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Comorbidity: The Ultimate Geriatric Syndrome

Special Article

Comorbidity in Older Adults: Nosology of Impairment, Diseases, and Conditions

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Older adults generally have multiple medical problems as well as subclinical changes in several physiologic systems. This special article presents a framework (based on the World Health Organization International Classification of Functioning, Disability, and Health) for organizing comorbid processes and diseases to facilitate research and assist clinicians caring for older adults. The nosology begins with physiologic systems (e.g., cardiovascular, endocrine) and assesses each system in several domains (e.g., coronary blood flow, systemic blood pressure, and cardiac function in the cardiovascular system). Functioning in each domain can range from high-functioning, even protective, zones (e.g., high levels of high-density-lipoprotein cholesterol) to severe dysfunction (as in end-stage disease). The approach has four advantages. First, it explicitly recognizes that decrements in health begin before onset of symptomatic disease. Second, it accommodates the full range of possible performance for each system instead of measuring only negative aspects. Third, it avoids arbitrary diagnostic thresholds. Fourth, it sets up an exhaustive and mutually exclusive classification system that can stimulate development of summary indices of total comorbidity burden for both research and clinical settings. As the knowledge base grows, the nosology can be updated to add new domains and refine extant ones.

OLDER adults generally have multiple medical problems, and no single medical issue can be evaluated and treated in isolation (1). In population studies, the prevalence of comorbidities and number of comorbid conditions increase with age (2,3). In 1999, 24% of Medicare beneficiaries, aged 65 years or older, had four or more chronic conditions. The proportion was 31.4% among those persons 85 years or older (3). Even healthy older adults and those with a single clinically manifest disease are likely to have subclinical pathology in multiple organ systems (4). Moreover, many older men and women experience a gradual decline in physical strength, gait speed, manual dexterity, memory, and cognitive skills, in the absence of a clinically manifest disease process (2,5). Coexistence of multiple such impairments complicates the diagnosis, treatment, and natural course of individual health conditions in older adults.

A nosology of comorbidity is suggested in this article for use by researchers, clinicians, and policy makers. A comprehensive classification of comorbidities that includes clinically manifest diseases and subclinical biological processes has several potential uses, not only in clinical care, but also in design of research studies and in translation of research findings from clinical trials to the bedside. Improved assessment of comorbidity burden has potential applications both at the individual patient level and at the institutional/societal level (Table 1). Although age is often used as a proxy for comorbidity burden, because of the tremendous variability in the number and severity of comorbidities among older adults, age alone is inadequate to represent an individual's comorbidity burden (6).

Criteria and Definitions

Comorbidities are frequently considered in the context of an index disease (e.g., a newly diagnosed cancer) (7); yet, the index disease focus is not sufficiently comprehensive for a general nosology, and may not be suitable for use in primary care settings. We propose that comorbidity is the total burden of biological dysfunction. Traditionally, comorbidity assessments primarily include overt diseases; we also include processes that do not meet current diagnostic criteria for disease, because subclinical dysfunction and impairments are highly prevalent in older adults and contribute to health outcomes (2,8), particularly when they occur in multiple systems (9,10).

For the purpose of this nosology, attention is restricted to biological processes intrinsic to the individual. Thus, lifestyle issues, socioeconomic factors, and health care access

Table 1. Potential Applications of a Comorbidity Nosology

At the level of the individual patient:

1. Global assessment of the aggregate health status of an older adult for estimating life expectancy, risk for future disability, and health care utilization.
2. Improved assessment of the relevance of results from clinical studies, based on comparing comorbidity burdens of study participants with patients.
3. Improved assessment of the untreated prognosis of a newly diagnosed condition and likelihood of success of different treatment options.
4. Context for the older individual (and family) in which informed treatment decisions are made.
5. Improved postintervention assessment of benefits from the intervention.

