The American Geriatrics Society/National Institute on Aging Bedside-to-Bench Conference: Research Agenda on Delirium in Older Adults

AGS/NIA Delirium Conference Writing Group, Planning Committee and Faculty

BACKGROUND

Delirium can be thought of as acute brain failure that occurs when stressors exceed the brain’s homeostatic reserve (Figure 2). Celsus initially described delirium in the 1st century CE (c. 47 CE, Aulus Cornelius Celsus, De Medicina, 2.7.28), but little in the way of progress was made until the early 1980s, when delirium first appeared in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM III). The most current definition of delirium was recently published in the 5th edition of the DSM and includes a disturbance in attention and awareness; a change in cognition that is not better accounted for by a preexisting, established, or evolving dementia; that the disturbance develops over a short period and tends to fluctuate during the course of the day, and that there is evidence that a direct physiological consequence of a general medical condition, an intoxicating substance, medication use, or more than one etiology causes the disturbance. The DSM definition can be difficult to operationalize or quantify in certain settings. Although a number of approaches exist, the diagnostic approach most commonly used is the Confusion Assessment Method (CAM) four-item diagnostic algorithm, which trained physicians and nurses and other allied health personnel can apply; the use of the CAM format for delirium evaluation has expanded widely, and valid and reliable forms are now in use in numerous healthcare settings (e.g., b-CAM for “brief” emergency medicine evaluations, p-CAM intensive care unit (ICU) for pediatric use, and CAM-ICU for intensive care unit use). Different clinical phenotypes have been described, including the psychomotor variants of hyperactive and hypoactive delirium, frank hallucinations or delusions, and abnormal levels of consciousness. The incidence of delirium varies widely depending upon the population studied, ranging from approximately 15% after some types of elective surgery to as high as 80% in ICU populations. Delirium is associated with a variety of poor outcomes, including cognitive and functional decline, longer hospital stay, greater healthcare use, and long-term morbidity and mortality. The number of indexed articles in standard bibliographic databases on delirium has increased from fewer than 50 per year in the 1980s to more than 350 per year in 2012, highlighting increased efforts to differentiate delirium from other cognitive disorders and the impetus for developing novel treatment strategies.

DELIRIUM: INTERFACE WITH OTHER GERIATRIC SYNDROMES

The relationships between delirium and other geriatric syndromes such as sleep disorders, voiding dysfunction, and...
Delirium is a common geriatric syndrome characterized by disturbances in attention and cognition. Sleep disturbances are frequently accompanied by delirium, and the two are often associated. Sleep disorders, including insomnia, sleep apnea, and restless legs syndrome, can contribute to delirium in some clinical settings.

The relationship between sleep and delirium may be linked through impaired circadian rhythms and lower melatonin secretion observed during delirium. Sleep disturbances and delirium may be linked through impaired circadian rhythms and lower melatonin secretion observed during delirium. Sleep disturbances and delirium are common in older adults and may result from a combination of age-related changes in sleep physiology, co-morbid conditions, medications, primary sleep disorders, and other factors. Thus, sleep complaints in older adults may be viewed as a geriatric syndrome. Sleep disturbances and delirium may be linked through impaired circadian rhythms and lower melatonin secretion observed during delirium. Alternatively, sleep deprivation and other primary sleep disorders such as obstructive sleep apnea may contribute to delirium in some clinical settings. Sleep disturbance and disruption of circadian cycling is a common feature accompanying delirium. Additional data suggesting an association between sleep disturbances and delirium come from studies that seek to improve sleep of hospitalized individuals that have also observed reductions in delirium. The multifactorial Hospital Elder Life Program intervention strategy and the Johns Hopkins quality improvement intervention included nonpharmacological sleep protocols and demonstrated that fewer people developed delirium. Although a variety of interventions have been developed, research is needed to better understand the pathophysiological basis of the relationship between altered sleep and delirium in older adults and to use such information to develop and validate interventions that are optimally suited for individuals at risk for both conditions.

Voiding dysfunction and delirium are classic geriatric syndromes that share multifactorial etiologies and often coexist in the same individual. Nevertheless, there has been little exploration of the relationship between these two syndromes. A wealth of knowledge has been gained from functional and structural neuroimaging studies exploring the role of specific brain circuits in the ability of the nervous system to sense, process, and implement actions relevant to continence and voiding based on bladder filling and a variety of other nongenitourinary factors, which indicates an important role of the brain in voiding dysfunction. Nevertheless, the hypothesized association between delirium and bladder function or incontinence is based more on clinical observations than systematic research reports, yet three lines of evidence support an association between these two syndromes. First, voiding dysfunction and urinary incontinence are common in patients with delirium and can be challenging to manage in individuals with clouded sensorium who may have difficulty attending to their voiding needs. Second, a condition known as cystocerebral syndrome, in which cognitive decline is observed in the setting of acute or subacute urinary retention, is likely to be much more common than the six case reports in the literature would suggest.

