 0749–0690/98 $8.00 + .00

DELIRIUM IN HOSPITALIZED OLDER PATIENTS

Sharon K. Inouye, MD, MPH

Delirium, characterized as an acute disorder of attention and cognition, is a common, serious, and potentially preventable source of mortality and morbidity for older hospitalized patients. The problem of delirium in older hospitalized patients has assumed particular importance because patients aged 65 and older currently account for more than 48% of all days of hospital care.[1] Based on extrapolations from US vital health statistics,[76] each year delirium complicates hospital stays for more than 2.3 million older persons, involving more than 17.5 million inpatient days and accounting for more than $4 billion (1994 dollars) of Medicare expenditures. Moreover, substantial additional costs associated with delirium accrue after hospital discharge because of the increased need for nursing home placement, rehabilitation services, and home health care. These figures highlight the importance of delirium as a clinical and health policy problem.

This article discusses the epidemiology, risk factors, clinical manifestations, diagnosis and assessment, treatment, outcomes and prognosis, and potential preventive strategies for delirium.

Supported in part by grants from the National Institute on Aging (#RO1AG12551), the Commonwealth Fund (#95–47 and 94–90), and the Retirement Research Foundation (#94–71).

From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

EPIDEMIOLOGY

Prospective studies have demonstrated a prevalence of delirium—that is, cases present at the time of hospital admission—of 14% to 24%.* The incidence of delirium—that is, new cases arising during hospitalization—has been measured from 6% to 56%.[21,28,30,33,62,66] Postoperative delirium has been estimated to occur in 10% to 52% of patients.† Higher rates of delirium were found in studies that used more frequent and sensitive surveillance methods and that included older, surgical, and intensive care populations. These figures document the high occurrence rates of delirium in hospitalized older populations.

RISK FACTORS

Delirium represents an intrinsically multifactorial syndrome, similar to other common geriatric syndromes (e.g., falls, incontinence, and pressure sores). The multifactorial model (Fig. 1)[30] represents the complex interrelationship between a vulnerable patient with pertinent predisposing factors and noxious insults or precipitating factors. Thus, patients who are highly vulnerable to delirium at baseline (e.g., cognitively impaired or severely ill patients) may develop delirium with even relatively benign precipitating factors, such as a single dose of sleeping medication. Conversely, patients who are not vulnerable are relatively resistant, developing delirium only after exposure to multiple noxious insults. The effects of these risk factors may be cumulative, as demonstrated in previous studies.[30] The clinical importance of this multifactorial cause is that removing or treating one factor in isolation usually is not sufficient to resolve the delirium. Rather the full spectrum of vulnerability and precipitating factors needs to be addressed. Table 1 summarizes prospective risk factor studies for delirium, which identify both predisposing and precipitating factors for delirium.

Predisposing Factors

Predisposing factors identified in previous studies include baseline cognitive impairment or dementia, severe underlying illness and comorbidity, functional impairment, advanced age, chronic renal insufficiency, dehydration, malnutrition, and vision or hearing impairment. Dementia is an important and consistent risk factor for delirium across most studies, with demented patients having a two to five-fold increased risk for delirium. Moreover, one third to one half of delirious patients have underlying dementia. Virtually any underlying chronic medical illness can predispose to delirium, including primary central nervous system diseases (e.g., Parkinson's disease, cerebrovascular disease, mass lesions, trauma, infection,

*References 6, 11, 12, 16, 21, 27, 28, 37, 45, 62, 65.
†References 6, 7, 11, 15, 25, 26, 28, 37, 60, 67, 74, 79.