At the institutional/societal level:

6. Common language for communication among health professionals.
7. Assistance in planning/allocation of limited health care resources.
8. Improved assessment of quality and cost effectiveness of services.
9. Common benchmark for comparing findings from different research studies.
10. Enhanced adjustment for comorbid conditions in observational studies.
11. Improved design of clinical trials allowing for comparison of (or stratification by) comorbidity burden across arms of the trial.
12. Ability to create clinical (prevention and treatment) guidelines based on comorbidity burden rather than age alone.

and quality are not included, nor are genetic factors, although we recognize that both affect health outcomes and mitigate or accentuate the effects of comorbidity on outcomes. The effect of these factors on health may be captured, at least partially, by measurements of biological processes included in this nosology. Disabilities in activities of daily living [representing interaction of an individual with her/his environment (11)] are also not included in this nosology. In the terminology of the Nagi pathway (12), physical impairments and limitations are considered comorbidities, but disabilities are not.

Organizing Framework

The thesis proposed is that comorbidity may be assessed by assessing functioning in physiological and psychological systems, parallel to the World Health Organization's (WHO) International Classification of Functioning, Disability and Health (ICF) (11), and listed in Table 2. Functioning of each system extends from high-functioning, protective zones to early subclinical changes, to overt disease of increasing severity, to end-stage disease. This approach has several advantages. First, recognition that decrements in health begin before onset of symptomatic disease is explicit. Second, it does not rely solely on clinically diagnosed diseases, which depend on access to health care, diagnostic thresholds that change over time, and other nonintrinsic factors. Third, it accommodates the full range of performance for each system, instead of measuring negative aspects only. For example, affect, bone strength, and muscle strength can each be measured throughout the spectrum, and their positive aspects can be protective (13).

Each system has multiple domains in which functioning should be assessed. Functioning in the glucose regulation domain (in the endocrine system), for instance, ranges from normoglycemia to prediabetes (impaired fasting glucose) to overt diabetes mellitus. In this classification scheme, uncomplicated diabetes mellitus would be reflected only in the glucose regulation domain (with blood-glycosylated hemoglobin and fasting blood glucose serving as indices of function), and diabetes with complications such as retinopathy, neuropathy, and nephropathy would be reflected in multiple domains in several systems, each of which would contribute to the total comorbidity burden.

Table 2. Systems for Comorbidity Assessment

1. Mental functions
2. Sensory functions and pain
3. Voice and speech functions
4. Cardiovascular
5. Hematological
6. Immunological
7. Respiratory
8. Digestive
9. Metabolic
10. Endocrine
11. Genitourinary and reproductive/sexual
12. Neuromusculoskeletal and movement functions
13. Skin

Note: Listing of systems adapted from World Health Organization's International Classification of Functioning, Disability, and Health (11).

Examples of domains of functioning within the 13 systems are listed in Table 3. In addition to assessing function in traditional organ system–based domains that cover the leading causes of death and the most prevalent chronic health conditions among older adults (14), it is important to assess psychological functioning, physical and cognitive functioning, and sensory functioning, all of which have prognostic implications for loss of independence, health care utilization, quality of life, and mortality in older Americans (15–19).

The range of function within each domain is conceptualized as a continuum from high to low normal functioning, to asymptomatic pathology, to symptomatic clinical disease. In some domains, clinical indices (e.g., bone mineral density, fasting blood glucose, creatinine clearance, cardiac output) capture the level of functioning in the domain over the entire range. In other domains, progression of dysfunction may be represented by distinct categories of increasing disease severity (e.g., normal flow, asymptomatic occlusion, and angina pectoris can represent ordered categories of coronary flow) or by a combination of categorical and continuous indices (e.g., both ankle–arm index and symptom categories can be used to assess peripheral blood flow).