Third, urinary tract infections, as with all infections, are a common cause of delirium. Finally, although treatments for voiding dysfunction, including urinary catheters and anticholinergic medications, may be associated with delirium, bladder antispasmodics alone appear to be a rare cause of delirium. From a pathophysiological standpoint, further research is needed to understand the bidirectional relationships between sleep disturbances, incontinence, and delirium, including their underlying central processes in elderly adults, and to use such information to develop and validate interventions optimally suited for individuals with these overlapping conditions.

The geriatric conditions of delirium and frailty, although phenotypically distinct, may represent different clinical manifestations of age-related vulnerability and yet the potential associations between these conditions are not well understood. From an epidemiological perspective, frailty may serve as a risk factor for delirium and vice versa. For example, in individuals undergoing noncardiac or vascular surgery, preoperative frailty is independently associated with greater odds of developing postoperative delirium. Conversely, although no studies have directly linked delirium with the subsequent development of frailty, evidence supports an association between delirium and poor outcomes. For example, delirium after an acute illness or surgery is an independent predictor of cognitive
The pathophysiological mechanisms common to delirium and frailty include high baseline levels of inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha, high oxidative stress, mitochondrial dysfunction, high free radical production, cellular senescence, and dysregulation of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system that may result in aberrant stress responses. Alone or in combination, these mechanisms are implicated in the dysregulation of neuronal activity (delirium) and the loss of network complexity between physiological systems (frailty). A better understanding of the common mechanisms between delirium and frailty may aid in the development of multicomponent prevention and treatment strategies for both conditions.

**STRESS PHYSIOLOGY, IMMUNOLOGY, AND DELIRIUM**

By definition, most delirium in older adults is associated with concomitant medical or surgical illness, an observation that has suggested a role for one or more stressors. In general, older adults are thought to have less physiological reserve and therefore less capacity to maintain homeostasis in response to stress (homeostenosis) than younger individuals. The effects of stressors are probably coordinated rather than independent, and the affected systems are interrelated rather than isolated. Psychoneuroimmunology is the study of the complex interactions between psychological, neural, and immunological processes in response to stress. Neuroimmunology systems appear to be related to the pathophysiology of delirium, specifically because delirium may be the human manifestation of an exaggerated or maladaptive form of “sickness syndrome,” which is the sum of the coordinated adaptive changes that occur in individuals, primarily in response to infection.

Two lines of experimental evidence highlight the role of neuroinflammation in delirium pathophysiology through alteration of the blood–brain barrier (BBB) and de novo synthesis or elaboration of inflammatory mediators in the central nervous system (CNS). The BBB normally protects the CNS, but BBB dysfunction can expose neuronal tissue to systemic inflammatory mediators and may lead to delirium. Alteration of BBB endothelial cells has been associated with greater BBB permeability and impaired brain microcirculation, and systemic endothelial dysfunction is associated with delirium during critical illness.

Neuroinflammatory activity also appears to play a role in neurotransmitter dysregulation. Cholinergic hypofunction has been implicated in delirium and demonstrated as a susceptibility factor for acute inflammation-induced cognitive dysfunction in mice. High CNS IL-6 levels are associated with degeneration of gamma-aminobutyric acid (GABA)ergic interneurons and the development of delirium. IL-1β and cyclooxygenase-1-derived prostaglandins have been shown to be causative of acute cognitive dysfunction in an animal model of delirium superimposed on dementia. Studies of GABAergic medications (e.g., benzodiazepines), which have been associated with a high incidence of delirium, provide clinical data in support of GABAergic dysregulation contributing to delirium.

One of the interesting implications of the construct of psychoneuroimmunology in relationship to delirium is the potential for psychological factors to play a role. Factors influencing resilience (the capacity to manage or adapt to insult) have recently been described as components of the construct of reserve capacity. Conceptually, enhanced emotional and physiological reactivity to stress may be due to a deficiency in reserve capacity or limited opportunities to replenish reserve resources. Psychosocial therapeutic approaches attempting to improve reserve may present a novel treatment strategy to reduce the severity of pathophysiological insults and thereby improve delirium and long-term cognitive outcomes.

Understanding the cognitive manifestations of the specific and interrelated mechanisms underlying delirium remains a fundamental challenge. Animal models provide a unique opportunity to determine whether purported associations are actually causal. Pragmatically, an animal model may examine a subset of crucial processes in delirium. A recurring debate throughout the conference was the relevance of animal models to understanding the multifaceted complexity of delirium in humans and their role in promoting translation of mechanistic findings to potential therapies. Animal research has focused on specific mechanisms by which psychoneuroimmunological systems may lead to delirium. We are only beginning to understand the ways in which mechanisms such as predisposing factors (neurodegenerative disease, hypocholinergia, or primed microglia) may interact with precipitating factors such as inflammation to cause delirium.

