SPECIAL ARTICLE

Delirium—A Framework to Improve Acute Care for Older Persons

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ABSTRACT: This article is based on the M. Powell Lawton Award Lecture that I delivered at the 2016 Gerontological Society of America Annual Meeting. I provide an overview of my journey in geriatric medicine and delirium research. I created new measures, including the Confusion Assessment Method, for identification of delirium; conceptualized a multifactorial risk model; and developed and tested intervention strategies for delirium prevention. The Hospital Elder Life Program arose from this work. In addition, like Dr. Lawton, I am working to apply my work to the policy arena. As the population ages, we face an unprecedented opportunity to realize the full benefit of aging in our society, an untapped resource. The field of aging is facing innumerable challenges in terms of continued stigma and funding shortfalls for clinical care and research. I issue a call to action to clinicians, researchers, and leaders in aging to seize this opportunity to use our know-how and expertise to transform the experience of aging for all. **J Am Geriatr Soc 66:446–451, 2018.**

Key words: Acute care for elders; Confusion Assessment Method; Delirium; Hospital Elder Life Program

MY JOURNEY INTO MEDICINE AND GERIATRICS

My story begins at age 3, with the desire to spend time with my father, Dr. Mitsuo Inouye, a general practitioner in California. When he was trying to leave for work, I would hang on his leg until he was forced to take me with him on hospital rounds, where I spent many happy hours. I pursued medical school intending someday to take over his practice.

During medical school, I loved every clinical rotation, and I had great difficulty narrowing down my interests to a single field. After a long struggle with indecision, I chose internal medicine for my residency at the University of California at San Francisco, because I felt it was the broadest field and would offer me a wide array of career choices. Upon completion of residency, I was unable to narrow the choices of subspecialty areas and decided to pursue general medicine practice opportunities. By accident, I interviewed for a job in geriatric medicine at the West Haven Veterans Affairs Medical Center. To my surprise, this was the position that most appealed to me, and I started there in 1985. I loved geriatric medicine from the start and have never looked back. The field is tremendously challenging and rewarding. I enjoyed the patient population—their stories, wisdom, and appreciation for small things—and I found great satisfaction in helping to address the challenges that multimorbidity superimposed on often complex patient and family dynamics posed.

DELIRIUM, THE ADVENTURE

As a geriatrician, I observed that older adults were often ignored and undervalued—particularly those who were confused. I witnessed acute confusional states in many older persons during hospitalization—associated with acute illness or major surgery. When I asked my senior colleagues and mentors about these confusional states, the response was invariably some version of "That just happens in older people; don't worry about it," but I could not stop thinking about it.

I wanted to understand why it was happening. In particular, I could not stop thinking about 6 older adults on my service who had developed acute confusional states and had poor outcomes. Two had to be transferred to the intensive care unit, 1 died, and 3 went to nursing homes. I reviewed their charts, recording all their activities, medications, procedures, and laboratory abnormalities and correlated that information with their mental status recorded in my notes. I became convinced of a pattern: that aspects of the hospital care they received—such as psychoactive

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DOI: 10.1111/jgs.15296

0002-8614/18/$15.00

medications, procedures, immobilization, sleep deprivation—contributed to the problem. I wanted to explore this further—to gain understanding through research.

Maybe because no one else was paying much attention to the problem, coupled with my lifelong desire to advocate for underrepresented, vulnerable people, I delved further into the area of delirium. After scouring the literature in 1987–88, I discovered that there was no validated approach to screening for delirium. Thus, from necessity, I developed and validated the Confusion Assessment Method (CAM), a new screening instrument for delirium.