In some domains, dysfunction occurs with changes in physiological markers in either direction, characterized by U-shaped or J-shaped relationships with outcomes. For instance, low and high blood pressure are both associated with poor outcomes, as are low and high heart rates, and hypocoagulability and hypercoagulability. Similarly, whereas central adiposity is associated with higher risk of cardiovascular events, involuntary weight loss in older adults is associated with increased mortality (20). In domains such as these, dysfunction may be measured as deviation from an optimal value/region in either direction (21). In other

Table 3. Examples of Domains of Functioning within Individual Systems

Mental Functions
Affect, range of emotion
Memory (short and long term)
Alertness, attention, orientation
Language fluency
Calculation
Abstraction, insight, judgment
Executive function
Quality of sleep
Sensory Functions
Visual acuity, fields
Color, contrast perception
Hearing acuity
Localization, discrimination
Vestibular function
Proprioception
Taste, touch, smell
Voice and Speech
Voice loudness
Speech articulation
Cardiovascular
Heart rate, rhythm
Blood pressure
Postural blood pressure stability
Cardiac function: systolic, diastolic
Cardiac valvular function
Coronary blood flow
Carotid blood flow
Peripheral blood flow
Exercise tolerance
Venous valvular competence
Hematological
Blood cell production, maintenance
Clotting function
Lymphatic competence
Immunological
Immunological competence
Hypersensitivity
Autoimmunity
Nonspecific inflammation
Infections, acute and chronic
Dysplasia/neoplasia
Respiratory
Peak expiratory flow
Diffusion capacity
Lung volume
Digestive
Salivation, chewing
Swallowing
Motility: gastric, intestinal, colonic
Biliary flow
Nutrient absorption
Food tolerance
Fecal continence
Metabolic
Appetite
Adiposity, weight stability
Lipid regulation
Water and sodium balance
Thermal regulation
Endocrine
Pituitary function
Thyroid function
Adrenal function
Parathyroid function
Gonadal steroid levels
Glucose regulation
Genitourinary
Renal function
Bladder and outlet function
Libido
Genital function
Orgasm
Neuromusculoskeletal
Bone density, strength
Joint integrity, stability, range
Muscle strength, endurance
Muscle tone, control
Dexterity, coordination
Postural balance
Gait quality, speed
Skin
Fragility and repair
Sweat production

domains, dysfunction is manifest as reduced variability and decreased reserves, or homeostenosis (22). Reduced heart rate variability is one example of dysfunction that is associated with cognitive impairment (23) and mortality (24). Hypersensitivity and autoimmunity are examples of dysregulation of the immune system. Frequent and recurrent infections, chronic infections (e.g., chronic hepatitis and HIV), dysplasia, and neoplasia are markers of immune system dysfunction that can have profound effects on overall health.

Summary Indices Of Comorbidity

A comprehensive system of classifying intrinsic biological functioning can be used to construct summary comorbidity indices. Although comorbidity burden is multidimensional and unlikely to be captured by a single index, there is need for summary measures for tasks such as comparing participants across arms of a clinical trial and contrasting patients with study participants. The structure and composition of indices formed from this nosology will depend on their proposed use. As a general principle, we envision comorbidity indices based on this nosology to assign points for level of functioning within a domain (e.g., positive points at the harmful end and negative points at the protective end) and to combine contributions from different domains using a second set of weights. Separate scoring systems may be developed for different outcomes (e.g., quality-adjusted life expectancy, health care utilization, loss of independence), using weights specific to the outcome of interest.

Previous and Current Therapies

As ongoing treatment and history of prior interventions can modify health implications of a biological assessment,

comorbidity scoring systems need to appropriately account for them. For instance, a systolic blood pressure of 150 mmHg is associated with greater health risks if it reflects blood pressure on pharmaceutical therapy as opposed to untreated blood pressure. Accordingly, the Framingham risk score for predicting cardiovascular event risk assigns more points to the former (25,26). Likewise, a history of revascularization modifies the relationship between severity of blood flow occlusion and the risk of adverse outcomes, and point assignments for blood flow occlusion will need to vary by history of revascularization.