**DELIRIUM BIOMARKERS: ASSOCIATIONS WITH DEMENTIA**

The term “biomarker,” a portmanteau of “biological marker,” refers to a broad subcategory of medical signs—that is, “objective indications of medical state observed from outside the patient—which can be measured accurately and reproducibly.” Biomarkers could potentially be used to clarify diagnoses, distinguish subtypes or phenotypes of delirium, and evaluate responses to interventions. Biomarkers for delirium might be developed using four broad technological approaches: body fluids (e.g., cerebrospinal fluid (CSF), blood, urine), yielding genetic, molecular or cellular measures; solid tissue samples, yielding molecular, cellular, or histopathological measures; physiological measures such as electroencephalography (EEG); or imaging measures from modalities such as magnetic resonance imaging (MRI) and positron emission tomography.

Of the body fluids, CSF provides perhaps the best insight into the CNS but can be difficult to obtain, particularly on a longitudinal basis. Although blood is much more accessible, the sensitivity and specificity of blood markers for delirium remain problematic. Much of the work in delirium has evolved from work on inflammation and dementia. Previous studies suggest that the pathological hallmarks of Alzheimer’s disease (AD) such as amyloid-beta (Aβ) and tau may signal the presence of neuroinflam-
mation, which may in turn increase vulnerability to postoperative delirium. Low Aβ:tau ratios in the CSF are typically seen in individuals with AD, and a study of 133 individuals who underwent total hip or knee replacement using spinal anesthesia demonstrated that individuals with the lowest quartile of preoperative CSF Aβ:tau ratios had higher incidence and greater symptom severity of postoperative delirium.55 Other evidence points to the role of genetic risk factors, such as apolipoprotein E (APOE) genotype, in delirium.56 Currently, the presence of one or more APOE ε4 alleles has been reported to be an independent predictor of delirium duration in critical illness, after adjusting for covariates,57 and it increases the risk of delirium in older adults undergoing surgery,58 although other studies report no association between APOE genotype and delirium.59,60

With aging, the brain shows dramatic systematic changes under general anesthesia. These dynamics are readily visible on EEG and can be used to monitor the state of elderly adults under general anesthesia. This approach offers a more-principled way of dosing anesthetics and may also help reduce the incidence of delirium and postoperative cognitive dysfunction in elderly adults after surgery and anesthesia.60 EEG provides a temporal precision that other imaging modalities do not afford in that polysomnography, examining sleep-wake architecture, and quantitative EEG, direct assessment of electrical activity in the brain, can be used to quantify the presence, severity, and duration of delirium in a reproducible manner. EEG as a diagnostic tool has been thought to be second only to the CAM in sensitivity and specificity as a delirium assessment.61

Numerous neuroimaging studies have explored the association between delirium and structural and functional changes in the brain.62 Cross-sectional evidence supports an association between delirium severity and several neuroimaging findings, including grey matter atrophy and white matter hyperintensities (WMHs) on MRI.63 White matter changes indicative of vasogenic edema on diffusion-weighted imaging (DWI),64 loss of white matter integrity evidenced by low fractional anisotropy (FA) on diffusion tensor imaging (DTI),65 low regional cerebral blood flow (rCBF) measured using positron emission tomography,66,67 and alteration in functional connectivity measured by resting-state functional MRI (fMRI).68 Longitudinal studies, although limited, suggest that greater severity of delirium is associated with subsequent grey matter atrophy,69 loss of white matter integrity,70 and low rCBF in AD-relevant regions.66 Regional anatomical changes in the frontosubcortical network65 and altered functional connectivity in these areas provide biological substrates for clinical symptoms of delirium. Major limitations of these studies include poor pre- and postdelirium structural and functional characterization of the brain, heterogeneous etiologies of delirium and neuroimaging findings, broad range of age groups studied, and limited statistical adjustment for multiple confounders linked to delirium, dementia, and age-related brain changes.

Last, clinical biomarker use increases back-translation for preclinical models of delirium. Similar CNS alterations measured using EEG and imaging modalities, as described above, have been recapitulated in rodent models of inflamma-

**DELIRIUM AND COGNITIVE SEQUELAE**

Delirium can develop in individuals along the spectrum of cognitive function, although a growing body of evidence supports baseline cognitive impairment or dementia as one of the strongest predisposing risk factors for delirium.72–75 Delirium was previously thought to be a self-limiting syndrome, but the long-term effects of delirium on cognitive function are now recognized. First, those with baseline cognitive impairment and dementia who develop delirium experience a more-rapid decline in cognitive function than those who never develop delirium.76,77 Delirium also appears to fundamentally alter the slope of cognitive decline in persons with dementia.78 Second, in cognitively intact individuals undergoing cardiac surgery, delirium was associated with an acute decline in cognitive status and prolonged cognitive dysfunction that did not fully resolve even 12 months after surgery.25 Finally, in critically ill individuals, many of whom did not have evidence of cognitive impairment before their illness, the duration of delirium was independently associated with cognitive decline or new cognitive impairments, independent of age or other comorbidity medical conditions.79 Thus, delirium appears to worsen cognitive functioning in those with preexisting cognitive impairment and dementia and may result in de novo cognitive impairment in those with previously normal cognition.

