Third, the increased prevalence of functional limitations associated with extremes of age (e.g., impaired swallowing and cough reflex), dwelling in crowded extended-care facilities, and instrumentation with prosthetic devices (e.g., long-term bladder catheterization, implantable cardiac devices, and artificial joints) leads to an increased risk for aspiration pneumonia, hospital-and/or long-term care facility–associated influenza, Clostridium difficile colitis, recurrent urinary tract infection, and infection of prosthetic devices [9]. The complexity of the elderly population mandates that clinical research of infectious syndromes in older adults account for the multiple determinants of disease in elderly individuals [10, 11].

Physicians must be cognizant of these unique predispositions to infection among elderly adults and must seek early recognition and diagnosis of disease and early initiation of therapy. A challenge of early diagnosis is the often subtle and unique presentation of infections among elderly adults. For example, the basal body temperature of older adults may be lower than the standardized mean temperature of 37°C (or 98.6°F) [12, 13]; in one study of elderly nursing home residents, the sensitivity of a single temperature of 38.3°C (or 101°F) was only 40% among elderly residents with infection [14]. Furthermore, common infections, such as pneumonia and urinary tract infection, are less likely to present with classically recognized features (e.g., cough and sputum production, or dysuria), and they more commonly present with a change in cognitive function (e.g., confusion) or physical function (e.g., inability to perform activities of daily living [ADL]) [15]. This altered presentation is fostered by underlying sensory deficits (e.g., impairment of hearing and vision) and dementia in the elderly host. The impaired vaso pressin responses that occur in association with age lead to dehydration, hypernatremia, and azotemia when infection develops, and they also contribute to cognitive and functional decline [16].

The subtle presentation of infection in older adults can have adverse consequences for both the underrecognition of disease
and the overuse of empirical antibiotics. Because it is often difficult to distinguish true infection, overuse of antibiotics is common, particularly among individuals who reside in long-term care facilities, for whom 25%–75% of antibiotic use has been found to be “inappropriate” and for whom strict adherence to the minimum criteria for initiation of antibiotics should be practiced [17].

When infection does occur, systemic impairment of immune function, underlying comorbidity, functional deficits at baseline, and delayed recognition of infection make elderly adults more prone to adverse outcomes. Compared with studies of younger adults, studies of older adults have shown increases in morbidity or mortality in association with a variety of infections, including community-acquired pneumonia [18], bacteremia [19], infective endocarditis [20], and HIV infection (even after adjustment for the CD4 cell count at diagnosis) [21]. The precise contribution of an underlying predisposition of the host (i.e., an underlying comorbidity or a functional impairment) versus disease severity (i.e., in relation to immune deficits or delayed therapy) is difficult to discern from current data.

UNDERLYING MECHANISMS RESULTING IN ASSOCIATIONS BETWEEN INFECTION, INFLAMMATION, AGING, AND DISABILITY

Chronic inflammatory conditions are associated with high levels of circulating cytokines, such as TNF-α, that induce muscle wasting and disability, but this association takes on special meaning for older adults. Epidemiologic data suggest that chronic inflammation is associated with a variety of adverse outcomes for older adults, including death [22–24] and disability [25–32]. “Frailty,” which is defined as a wasting syndrome accompanied by increased vulnerability to functional disability, morbidity, and mortality [33], is theorized to be exacerbated by “trigger events” that enhance inflammation and that play a central role in the development of functional limitations in the elderly population (figure 1).

Although most immune responses wane in elderly adults, not all facets of immunity are equally affected [34–37]. In contrast to young adults, elderly adults demonstrate inflammatory responses that are significantly prolonged after either experimental administration of endotoxin [36] or natural infection with S. pneumoniae [35]. Even syndromes that are typically believed 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 cytokines [38]. Comorbidities that are common among elderly individuals may also be coupled with low-level inflammation. For example, mild depression is associated with an enhanced and prolonged inflammatory response after the relatively trivial stimulus of influenza vaccination in older adults [39]. Together, these data suggest that there is an inability to appropriately down-regulate inflammation after the occurrence of infectious events in older adults, and many investigators consider aging itself to be an inflammatory state [40].

Aging is associated with both a loss of muscle mass that is termed “sarcopenia” (i.e., a reduction in specific force) and a waning of the contractile force of the muscle fibers that remain
Figure 2. Hypothesized association between infection and/or inflammation and other risk factors that lead to sarcopenia and frailty. CHF, congestive heart failure. Reprinted with permission from [42].
the Barthel Index [64] and its derivative Functional Independence Measure [65] are sensitive and commonly used instruments with good scaling properties (i.e., properties with a wide range of values).