Identification of Delirium

The goal of the CAM was to provide a quick, accurate method to detect delirium that would be useful for nonpsychiatrically trained clinicians and researchers.[1] I assembled an expert panel to assist with identifying the 4 core features of delirium: acute onset and fluctuating course of symptoms, inattention, and either disorganized thinking or altered level of consciousness. Subsequently, I validated a 5- to 10-minute rating of the CAM after a brief cognitive screen against a 90-minute or longer reference standard rating by a psychiatrist. In 56 individuals, the CAM was demonstrated to have sensitivity of 94% to 100%, specificity of 90% to 95%, and a high likelihood ratio.[1]

Since that initial study, the CAM has become the most widely used method for identification of delirium worldwide, used in more than 5,000 original studies and translated into more than 20 languages.[2,3] The short CAM (4 items) is commonly used for screening, and the long CAM (10 items) is used for diagnostic confirmation, subtyping, and research purposes. The CAM has been adapted for use in a variety of settings, including the intensive care unit, nursing home, and emergency department.[4–6] The FAM-CAM has been developed to provide a validated proxy-based approach to assist with recognition of delirium by family members.[7,8] Dr. Edward Marcantonio has validated an abbreviated 3-minute assessment to score the CAM, called the 3D-CAM.[9] We have also developed a validated approach to identify delirium based on medical record review.[10]

Quantifying Delirium Severity

Working with my colleague Dr. Richard Jones, I recently developed and evaluated a new severity scoring system, the CAM-S, which provides an additive score of CAM features.[11] The scoring system applies to the short 4-item CAM, as well as the long 10-item version. Our validation study showed that a higher CAM-S score was strongly associated with poorer clinical outcomes, including functional decline, length of stay, healthcare costs, institutionalization, and death.[11] This was the first demonstration that delirium severity was directly associated with adverse clinical outcomes in an exposure-response fashion. We further evaluated the best measures of severity for an entire episode of delirium; measures combining intensity and duration provided the optimal predictive validity, such as the sum of CAM-S from all hospital days or the peak CAM-S measure for the hospitalization.[12] These studies helped to demonstrate the importance of delirium severity, which provides a continuous measure to track change over time, monitor clinical course and recovery, measure response to treatment, track burden of care and service use, and advance our pathophysiological understanding of delirium.

The Multifactorial Nature of Delirium

Early on, I hypothesized that delirium, like other common geriatric syndromes, was typically of multifactorial etiology. The onset of delirium was related to the interaction of patient vulnerability (predisposing) factors present before hospital admission and superimposed precipitating factors (noxious insults) occurring during hospitalization (Figure 1).[13] For example, persons with greater vulnerability due to multiple predisposing factors, such as cognitive impairment, vision and hearing impairment, and multiple comorbidities, might develop delirium with just a single dose of a sleeping medication. Conversely, an individual with no predisposing factors would have low vulnerability and might require multiple insults to develop delirium, such as many psychoactive medications, sleep deprivation, immobility, and dehydration. This multifactorial model would explain why older adults, who typically have multiple chronic conditions, are more vulnerable to delirium. The important message is that addressing single factors would not be likely to prevent or treat a delirium; rather, the full spectrum of vulnerability and precipitating factors needs to be considered for optimal management.

Baseline Predisposing Factors for Delirium. To examine predisposing factors, I developed and validated a predictive model for delirium based on characteristics present on hospital admission.[14] We assembled 2 prospective cohorts of hospitalized medical patients aged 70 and older: a development cohort of 107 patients followed by a validation cohort of 174 comparable patients. The patients had no evidence of delirium at baseline, and underwent daily interviews with cognitive testing and CAM ratings. Based on admission factors, 13 potential risk factors with bivariable relative risks of 1.5 or greater were entered into a stepwise multivariable model, and 4 final risk factors were selected: vision

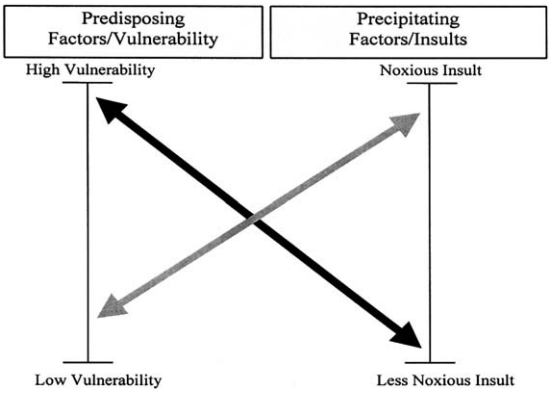

Figure 1. Multifactorial model for delirium: interaction of baseline (predisposing) factors and noxious insults (precipitating factors) in development of delirium.