The mechanisms underpinning the clinical associations between acute brain dysfunction and chronic cognitive impairments are incompletely understood and are an area of ongoing exploration. Neuroimaging studies in individuals with delirium reveal a variety of abnormalities noted above. Autopsy studies in individuals with cognitive decline in the setting of delirium reveal a pathological profile different from classical dementia profiles (e.g., AD or vascular dementia); when classical findings were present, the combination of delirium and such findings predicted worse cognitive outcomes than would be expected with either alone.77

**DELIRIUM INTERVENTIONS**

Interventions to prevent or manage an episode of delirium can be divided into pharmacological and nonpharmacological strategies. Pharmacological agents such as typical and atypical antipsychotics are the most commonly used drugs in clinical practice and have been studied for delirium prevention and treatment. Nevertheless, emerging literature suggests that these agents may have limited efficacy, particularly for treatment.80,81 Nonpharmacological measures have been more successful, particularly multicomponent preventive interventions that focus on assessment of delirium risk factors and proactive approaches to reduce these risk factors.82 Multicomponent treatment interventions typically include standardized delirium case identification strategies, assessment and treatment of modifiable predisposing and precipitating factors, prevention and management of common complications, and restoration of
cognitive and physical function. Evidence suggests that the effectiveness of these interventions may be specific to the clinical setting. It appears to be easier to prevent an episode of delirium than it is to treat delirium once present.

Most delirium prevention strategies have focused on delirium risk factor modification and reducing physiological stressors. An alternative method of preventing delirium may be to increase the individual’s homeostatic reserve to enhance the ability to compensate for physiological stress using methods such as “prehabilitation.” This may be especially pertinent when the stressor is preplanned, such as elective or semi-urgent major surgery (e.g., joint replacement). Prehabilitation is a multidisciplinary approach that combines physical (e.g., exercise, nutrition) and psychological strategies to minimize treatment-related mortality and morbidity. Enhancing resiliency is another potential approach. Optimism, coping strategies, and social engagement or support are associated with resiliency and, although not yet examined, may be applicable to delirium prevention.

Because no widely accepted delirium management intervention is available, novel strategies are needed. The ideal delirium intervention should be highly potent; simple and easily standardized; and acceptable to individuals, families, and hospital staff and have minimal adverse effects. Because delirium is a complex syndrome, it is likely that a multipronged pleiotropic approach will be needed to maximize the potency of any intervention. Although standardized protocols are preferred, certain components of any delirium intervention may be personalized. For example, cognitively stimulating recreational activities have been evaluated for the treatment of delirium, and these activities have been customized to individual abilities, interests, and preferences. Increasing understanding of the relationship between biomarkers, delirium, and outcomes may assist in designing targeted interventions based on biomarker profiles and tracking biological response to these interventions.

There are important methodological considerations when evaluating novel delirium interventions in clinical trials. The population, outcome, and exposure must be carefully described. Understanding the population is vital because effect sizes may vary depending on the proportion of individuals with dementia, frailty, or critical illness. Furthermore, delirium outcomes can be considered in a number of ways: occurrence (binary), absolute duration, time-varying outcomes, severity, or a combination of these. Exactly how outcomes are measured and operationalized directly influences statistical power.

Delirium duration is a common outcome variable in many delirium intervention trials and is often used as a surrogate for delirium severity, but this outcome can be biased because of death, and interventions that reduce delirium duration have not been shown to reduce mortality in the ICU. There is no universally accepted delirium severity scale. Many overemphasize the hyperactive symptoms of delirium and thus may underdetect or underrate hypoactive delirium, although the recently introduced four-item CAM severity score is an attempt to address this. Developing standardized delirium severity measures or adding objectively quantifiable measures (e.g., biomarkers) would not only potentially provide a more-valid outcome measure for intervention trials, but would also facilitate comparisons of results across future studies.

The effects of delirium on healthcare use and long-term needs (described above) are becoming clear. Thus, delirium trials are increasingly including relevant secondary outcomes such as healthcare resource utilization, hospital length of stay, institutionalization, and caregiver burden. Attrition, usually through death, complicates such studies involving older persons—highlighting the importance of appropriate use of statistical methods to avoid biased results. Premorbid cognition is often difficult to ascertain in many populations with delirium (other than elective surgery), although it could be more reliably determined if prospectively assessed in the context of a cohort study. Regardless of which population, exposure, and outcome are used, delirium intervention trials should have adequate sample sizes to allow for subgroup analyses. It is possible that specific subgroups of individuals (e.g., delirium superimposed on dementia or hypoactive delirium) may vary in their response to different intervention strategies.