**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 balance on standing, a timed 8-ft walk, and a timed test of 5 repetitions of rising from a chair and then sitting was shown to predict both disability in performing ADL and limitations in mobility, in a cohort study [66]. 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 ft, 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 8 tasks that simulate ADL [69].

**Measuring cognitive functioning.** Cognitive impairment in elderly patients adversely affects functional status, and it is most often due to dementia or delirium. Infectious diseases are among the most common causes of delirium. Cognitive function is assessed through the use of questionnaires that include questions about ADL items, as well as through the use of 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 for nonhospitalized patients [70]. The Short Portable Mental Status Questionnaire, a 10-item instrument, is a practical instrument to use for hospitalized patients [71]. The Confusion Assessment Method, which is used to diagnose delirium in studies of hospitalized patients, measures acute changes in mental status and fluctuations in inattention, disorganized thinking, and level of consciousness [72].

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

**Functional status of residents of long-term care facilities.** For institutional long-term care, the federally mandated Minimum Data Set (MDS) provides patient data, including demographic characteristics, dementia severity, comorbidity, and measures of physical disability. ADL summary scales derived from the MDS can be used in health services research [74].

**Comorbidity measures.** Many measures of comorbidity exist and are used to adjust for the effects of chronic disease on outcomes of therapy. The Charlson comorbidity index, which weights chronic diseases by assigning a point score, is widely used in studies of ambulatory and hospitalized elderly patients [75], and it can be adapted for use for infectious diseases research.

**Overall recommendations for measuring functional status.** Recommended functional assessment measures are summarized in table 1. Specific tools are selected on the basis of study goals. For example, general instruments provide a breadth of information that is most useful in community-based studies or in studies of large populations, whereas more-specific measures, such as ADL items, are useful for hospitalized patients or for patients receiving long-term care.

**EXISTING LITERATURE ON THE FUNCTIONAL STATUS OF AND RESPIRATORY TRACT INFECTIONS AMONG OLDER ADULTS**

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 tract infections, which are one of the greatest threats to the health of older adults [76]. A brief review of the data is presented here as an example of the current literature. That nearly all studies are small and have involved residents of long-term care facilities raises issues regarding the power to detect differences and the generalizability of the results.

Studies can be broadly categorized into 1 of 2 groups: assessment of functional status as (1) a risk factor for infection or (2) an outcome after an infectious episode. Relatively few studies exist in the former category, but one prospective cohort study, which involved 475 residents of 5 nursing homes, demonstrated that immobility (which was defined in the study as dependency in bathing, dressing, transferring, toileting, continence, and feeding) was an independent risk factor for lower respiratory tract infection [77].

Studies have addressed functional status as an outcome after infection, with mixed results. For example, a prospective study conducted in a Veterans Affairs facility examined the clinical course of pneumonia in patients. The majority of patients who survived did not show a significant reduction in functional status, as measured by an ADL score determined every 3 months for 1 year from the time of admission [58]. This was likely the result of a “floor effect” (i.e., a limited ability to detect a reduction in functional status because of the limits of the scale itself, despite true reductions in function). The median ADL score before infection was 17 (of a possible score of 18). Poor functional status was associated with increased mortality. In contrast, in a retrospective cohort study designed to assess predictors of death for 378 nursing home residents with pneumonia, poor functional status (ADL score, >14) was not associated with the risk of death [78].
did not have infection develop. For residents with pneumonia, a deterioration in functional status than were the residents who lower respiratory tract infections were no more likely to have demonstrated that the residents who had pneumonia or other nursing home residents who did not have pneumonia [77]. Compare nursing home residents who had pneumonia with having pneumonia was performed. A prospective study that did hospitalization, whereas 47 (19%) of 243 residents had worsened functional status at 30 days from the time of infection. Furthermore, there was a dose response with the decline was more rapid among study subjects who developed infection. Furthermore, there was a strong interaction between these 2 factors [81]. For residents of a long-term care facility who were aged 65 years (n = 1324), functional status was assessed at baseline and at 3 months and 6 months after initiation of the study. Moderate impairment (ADL score, 2–4) and severe impairment (ADL score, >4) of functional status at baseline were independent risk factors for infection (figure 3A). In addition, although a decline in functional status occurred, on average, for all study subjects, the decline was more rapid among study subjects who developed infection. Furthermore, there was a dose response with an increased risk of functional decline as the number of infectious episodes increased from 0 to 1 to ≥2 (figure 3B).