Interactions and Synergy

Models used to create comorbidity indices would also include interactions between domains. Certain interactions are currently recognized. For example, hypertension confers different risk for adverse outcomes in the presence or absence of diabetes, and the same value of low-density-lipoprotein cholesterol is associated with different levels of risk for cardiovascular events in those with and without coronary artery disease or diabetes (27). Similarly, there is known synergy between depression and coronary heart disease (28,29), visual impairment and arthritis (30), hypertension and hyperlipidemia (31–33), and between elevated C-reactive protein levels and diabetes mellitus (34) in the risk for adverse health outcomes. There is also likely to be synergy between domains in protective high-functioning zones, such as between positive affect and high exercise tolerance, as well as interactions between protective zones in one domain and harmful zones in another.

Trajectories of Change

In addition to the current level of functioning, current health also depends on accumulated effects of past (dys)functioning. For instance, duration of diabetes mellitus is a strong predictor of mortality, independent of other risk factors (35,36). Historical levels of glucose control can have long-term impact on health, as suggested by the observational follow-up of the Diabetes Control and Complications Trial (37). Past history of lipid levels is similarly important. Among older men from the Honolulu Heart Program, remote measurements of serum total cholesterol had stronger associations with coronary disease incidence than did more recent measurements (38). Likewise, single assessments of remitting and relapsing processes (such as depression and cancer) cannot capture the true impact of past changes. Additionally, the rate of change of functioning within a domain over time may have important prognostic significance that is not captured in a single assessment. Similarly, frequent variability in physiological parameters such as serum albumin can reflect underlying poor health. Therefore, a complete assessment of comorbidity will require, in addition to assessment of current functioning, some historical data regarding prior levels of functioning and duration of dysfunction.

Comorbidity Is Not Static

Comorbidity, characterized in this article as aggregate biological dysfunction, is dynamic. Gradual increases in comorbidity burden are associated with aging, albeit at different rates in different individuals. Superimposed are transient changes from the underlying trajectory because of acute events (e.g., acute infections, surgical procedures, heart attacks, strokes, episodes of delirium) and/or stressful developments (e.g., institutionalization, new diagnosis of debilitating disease in family members or friends, loss of a spouse). The comorbidity burden may return to the baseline trajectory after some acute events; others may trigger a step change in trajectory.

Multiple Summary Indices

In many clinical and research settings, summary comorbidity indices will not assess subclinical factors and will focus on overt diseases, to avoid excessive testing and screening in asymptomatic patients. The importance of subclinical processes in comorbidity, however, cannot be overstated, especially for older adults with few or no overt diseases. With improving clinical laboratory technology, the burden of testing/assessment need not be excessive. For instance, several biomarkers including C-reactive protein and glycosylated hemoglobin can be measured from blood spots collected by finger pricks using lancets of the type used to monitor blood glucose (39,40).

It is likely that different indices of comorbidity are needed for different groups of patients and for different applications (e.g., research vs clinical use), and specific factors will be included in some indices and not in others. At times, a few simple assessments of overall physical functioning (e.g., endurance and gait speed) could adequately summarize global comorbidity burden for clinical purposes, because they are affected by multiple systems.

Because of the multidimensional nature of health and the limits of current knowledge, no index of comorbidity will be complete. In theory, both types of limitations can be addressed—by the use of multidimensional scores and by regularly updating the scoring system.

Conclusion

In closing, there is a widely felt need to improve understanding of the role of multiple comorbid conditions in the health of older adults. A comprehensive nosology of comorbidity is the first step towards this goal. A nosology of comorbidity in older adults is suggested to encourage the development of comorbidity measures for use in research and clinical practice, spark the discovery of interactions between co-occurring conditions, and lead to the identification of a core set of markers (biological, psychological, and functional) for assessment of the aggregate health status of older adults.

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