Accurate delirium ascertainment is fundamental to trial validity. Delirium is a clinical diagnosis and therefore requires standardized training of study personnel and continuous quality control to ensure reliable assessment throughout the conduct of trial. It is also important to describe the training methods and quality control efforts in the resulting manuscript. Fluctuations in delirium may also demand repeated assessment schedules to minimize false negatives. Moreover, diagnosis of delirium can be difficult in certain populations, such as individuals with dementia and those with hypoactive delirium. Consensus panel adjudication is more costly but reduces variability even among well-trained researchers and clinicians. Novel statistical approaches, such as item-response theory, can help harmonize case-ascertainment methods across different studies by accounting for mixtures of clinical populations, although there is no substitute for carefully operationalized delirium outcome measures.

Specific intervention approaches may pertain in special populations, such as individuals undergoing surgery and receiving anesthesia. The acute stress and inflammation associated with surgery places vulnerable older adults at risk of delirium. The risk of postoperative delirium is believed to be related to the invasiveness of the surgical procedure and is affected by a number of other factors including comorbid conditions, timing of anesthetic administration in relation to surgical incision, and factors associated with recovery from the operation such as medications, pain, and anxiety. The type and method of anesthetic administration can modify the stress response and thus may serve as one way to decrease the risk of postoperative delirium. For example, although inhaled anesthetics only mildly suppress the cortisol response to surgery, total intravenous anesthesia with propofol significantly blunts the stress response whereas neuraxial (spinal or epidural) anesthesia may result in near-complete suppression of the stress response. Thus, it is hypothesized that the choice of anesthetic or anesthesia technique could influence the incidence of postoperative delirium. Although the existing literature has not shown a difference, this is an area of ongoing study.
The choice of anesthetic or anesthesia technique and other hypotheses are the focus of 28 ongoing trials identified in ClinicalTrials.gov evaluating delirium prevention and treatment in the perioperative setting as a primary or secondary outcome. The majority of these studies are enrolling participants aged 60 and older who are undergoing cardiovascular, orthopedic, or other “major” surgical interventions. Ten of these trials are evaluating pharmacological treatment of delirium and are evaluating a variety of drugs including dexmedetomidine, statins, beta-blockers, antipsychotics, and insulin. Intraoperative management strategies are being evaluated in eight trials comparing novel and conventional anesthetics, intravenous and inhaled anesthetics, and “light” and “deep” anesthesia. Postoperative pain management strategies (e.g., regional vs intravenous analgescs) are the focus of five trials. Finally, five studies are evaluating nonpharmacological interventions including physical therapy, hypnotherapy, the Hospital Elder Life Program, treatment of sleep apnea, and remote ischemic preconditioning.

Once a delirium intervention is available, wide-scale implementation in clinical practice remains a challenge. Traditionally, the translational cycle from discovery to delivery has been inefficient, taking an average of 17 years and costing more than $1 billion, with limited generalizability and success.100 There is major opportunity to shorten this cycle and enhance its efficiency through collaborative clinical networks using well-tested methods for widespread dissemination of information and technology.

CONCLUSIONS AND FUTURE RESEARCH PRIORITIES

A number of conclusions and research priorities emerged from the talks and discussions at the conference. These are listed below, according to broad categories.

Delirium and Geriatric Syndromes

Studies should examine the clinical, physiological, and molecular commonalities between delirium and other geriatric syndromes, including sleep disorders and voiding dysfunction, and search for intervention opportunities that might be appropriate for individuals at risk of, or experiencing, more than one of these syndromes.

Examination of the relative strengths of frailty measures to predict delirium in a variety of clinical settings should be evaluated, as should the role of delirium in the subsequent development of frailty in medical and surgical settings. Such studies should consider clinical, physiological, and molecular predictors of both entities.

Delirium Phenomenology

Better understanding of and ability to distinguish differing manifestations of delirium (e.g., hypoactive, hyperactive, superimposed on dementia) will be vital to disentangling the relationship between delirium, dementia, and other neurological conditions.

Through better understanding of phenomenology, etiology, and pathogenesis of delirium, whether delirium represents a single coherent syndrome or whether it would be preferable to divide delirium into several distinct entities needs to be determined. One such division could be delirium in individuals with preexisting or preclinical dementia versus delirium in individuals with otherwise healthy brains.

Delirium Pathophysiology and Basic Mechanisms

Study of psychoneuroimmunological systems is imperative to advancing the understanding of delirium pathophysiology and may provide potential targets (e.g., modulation of endothelial function, BBB permeability, neuroinflammation, cognitive reserve) for developing novel approaches to delirium prevention and treatment.

Examination of the interaction between multiple neurotransmitter systems and psychoneuroimmunological pathways could provide opportunities to maximize resilience to stress and decrease delirium incidence.

