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Delirium—A Framework to Improve Acute Care for Older Persons

Sharon K. Inouye, M.D., MPH^{1,2}

¹Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

²Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife

Abstract

This paper is based on the M. Powell Lawton Award Lecture delivered by Dr. Sharon Inouye at the 2016 Gerontological Society of America Annual Meeting. She provides an overview of her journey in geriatric medicine and delirium research. She created new measures, including the Confusion Assessment Method (CAM) for identification of delirium, conceptualized a multifactorial risk model, and developed and tested intervention strategies for delirium prevention. The Hospital Elder Life Program (HELP) arose from this work. In addition, like Dr. Lawton, she is working to translate her work to broader policy implications. 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. As clinicians, researchers, and leaders in aging, she issues a call to action to seize this opportunity to use our know-how and expertise to transform the experience of aging for all.

My Journey into Medicine and Geriatrics

My story begins around age 3, motivated by 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 to someday 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 UCSF, since 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. Just 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 posed by multi-morbidity superimposed on often complex patient and family dynamics.

Delirium, the Adventure

As a geriatrician, I observed older adults were often ignored and undervalued. This was heightened greatly in 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 the condition, 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 patients on my service who had developed an acute confusional state, and went on to have poor outcomes. Two of them had to be transferred to the ICU, 1 died, and 3 went to nursing homes. I reviewed their charts, recording all their activities, medications, procedures, laboratory abnormalities, and correlated that 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 medications, procedures, immobilization, sleep deprivation -- had 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 the under-represented and vulnerable, I delved further into the area of delirium. After scouring the world's literature in 1987–88, I discovered that there was no validated approach to screen 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 for detection of delirium that would be useful for non-psychiatrically trained clinicians and researchers.¹ I assembled an expert panel to assist with identifying the 4 core features of a delirium: acute onset and fluctuating course of symptoms, inattention, and either disorganized thinking or altered level of consciousness. Subsequently, I validated a 5–10 minute rating of the CAM following a brief cognitive screen against a >90-minute reference standard rating by a psychiatrist. In 56 patients, the CAM was demonstrated to have a sensitivity of 94–100%, specificity of 90–95%, and high likelihood ratio.¹

Since that initial study, the CAM has become the most widely used method for identification of delirium worldwide, used in >5,000 original studies and translated into over 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 across 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} An abbreviated 3-minute assessment to score the CAM, called the 3D-CAM⁹ has been validated by Dr. Edward Marcantonio. We have also developed a validated approach to identify delirium based on medical record review.¹⁰

Quantifying Delirium Severity

Working with colleague Dr. Richard Jones, we 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 both 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 both intensity and duration provided the optimal predictive validity, such as the sum of CAM-S across 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 utilization, and advance our pathophysiologic understanding.

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 high 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 age 70 years, first a development cohort with 107 patients, followed by a validation cohort with 174 comparable patients. The patients had no evidence of delirium at baseline, and underwent daily patient interviews with cognitive testing and CAM ratings, with nursing

interviews. Based on admission factors, 13 potential risk factors with bivariable relative risks 1.5 were entered into a stepwise multivariable model, and 4 final risk factors were selected: vision impairment, severe illness, cognitive impairment, and blood urea nitrogen/creatinine ratio 18. A risk stratification system was developed by adding up the number of these risk factors which were present at baseline. Patients with no risk factors were categorized into the low risk group; with 1–2 risk factors into the intermediate risk group; and 3–4 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 (referent) to 4.7 to 9.5. Thus, this predictive model was able to successfully stratify patients for 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 age 70 years, first a development cohort with 196 patients, followed by a validation cohort with 312 comparable patients. The patients had no evidence of delirium at baseline, and underwent daily patient interviews with cognitive testing and CAM ratings, with nursing interviews. We selected 25 candidate variables which 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, > 3 medications added in a 24 hour period (70% were psychoactive medications), use of an indwelling bladder catheter, and any iatrogenic event.¹⁵ A risk stratification system was developed by adding up the number of these precipitating factors which were present during hospitalization. Patients with no precipitating factors were categorized into the low risk group; with 1–2 factors into the intermediate risk group; and 3–5 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 (referent) to 5.0 to 8.9. However, for this analysis, the more appropriate unit of analysis was the patient-day, since each day represented an opportunity for the patient 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 (referent) 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 two predictive models in cross-stratified analyses (Figure 2).¹³ Applying both models simultaneously to our cohorts and examining delirium rates per 100 patient-days (% developing delirium per day), we found that the delirium rates increased progressively from the low-to high-risk groups in all directions, i.e., across the

rows, down the columns, or diagonally. This phenomenon, known as the “double-gradient phenomenon”¹⁶ indicates that both the baseline and precipitating factors are contributing 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 both baseline and precipitating factors. Moreover, these two predictive models helped us to identify patients at risk for delirium, and to select risk factors which may be amenable to intervention.