As indicated above, the major focus on functional status has involved elderly individuals in long-term care settings. There are no large studies that evaluate functional status longitudi-

### Table 1. Some recommended measures of functional status.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measure</th>
<th>Example or comment</th>
<th>Range of scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health-related quality of life</td>
<td>SF-36</td>
<td>Community-based study of a chronic infection and its treatment (e.g., osteomyelitis or endocarditis)</td>
<td>0–100&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Basic ADL</td>
<td>Index of ADL, physical functioning subscale of SF-36</td>
<td>Predictors and outcomes of nosocomial pneumonia among nursing home patients</td>
<td>ADL: 0–6&lt;sup&gt;b&lt;/sup&gt;; SF-36: 0–100&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IADL</td>
<td>Lawton IADL, OARS IADL</td>
<td>Follow-up of patients after hospitalization for abdominal wound infection</td>
<td>0–7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mobility</td>
<td>TUG, SPPB</td>
<td>Study of physical limitations after systemic infection; the SPPB for community-based prospective studies to define quality of life after treatment of infections</td>
<td>TUG: 0–30 s&lt;sup&gt;b&lt;/sup&gt;; SPPB: 0–12&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cognition</td>
<td>MMSE, SPMSQ</td>
<td>Cognitive function of patients with delirium secondary to infection</td>
<td>MMSE: 0–30&lt;sup&gt;a&lt;/sup&gt;; SPMSQ: 0–10&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Delirium</td>
<td>Confusion Assessment Method</td>
<td>Incidence of delirium associated with acute infections</td>
<td>0–4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Depression</td>
<td>15-Item Geriatric Depression Scale</td>
<td>Study of neuropsychiatric effects of chronic infection</td>
<td>0–15&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Residents of LTC facilities</td>
<td>MDS</td>
<td>ADL summary scales can be derived from the MDS</td>
<td>0–10&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Charlson comorbidity index</td>
<td>Assigns points for underlying comorbidities and allows adjustment for their effects</td>
<td>0 to &gt;5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
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</table>

**NOTE.** ADL, activities of daily living; IADL, instrumental ADL; LTC, long-term care; MDS, Minimum Data Set; MMSE, Mini-Mental State Examination; SF-36, 36-Item Short-Form Health Survey; OARS, Older American Resources and Services; SPMSQ, Short Portable Mental Status Questionnaire; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go.

<sup>a</sup> Ranges for which a higher score denotes better functional status.

<sup>b</sup> Ranges for which a higher score denotes poorer functional status.

A prospective study of 781 episodes of lower respiratory tract infection among 1044 residents of long-term care facilities revealed that the incidence of decline in functional status was 29%, with decline in functional status defined as a 3-point decrease on the MDS ADL long-form scale [74]. The variables associated with a decline in functional status included a decline in both self-performance of toileting in the 24 h before evaluation and the ADL score at baseline. The addition of treatment variables to the model showed that initial hospitalization was also associated with a decline in the ADL score. Residents who had a decline in functional status at 30 days from the time of lower respiratory tract infection were less likely to recover to their baseline status at 90 days.

In a retrospective study conducted in a long-term care facility, 116 nursing home residents who had pneumonia were compared with 127 randomly selected residents who did not have pneumonia [80]. Significantly more case patients (25%) than control subjects (16%) experienced a decline in functional status [80].

Finally, in one large, prospective trial of older adults, functional status was investigated as both a risk factor and an outcome variable; the findings of the trial suggested that there is a strong interaction between these 2 factors [81]. For residents of a long-term care facility who were aged ≥65 years (n = 1324), functional status was assessed at baseline and at 3 months and 6 months after initiation of the study. Moderate impairment (ADL score, 2–4) and severe impairment (ADL score, >4) of functional status at baseline were independent risk factors for infection (figure 3A). In addition, although a decline in functional status occurred, on average, for all study subjects, the decline was more rapid among study subjects who developed infection. Furthermore, there was a dose response with an increased risk of functional decline as the number of infectious episodes increased from 0 to 1 to ≥2 (figure 3B).

As indicated above, the major focus on functional status has involved elderly individuals in long-term care settings. There are no large studies that evaluate functional status longitudi-
should include parameters that describe functional status before, during, and after the intervention.

2. In the performance of these studies, the involvement of a multidisciplinary research team with expertise and experience in infectious diseases and geriatrics is ideal and should be encouraged.

3. Journal editors, scientific program reviewers, and funding agencies should request that information on functional parameters be included in studies of infectious syndromes in older adults.

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