Pharmacological and psychosocial treatment strategies should be used as physiological probes to better understand the role of aberrant chemical imbalances in the CNS (e.g., cholinergic hypofunction, gabaminergic dysregulation), stress triggers (e.g., sepsis, malnutrition), and cognitive and systemic health factors (e.g., exercise, resilience, sleep hygiene) in delirium pathophysiology.

Biomarkers of Delirium

Identification of clinically relevant biomarkers for different potential pathways of delirium, including inflammation, microglial activity, and brain injury; EEG patterns; and imaging protocols for various neural networks and the BBB will advance basic understanding and clinical management of delirium. Moreover, distinction between markers of delirium risk, presence, and severity remains to be developed.

Application of concurrent multimodal neuroimaging techniques before and after delirium should be used to examine brain alterations such as amyloid deposition, neuropeptide and neurotransmitter tracers, cerebral microbleeding, and cerebral arterial blood flow measures along with more-standard neuroimaging techniques (MRI, fMRI, DTI, perfusion-weighted imaging) to provide a broad-based assessment of neuroimaging correlates of delirium.

Identification of neuroimaging biomarkers of delirium using existing neuroimaging data sets such as the Alzheimer’s Disease Neuroimaging Initiative could provide an efficient approach to moving the field forward.

MEASUREMENT AND QUALITY CONTROL IN DELIRIUM RESEARCH

There is a need to develop minimum standards for delirium assessment and quality control for implementation in all patient-oriented research studies.

There is a need to develop similar standards for definition of delirium in animal models.

Minimum standards should be also developed for data collection of outcomes and biomarkers to be applied to large, ongoing observational delirium studies.
Clinical and Intervention Studies for Delirium

Strong consideration should be given to including cognitive impairment as a primary or secondary outcome of clinical interventions for delirium regardless of age or comorbidity. Similarly, functional and economic measures closely related to delirium (e.g., acute hospital length of stay) should also be strongly considered as secondary outcomes.

Increasing the individual’s homeostatic reserve to withstand physiological stress is an emerging concept in delirium prevention. Prehabilitation and increasing resiliency may be useful to increase homeostatic reserve.

There is an ongoing need to investigate the role of anesthetics in modulating the perioperative acute stress response and other potentially modifiable risk factors for delirium in the perioperative setting.

The creation of a delirium research consortium for leveraging existing data to advance the study of delirium would be extremely useful.