Prevention of Delirium

Now, I had completed nearly 10 years of work in the delirium field, and had not yet 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 the risk of delirium and because they were amenable to intervention strategies considered to be both 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/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 the usual care controls. We studied 852 patients (426 intervention, 426 controls) age 70 years admitted to the medicine service who had no evidence of delirium at baseline, but who were at moderate to high risk for developing delirium based on our predictive model. Delirium was assessed daily by cognitive testing and CAM ratings, along with daily nurse interviews by trained clinical research staff who were blinded to the study hypotheses. Incident delirium developed in 9.9% of the intervention group, compared with 15% of the usual care group (matched odds ratio, OR = 0.60, 95% confidence interval, CI, 0.39–0.92). The total number of delirium days (105 vs. 161, $P = .02$) and number of delirium episodes (62 vs. 90, $P = .03$) were significantly reduced in the intervention group. However, the 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 had potency for this condition. Importantly, 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 (HELP)—The intervention strategy for the Delirium Prevention Trial has been systematized as the Hospital Elder Life Program,¹⁸ and the program has been implemented in over 200 hospitals worldwide. Over 20 published studies have demonstrated the program’s effectiveness for prevention of delirium and falls,

reduction of cognitive and functional decline, shortening length of stay, decreased institutionalization rates, and decreased use of sitters.^{8,19} Importantly, HELP has been demonstrated to be cost saving, with over \$1000 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 of 0.47, 95% CI 0.38–0.58).²⁴ Moreover, the rate of hospital falls decreased significantly among intervention patients in 4 studies (combined OR of 0.38, 95% CI 0.25–0.60). Thus, delirium serves as a powerful indicator of the quality of hospital care for 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. While acknowledged to have severe short-term consequences, the long-term consequences remain unclear. Recent evidence suggests that delirium might be associated with an increased risk of subsequent dementia.^{26,27} Thus, we launched an NIH-funded Program Project in 2010 designed specifically to examine the epidemiology, risk markers, and long-term outcomes associated with delirium. For this study, called SAGES (Successful AGing after Elective Surgery), we assembled a prospective cohort of 560 patients age 70 and older undergoing major scheduled surgery who had no evidence of dementia.^{28,29} All patients underwent detailed neuropsychological testing at baseline, 1, 2, 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 one month. However, the non-delirium group recovered above baseline at 2 months, then demonstrated a gradual decline out to 36 months, yet remaining above their baseline level. By contrast, the delirium group also recovered above baseline at 2 months, 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 delirium group demonstrated a substantial long-term cognitive decline at 3 years following delirium. While causation cannot be established in this prospective 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. IL-6 is markedly elevated with delirium at post-operative day 2, and may serve as an important disease marker for delirium.³¹ With delirium, CRP is elevated at baseline, immediately post-operative, and post-operative 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 ApoE-E4³³ and MRI volumetric changes typical of AD³⁴ were not risk factors for delirium. These results suggest that in patients who are free of dementia, important risk factors for AD do not confer increased risk for delirium, and raise the possibility of alternative mechanistic pathways.

We hope to continue to probe the pathophysiologic underpinnings of delirium and its long-term outcomes. We plan further examination of delirium that is associated with accelerated long-term cognitive decline, which we call “complicated delirium”. We hope to examine both the characteristics of the delirium³⁵ and of the patients³⁶ that increase vulnerability to development of complicated delirium. This work is of fundamental importance, since we already know that at least 40% of delirium is preventable, and thus, 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 impact and to lead to improved systems of care for older adults. Recently, my father developed delirium following coronary artery bypass surgery. As I sat at his bedside, monitoring his condition and speaking with clinicians 24–7, 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 healthcare 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, DC based at the Centers for Medicare and Medicaid Innovation in Baltimore, MD. I hope to learn how to create policy change through working at the Centers for Medicare and Medicaid Services, particularly in improving quality and outcomes in the acute care setting with prevention of delirium and falls. I also hoped to gain insight into other critical policy areas to enhance care for older persons, such as implementation and dissemination of effective approaches to care—so broadly important to our field.

While my work has focused on the area of 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 us...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 us....can spearhead the changes that need to happen?

Who but us...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 multi-morbidity, 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 us...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 us...can teach our patients, families, caregivers, healthcare professionals, and policymakers how to best 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 us...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's seize the opportunity to transform aging into an extended period of healthful and rewarding longevity for all.

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Figure 1.
Multifactorial Model for Delirium.
This figure demonstrates the interaction of baseline (predisposing) factors and noxious insults (precipitating factors) in the development of delirium. See text for details.

RATE OF DELIRIUM(per 100 person-days)				
<u>Baseline Risk</u>	<u>Precipitating Factors Group</u>			
	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.

Inter-Relationship of Baseline and Precipitating Factors: Double Gradient Phenomenon (Validation Cohort, N=312)

“The double-gradient” phenomenon is shown by the increasing risk of delirium when moving from low-risk to high-risk groups in all directions (across rows, columns, or diagonally). The delirium rates shown correspond to the ratio of patients developing delirium per 100 patient-days (percentage developing delirium per day)

TABLE 1**Delirium Risk Factors and Targeted Interventions**

RISK FACTOR	INTERVENTION PROTOCOL
Cognitive impairment	<ul style="list-style-type: none"> • Orienting communication, including orientation board • Therapeutic activities program
Immobilization	<ul style="list-style-type: none"> • Early mobilization (e.g., ambulation or bedside exercises) • Minimizing immobilizing equipment (e.g., restraints, bladder catheters)
Psychoactive medications	<ul style="list-style-type: none"> • Restricted use of PRN sleep and psychoactive medications (e.g., sedative–hypnotics, narcotics, anticholinergic drugs) • Nonpharmacological protocols for management of sleep and anxiety
Sleep deprivation	<ul style="list-style-type: none"> • Noise-reduction strategies • Scheduling of nighttime medications, procedures, and nursing activities to allow uninterrupted period of sleep.
Vision impairment	<ul style="list-style-type: none"> • Provision of vision aids (e.g., magnifiers, special lighting) • Provision of adaptive equipment (e.g., illuminated phone dials, large-print books)
Hearing impairment	<ul style="list-style-type: none"> • Provision of amplifying devices; repair hearing aids • Instruct staff in communication methods
Dehydration	<ul style="list-style-type: none"> • Early recognition and volume repletion

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