impairment, severe illness, cognitive impairment, and blood urea nitrogen:creatinine ratio of 18 or greater. A risk stratification system was developed by adding the number of these risk factors present at baseline. Patients with no risk factors were categorized into the low-risk group, those with 1 or 2 risk factors into the intermediate risk group, and those with 3 or 4 risk factors into the high-risk group. In the validation cohort (n=174), rates of delirium increased progressively from low- to high-risk groups, from 3% to 16% to 32%, with associated relative risks increasing from 1.0 (reference) to 4.7 to 9.5. Thus, this predictive model was able to stratify patients according to their delirium risk at hospital admission.

Precipitating Factors for Delirium During Hospitalization. Next we wanted to examine noxious insults during hospitalization that might precipitate delirium using a similar approach.[13] Thus, we assembled 2 prospective cohorts of hospitalized medical patients aged 70 and older: a development cohort of 196 patients followed by a validation cohort of 312 comparable patients. The patients had no evidence of delirium at baseline and underwent daily interviews with cognitive testing and CAM ratings. We selected 25 candidate variables that we categorized into 4 axes: immobility, medications, iatrogenic events, and intercurrent illness factors. Subsequently, variables were narrowed within axes, and 11 variables were entered into a multivariable model. From this model, 5 final precipitating factors were selected: use of physical restraints, malnutrition, more than 3 medications added in a 24 hour period (note: 70% of these were psychoactive medications), use of an indwelling bladder catheter, and any iatrogenic event.[15] A risk stratification system was developed by adding the number of these precipitating factors present during hospitalization. Patients with no precipitating factors were categorized into the low-risk group, those with 1 or 2 factors into the intermediate-risk group, and those with 3 to 5 factors into the high-risk group. In the validation cohort (n=312), rates of delirium increased progressively from low- to high-risk groups, from 4% to 20% to 35%, with associated relative risks increasing from 1.0 (reference) to 5.0 to 8.9. For this analysis, the more appropriate unit of analysis was the person-day, because each day represented an opportunity for the individual to be exposed to different precipitating factors and to develop delirium. In the validation cohort, the delirium rate per 100 person-days (% developing delirium each day) across risk strata increased from 0.5% to 3.3% to 8.2% per day, with associated relative risks increasing from 1.0 (reference) to 7.1 to 17.5, again demonstrating a strong risk gradient. The delirium rate of 8.2% per day translates to a 53.7% rate of delirium for a 9-day hospital stay. Thus, this predictive model works well to stratify patients for their delirium risk according to precipitating factors throughout hospitalization.

Interrelationship of Baseline and Precipitating Factors. Next, we wanted to test our initial hypothesis about the interrelationship of baseline and precipitating factors by examining the cumulative effects of our 2 predictive models in cross-stratified analyses (Figure 2).[13] Applying both models simultaneously to our cohorts and examining delirium rates per 100 person-days (% developing delirium per day), we found that delirium rates increased progressively from the low- to high-risk groups in all directions (across the rows, down the columns, diagonally). This phenomenon, known as the "double-gradient phenomenon,"[16] indicates that baseline and precipitating factors contribute to delirium in independent and substantive ways. The relationship is more than additive; it is multiplicative when formally tested. These important findings empirically confirmed our initial hypothesis about the multifactorial nature of delirium and the interaction of baseline and precipitating factors. Moreover, these two predictive models helped us to identify patients at risk of delirium and to select risk factors that may be amenable to intervention.

RATE OF DELIRIUM (per 100 person-days)

Baseline Risk	Precipitating Factors Group			
	Low	Int	High	Total
Low	0	0	0	0
Int	0.8	2.3	4.6	1.6
High	0	5.0	11.6	3.8
Total	0.5	3.5	8.2	

Figure 2. Interrelationship of baseline and precipitating factors: double gradient phenomenon (validation cohort, n=312). The increasing risk of delirium when moving from low- to high-risk groups in all directions (rows, columns, diagonally) illustrates the double-gradient phenomenon. Delirium rates shown correspond to the ratio of patients developing delirium per 100 person-days (percentage developing delirium per day)