APPENDIX. AUTHORS AND AFFILIATIONS

Multiple authors were engaged in the preparation of this paper through service on the Writing Group and the Planning Committee and as presenters. The following key identifies how an author was engaged with this paper: Writing Group (1); Planning Committee (2); Presenter (3). Alphabetical listing of authors: Cathy Alessi, MD, AGSF, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, and Geriatric Research, Education and Clinical Center, VA Greater Los Angeles Healthcare System, North Hills, CA (3); Andrew Auerbach, MD, School of Medicine, University of California, San Francisco, San Francisco, CA (3); Thiago J. Avelino-Silva, MD, University of São Paulo Medical School, São Paulo, Brazil (1); Malaz Boustani, MD, MPH, School of Medicine, Indiana University, Indianapolis, IN (2, 3); Emery Brown, MD, PhD, Harvard Medical School, Massachusetts General Hospital, Boston, MA, and Massachusetts Institute of Technology, Cambridge, MA (3); Nathan E. Brummel, MD, MSCl, School of Medicine, Vanderbilt University, Nashville, TN (1); Noll Campbell, PharmD, College of Pharmacy, Purdue University, West Lafayette, IN (1); Colm Cunningham, PhD, School of Biochemistry and Immunology, Trinity College Institute of Neuroscience, Trinity College Dublin, Ireland (3); Daniel Davis, MB ChB, University College London, London, UK (1, 3); Stacie Deiner, MD, MS, Icahn School of Medicine, Mount Sinai, New York, NY (1, 3); Laura Dugan, MD, School of Medicine, Vanderbilt University, Nashville, TN (3); Basil Eldadah, MD, PhD, National Institute on Aging, Bethesda, MD (2); E. Wesley Ely, MD, MPH, School of Medicine, Vanderbilt University and Tenessee Valley VA-Healthcare System, Nashville, TN (2, 3); Donna Fick, RN, PhD, College of Nursing, College of Medicine, Pennsylvania State University, University Park, PA (3); Robert Gould, PhD, School of Medicine, Vanderbilt University, Nashville, TN (1); Jennie Chin Hansen, RN, MSN, American Geriatrics Society, New York, NY (3); Jin Ho Han, MD, MSc, School of Medicine, Vanderbilt University, Nashville, TN (1); Kathleen M. Hayden, PhD, School of Medicine, Duke University, Durham, NC (1); Ramona O. Hopkins, PhD, College of Life Sciences, Brigham Young University, Provo, UT, and Intermountain Medical Center, Murray, UT (3); Christopher G. Hughes, MD, School of Medicine, Vanderbilt University, Nashville, TN (1, 3); William W. Hung, MD (AGS Junior Faculty Representative), Icahn School of Medicine, Mount Sinai, New York, NY (2); Sharon K. Inouye, MD, MPH, Harvard Medical School, Beth Israel Deaconess Medical Center and Hebrew Senior-Life, Boston, MA (2, 3); Dilip V. Jeste, MD, School of Medicine, University of California, San Diego, La Jolla, CA (3); Richard Jones, ScD, Alpert Medical School, Brown University, Providence, RI (3); Maura Kennedy, MD, Beth Israel Deaconess Medical Center, Boston, MA (1); Babar A. Khan, MD, School of Medicine, Indiana University, Indianapolis, IN (1); Eyal Kimchi, MD, PhD, Massachusetts General Hospital, Boston, MA (1); Neelesh K. Nadkarni, MD, PhD, FRCPC, School of Medicine, University of Pittsburgh, Pittsburgh, PA (1); George Kuchel, MD, (Principal Investigator for the Series of Beds-to-Bench Conferences), University of Connecticut Center on Aging, Farmington, CT (2); Hochang Benjamin Lee, MD, School of Medicine, Yale University, New Haven, CT (2, 3); Edward Marcantonio, MD, SM (Co-chair), Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA (1, 2, 3); Arvind Nana, MD, University of North Texas Health Science Center, Fort Worth, TX (1); Esther Oh, MD, PhD, School of Medicine, Johns Hopkins University, Baltimore, MD (1); Pratik Pandharipande, MD, School of Medicine, Vanderbilt University, Nashville, TN (3); Neil Resnick, MD, School of Medicine, University of Pittsburgh, Pittsburgh, PA (3); Thomas Robinson, MD, MS, School of Medicine, University of Colorado, Aurora, CO (1, 2, 3); Jane Szczyski, PhD, University of Massachusetts Medical School, Worcester, MA (1); Frederick Sieber, MD, School of Medicine, Johns Hopkins University, Baltimore, MD (3); Jeffrey H. Silverstein, MD, (Co-chair), Icahn School of Medicine, Mount Sinai, New York, NY (1, 2, 3); Lily Spanjevic, RN, BScN, MN, Joseph Brant Hospital, McMaster University, Burlington, ON, Canada (1); Judith Tate, PhD, RN, College of Nursing, The Ohio State University, Columbus, OH (1); Sarinappha (Fah) Vasunilashorn, PhD, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA (1); Jeremy Walston, MD, School of Medicine, Johns Hopkins University, Baltimore, MD (3); Zhongcong Xie, MD, PhD, Harvard Medical School and Massachusetts General Hospital, Boston, MA (2, 3).

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REFERENCES

40. van Munster BC, Korse CM, de Rooij SE et al. Markers of cerebral dam-
age during delirium in elderly patients with hip fracture. BMC Neuro-

41. Hughes CG, Morandi A, Girard TD et al. Association between endo-
theial dysfunction and acute brain dysfunction during critical illness. Anes-

42. vanGool WA, van de Beek D, Eikelenboom P. Systemic infection and
delirium: When cytokines and acetylcholine collide. Lancet 2010;
375:773–775.

43. Field RH, Gossen A, Cunningham C. Prior pathology in the basal fore-
brain cholinergic system predisposes to inflammation-induced working
memory deficits: Reconciling inflammatory and cholinergic hypotheses of

44. Dugan LL, Ali SS, Shekhtman G et al. IL-6 mediated degeneration of fore-
brain GABAergic interneurons and cognitive impairment in aged mice
through activation of neuronal NADPH oxidase. PLoS ONE 2009;4:
e5518.

45. Westhoff D, Witlox J, Koenderman L et al. Preoperative cerebrospinal
fluid cytokine levels and the risk of postoperative delirium in elderly hip

46. Griffin EW, Skelly DT, Murray CI et al. Cyclooxygenase-1-dependent
prostaglandins mediate susceptibility to systemic inflammation-induced

47. Pandharipande P, Shintani A, Peterson J et al. Lorazepam is an indepen-
dent risk factor for transitioning to delirium in intensive care unit

48. Stewart DE, Yuen T. A systematic review of resilience in the physically ill.

49. Jones RN, Fong TG, Metzger E et al. Aging, brain disease, and reserve:

50. Barnett JH, Salmond CH, Jones PB et al. Cognitive reserve in neuropsy-

51. Jeste DV, Savla GN, Thompson WK et al. Association between older age
and more successful aging: Critical role of resilience and depression. Am J

52. Murray C, Sanderson DJ, Barkus C et al. Systemic inflammation induces
acute working memory deficits in the primed brain: relevance for delir-

53. Cunningham C, Wilcockson DC, Campion S et al. Central and systemic
endotoxin challenges exacerbate the local inflammatory response and
increase neuronal death during chronic neurodegeneration. J Neurosci

54. Strimbu K, Tavel JA. What are biomarkers?Curr Opin HIV AIDS
2010;5:463–466.

55. Xie Z, McAuliffe S, Swain CA et al. Cerebrospinal fluid αf to tau ratio

56. Alexander SA, Ren D, Gunn SR et al. Interleukin 6 and apolipoprotein E
as predictors of acute brain dysfunction and survival in critical care

57. Ely EW, Girard TD, Shintani AK et al. Apolipoprotein E4 polymorphism
as a genetic predisposition to delirium in critically ill patients. Crit Care

58. Leung JM, Sands LP, Wang Y et al. Apolipoprotein E e4 allele increases
the risk of early postoperative delirium in older patients undergoing non-

59. Adams D, Van Munster BC, Macdonald AJ. The genetics of deliria. Int REV

60. Brown EN, Purdon PL. The aging brain and anesthesia. Curr Opin Anaes-

superimposed on dementia: A systematic review. J Am Geriatr Soc

62. Alsop DC, Fearing MA, Johnson K et al. The role of neuroimaging in elu-

63. Gunther ML, Morandi A, Krauskopf E et al. The association between
brain volumes, delirium duration, and cognitive outcomes in intensive care
unit survivors as determined by diffusion tensor imaging. J Neurol

64. Yokota H, Ogawa S, Kurokawa A et al. Regional cerebral blood flow in

507.

66. Jackson JC, Hopkins RO, Miller RR et al. Acute respiratory distress syn-
drome, sepsis, and cognitive decline: A review and case study. South Med

67. Morandi A, Rogers RP, Gunther ML et al. The relationship between delir-
ium duration, white matter integrity, and cognitive impairment in inten-
sive care unit survivors as determined by diffusion tensor imaging: The
VISIONS prospective cohort magnetic resonance imaging study*. J Crit

68. Semmler A, Herrmann S, Mormann F et al. Sepsis causes neuroinflamma-
tion and concomitant decrease of cerebral metabolism. J Neuroinflamma-
tion 2008;5:38.

69. Inouye SK, Viscoli CM, Horwitz RI et al. A predictive model for delirium
in hospitalized elderly medical patients based on admission characteristics.

70. Inouye SK, Zhang Y, Jones RN et al. Risk factors for delirium at dis-
charge: Development and validation of a predictive model. Arch Intern

71. Khan BB, Zawahiri M, Campbell NL et al. Delirium in hospitalized
patients: Implications of current evidence on clinical practice and future
589.

72. Davis DH, Skelly DT, Murray C et al. Worsening cognitive impairment

73. Davis DH, Muniz Terrera G, Keage H et al. Delirium is a strong risk fac-
tor for dementia in the oldest-old: A population-based cohort study. Brain

74. Gross AL, Jones RN, Hambelmann DA et al. Delirium and long-term
cognitive trajectory among persons with dementia. Arch Intern Med

75. Pandharipande PP, Girard TD, Jackson JC et al. Long-term cognitive

76. Friedmann JL, Soleiman L, McGuire DP et al. Pharmacological treat-
ments of non-substance-withdrawal delirium: A systematic review of pro-

77. Inouye SK, Marcantonio ER, Metzger ED. Doing damage in delirium:
The hazards of antipsychotic treatment in elderly persons. Lancet Psy-

78. Inouye SK, Bogardus ST Jr, Charpentier PA et al. A multicomponent
intervention to prevent delirium in hospitalized older patients. N Engl J

79. Bergmann MA, Murphy KM, Kielty DK et al. A model for management of
1825.

80. Miloson K, Lemengre J, Braes T et al. Multicomponent intervention stra-
tegies for managing delirium in hospitalized older people: Systematic

81. Silver JK, Baima J. Cancer prehabilitation: An opportunity to decrease
therapy-related morbidity, increase cancer treatment options, and
improve physical and psychological health outcomes. Am J Phys Med

82. Young J, Murthy L, West M et al. Diagnosis, prevention, and manage-

83. Kolanowski AM, Fick DM, Clare L et al. Pilot study of a nonpharmacolo-
logical intervention for delirium superimposed on dementia. Res Gerontol

84. Davis DH, Kreisel SH, Muniz Terrera G et al. The epidemiology of delir-
ium: Challenges and opportunities for population studies. Am J Geriatr

85. Vasilevskis EE, Han JH, Hughes CG et al. Epidemiology and risk factors
for delirium across hospital settings. Best Pract Res Clin Anaesthesiol

86. Adams D. Statistical methods for analysing longitudinal data in delirium

87. Inouye SK, Viscoli CM, Horwitz RI et al. Randomized ICU trials do not
present an association between interventions that reduce delirium
duration and short-term mortality: A systematic review and meta-analysis.