Prevention of Delirium

At this point, I had completed nearly 10 years of work in the delirium field and had not been able to make a difference at the bedside. Thus, I eagerly moved on to conceive the Delirium Prevention Trial.[17] We developed a multicomponent, nonpharmacological intervention strategy targeted at 6 known delirium risk factors (Table 1): cognitive impairment, sleep deprivation, immobilization, vision impairment, hearing impairment, and dehydration. These risk factors were selected because of their association with risk of delirium and because they were amenable to intervention strategies considered to be feasible and potent. The intervention protocols included reality orientation and therapeutic activities to address cognitive impairment; minimizing psychoactive medication; use of a nonpharmacological sleep protocol and sleep enhancement program to facilitate an uninterrupted period of sleep at night; early mobilization (walking) and minimizing immobilizing equipment; vision and hearing aids and adaptive equipment, along with training staff in communication methods for patients with sensory impairments; early recognition of dehydration with volume repletion; and attention to feeding and nutrition. The intervention was evaluated in a controlled clinical trial with one unit randomly selected as the intervention unit and 2 units as usual care controls. We studied 852 patients (426 intervention, 426 controls) aged 70 and older admitted to the medicine service who

Table 1. Delirium Risk Factors and Targeted Interventions

Risk Factor	Intervention Protocol
Cognitive impairment	Orienting communication, including orientation board Therapeutic activities program
Immobilization	Early mobilization (e.g., ambulation or bedside exercises) Minimizing immobilizing equipment (e.g., restraints, bladder catheters)
Psychoactive medications	Restricted use of as-needed sleep and psychoactive medications (e.g., sedative–hypnotics, narcotics, anticholinergic drugs) Nonpharmacological protocols for management of sleep and anxiety
Sleep deprivation	Noise-reduction strategies Scheduling of nighttime medications, procedures, and nursing activities to allow uninterrupted sleep.
Vision impairment	Provision of vision aids (e.g., magnifiers, special lighting) Provision of adaptive equipment (e.g., illuminated telephone dials, large-print books)
Hearing impairment	Provision of amplifying devices; repair of hearing aids Instruction of staff in communication methods
Dehydration	Early recognition and volume repletion

Adapted from: Inouye SK et al. *N Engl J Med.* 1999; 340: 669–676.[17]

had no evidence of delirium at baseline but were at moderate to high risk of developing delirium based on our predictive model. Delirium was assessed daily using cognitive testing and CAM ratings along with daily nurse interviews by trained clinical research staff who were blinded to the study hypothesis. Incident delirium developed in 9.9% of the intervention group and 15% of the usual care group (matched odds ratio (OR)=0.60, 95% confidence interval (CI)=0.39–0.92). There were significantly fewer delirium days (105 vs 161, P = .02) and delirium episodes (62 vs 90, P = .03) in the intervention group, although severity of delirium and recurrence rates were not significantly different once patients developed delirium. This trial provided the first demonstration that delirium was a preventable medical condition. We showed that a targeted, multicomponent risk factor strategy was effective and that practical, nonpharmacological protocols were potent in addressing this condition. This work highlighted the importance of primary prevention of delirium as the most effective approach to management of this often devastating condition.

The Hospital Elder Life Program. The intervention strategy for the Delirium Prevention Trial has been systematized as the Hospital Elder Life Program (HELP),[18] and the program has been implemented in more than 200 hospitals worldwide. More than 20 published studies have demonstrated the program's effectiveness in preventing delirium and falls, reducing cognitive and functional decline, shortening length of stay, decreasing institutionalization rates, and decreasing use of sitters.[8,19] HELP has been demonstrated to be cost saving, with more than $1,000 in savings per patient per hospitalization[20–22] and nearly $10,000 per person-year in long-term nursing home costs.[23] A recent meta-analysis of 14 clinical trials of delirium prevention programs based on HELP demonstrated substantial reductions in delirium (combined OR=0.47, 95% CI=0.38–0.58).[24] Moreover, the rate of hospital falls decreased significantly in intervention patients in 4 studies (combined OR=0.38, 95% CI=0.25–0.60). Thus, delirium serves as a powerful indicator of the quality of hospital care of older persons, and its prevention also decreases other important hospital complications, including falls, functional decline, immobility, and pressure ulcers.[25]

Does Delirium Lead to Dementia?

Delirium has long been considered to be a reversible condition. Although it is acknowledged that it has severe short-term consequences, the long-term consequences remain unclear. Recent evidence suggests that delirium might be associated with greater risk of subsequent dementia.[26,27] Thus, we launched a National Institutes of Health-funded program project in 2010 designed specifically to examine the epidemiology, risk markers, and long-term outcomes associated with delirium. For this study, called Successful AGing after Elective Surgery (SAGES), we assembled a prospective cohort of 560 patients aged 70 and older undergoing major scheduled surgery who had no evidence of dementia.[28,29] All underwent detailed neuropsychological testing at baseline; at 1, 2, and 6 months; and every 6 months thereafter. Delirium occurred in 24%. We examined the cognitive trajectories out to 36 months in patients with and without delirium.[30] Both groups developed acute cognitive decline at 1 month, but the group without delirium recovered to above baseline at 2 months and then demonstrated a gradual decline to 36 months yet remaining above their baseline level. The group with delirium also recovered to above baseline at 2 months and then demonstrated a more rapid decline out to 36 months to a level significantly below their baseline level. The slope of decline in the delirium group was equivalent to that seen in patients with mild cognitive impairment. Thus, on average, the group with delirium had substantial long-term cognitive decline 3 years after delirium. Although causation cannot be established in this observational study, the results raise the intriguing possibility that delirium may be a potentially important contributor to long-term cognitive decline.

Pathophysiology of Delirium. The SAGES study has also allowed examination of important risk markers for delirium. We examined inflammatory biomarkers in two recent studies. Interleukin-6 is markedly higher with delirium on postoperative day 2 and may serve as an important disease marker for delirium.[31] With delirium, C-reactive protein is high at baseline, immediately after surgery, and on postoperative day 2 and thus may serve as

a risk and disease marker.[32] We also examined several Alzheimer's disease (AD) risk markers for their relationship to delirium. Contrary to our hypotheses, we found that apolipoprotein E-ε4[33] and magnetic resonance imaging volumetric changes typical of AD[34] were not risk factors for delirium. These results suggest that, in individuals who are free of dementia, risk factors for AD do not confer greater risk of delirium and raise the possibility of alternative mechanistic pathways.

We hope to continue to probe the pathophysiological underpinnings of delirium and its long-term outcomes. We plan further examination of delirium associated with accelerated long-term cognitive decline, which we call "complicated delirium." We hope to examine the characteristics of delirium[35] and of patients[36] that increase vulnerability to development of complicated delirium. This work is of fundamental importance, because at least 40% of delirium is preventable, which may provide an unprecedented opportunity to effectively prevent or ameliorate long-term cognitive decline and dementia.

BROADER IMPLICATIONS: CREATING HEALTH SYSTEM CHANGE

Like Powell Lawton, I wanted my work to have a broader effect and to lead to better systems of care for older adults. Recently, my father developed delirium after coronary artery bypass surgery. As I sat at his bedside, monitoring his condition and speaking with clinicians around the clock, I realized that a single person—even a delirium expert—was powerless in the face of the lack of geriatric knowledge base in his clinical team combined with inadequate coordination and communication across the many teams involved in his care. As an individual clinician, educator, and researcher, I recognized that my influence on health care was minimal at best. I wanted to learn more about how to create broader change in healthcare systems to improve the health and well-being of older adults. Thus, this past year, I embarked on the Health and Aging Policy Fellowship and the American Political Science Association Congressional Fellowship in Washington, District of Columbia. I hope to learn how to create policy change through working at the Center for Medicare and Medicaid Innovation, particularly in improving quality and outcomes in the acute care setting with prevention of delirium and falls. I also hope to gain insight into other critical policy areas to enhance care of older persons, such as implementation and dissemination of effective approaches to care—so broadly important to our field.

Although my work has focused on delirium, the lessons I have learned extrapolate broadly across the field of aging. I have become acutely aware that aging in America is not a pretty picture. Our society is intensely youth oriented, and older age is often stigmatized. Our field is often devalued as well, resulting in a severe lack of research funding and an inadequate geriatric healthcare workforce. Amidst the rapidly growing aging population in our country and globally, along with rising healthcare costs and threatened Medicare funding, our expertise in aging is desperately needed. Geriatricians and experts in aging must be at the table for all critical decisions involved in funding and providing care for this vulnerable population.

Who but we can frame healthcare of older adults for the next century? We are committed interdisciplinary healthcare professionals and researchers. We possess the intellect, energy, passion, and position to improve quality of life for older adults and their families. Who but we can spearhead the changes that need to happen?

Who but we can provide the expertise and perspective to address the challenges of aging? We bring our unique focus on optimizing function and quality of life in older adults. We embrace complexity and multimorbidity, addressing the multifactorial etiology of age-related diseases and geriatric syndromes. We aim to maximize resiliency and comprehend the importance of prevention throughout the life course.

Who but we can bring value, recognition, and appreciation of older people? We recognize their unique contributions, including wisdom, experience, patience, and resilience. They have lived with adversity and survived with grace and aplomb. They have so much to teach us.

Who but we can teach our patients, families, caregivers, healthcare professionals, and policy-makers how best to care for older persons? We have shown time and again that good geriatric care is cost effective and enhances meaningful outcomes and quality of life.

Who but we can guide care for older persons to optimize complex healthcare systems and community care for all? I issue this call to action for our field: to all of us to provide the leadership to change the experience of aging in America. We have the know-how and the experience, let us seize the opportunity to transform aging into an extended period of healthful and rewarding longevity for all.

ACKNOWLEDGMENTS

Financial Disclosure: This work was supported in part by Grants P01AG031720, K07AG041835, R24AG054259, and R01AG044518 from the National Institute on Aging and the Milton and Shirley F. Levy Family Chair.

This manuscript is based on the Lawton Award lecture presented at the Gerontological Society of America Annual Scientific Meeting, November 16–20, 2016; New Orleans, LA, in recognition of significant and innovative contributions in gerontology that have led to practical applications that improve the lives of older persons. More information on delirium can be found at www.HospitalElderLifeProgram.org.

I would like to express my deepest gratitude to so many people and organizations that have made my work and this award possible. First, thank you to the GSA Lawton Award Committee and to my nominators and mentees, led by Drs. Donna Fick, Ann Kolanowski, and Cynthia Brown. I extend my deepest gratitude to my colleagues in the Aging Brain Center and SAGES study, including Drs. Edward Marcantonio, Richard Jones, Eva Schmitt, and Thomas Travison and the entire ABC Working Group; to my incredible staff in the Aging Brain Center—I accept this award on your behalf! Thank you to Dr. Lewis Lipsitz and my colleagues at the Institute for Aging Research, Hebrew SeniorLife, and to the Milton and Shirley F. Levy family, who endowed my chair. To my mentors, Drs. Mary Tinetti, Ralph Horwitz, Alvan Feinstein, Lisa Berkman, thank you for believing in me and

my work. To Dr. Mark Zeidel, Beth Israel Deaconess Medical Center and to Harvard Medical School, thank you for your steadfast support. To my funders at the National Institute on Aging, Retirement Research Foundation, Commonwealth Fund, John A. Hartford Foundation, and Donaghue Foundation, thank you for your support and trust; I could not have done this without you. To the Executive Leadership in Academic Medicine and Health and Aging Policy Fellowship Programs and colleagues, thank you for teaching me so much about leadership, service, passion, and change. Most of all, to my family, Stephen, Benjamin, and Jordan Helfand, you are my strength and the wind beneath my wings; you are the reason I work so hard to create a better world. To the precious and always present memory of my son (Joshua Helfand), father (Mitsuo Inouye), brother (Bradley Inouye), and dear friends (Jane McDowell, Lynne Morishita), I dedicate this work. There are too many others to name individually, but you know who you are. I thank every one of you from the bottom of my heart.

Conflict of Interest: The author has no conflicts to disclose

Author Contributions: The author conceptualized the paper, analyzed the results, drafted the article, and approved the final version for submission.

Sponsor's Role: None.

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