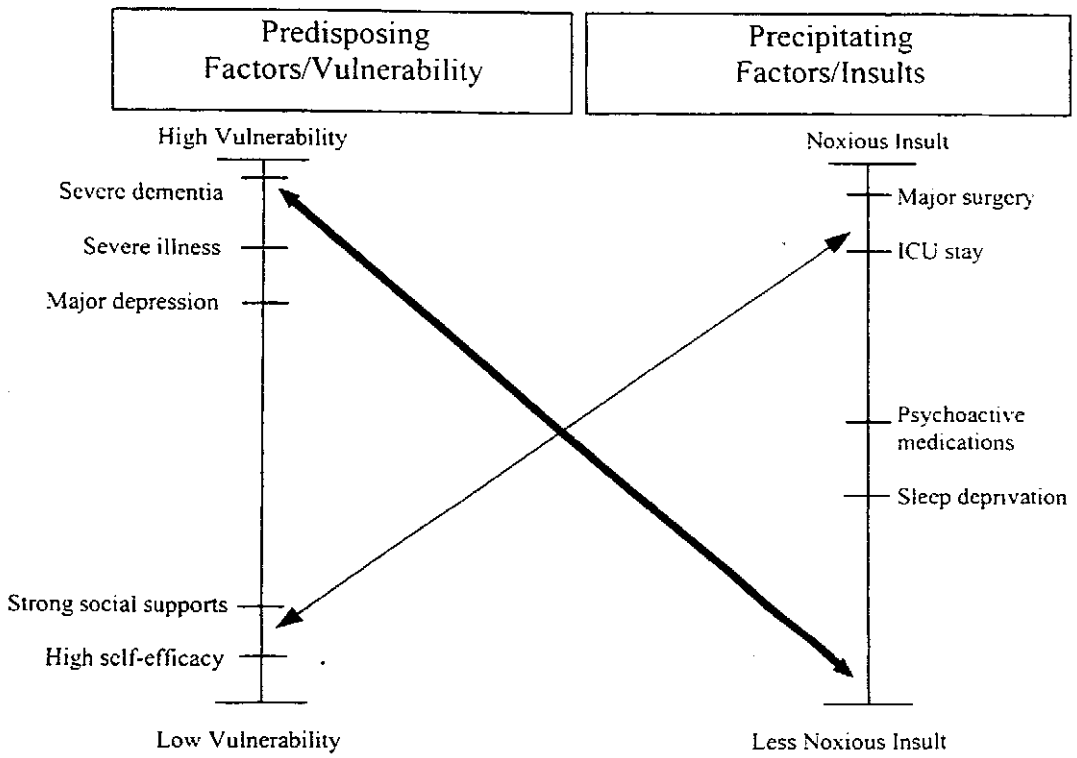

Figure 1. The development of delirium involves a complex interrelationship between baseline patient vulnerability (*left axis*) and precipitating factors or noxious insults occurring during hospitalization (*right axis*). For example, a patient with high vulnerability (e.g., severe dementia, severe underlying illness) may develop delirium with relatively benign insults (e.g., one dose of sleeping medication) (*black arrow*). Conversely, a patient with low vulnerability would require multiple noxious insults to develop delirium (*shaded arrow*). (*Data from* Inouye SK, Charpentier PA; Precipitating factors for delirium in hospitalized elderly persons: Predictive model and interrelationship with baseline vulnerability. JAMA 275:852, 1996.)

collagen vascular disease) as well as diseases outside the central nervous system, including infectious, metabolic, cardiac, pulmonary, endocrine, and neoplastic diseases. A clinical prediction rule,[29] developed to establish delirium risk at the time of hospital admission, identified the following independent predisposing factors: severe underlying illness, vision impairment, baseline cognitive impairment, and high blood urea nitrogen-to-creatinine ratio (an index of dehydration).

Precipitating Factors

Potential precipitating factors for delirium are innumerable and may include any noxious insult present during hospitalization. Leading factors identified in previous studies have included medications (see later), immobilization, use of indwelling bladder catheters, use of physical restraints, dehydration, malnutrition, iatrogenic events, medical illnesses, infections, metabolic derangement, alcohol or drug withdrawal, environmental influences, and psychosocial factors. Immobilization can lead to delirium and functional decline within just a few days,[13,41] yet physicians

Table 1. PROSPECTIVE STUDIES OF RISK FACTORS FOR DELIRIUM

Study	Population, Age (y), and Sample Size (n)	Independent Predictors for Delirium
Inouye, 1996[30]	Medical patients, age ≥70, n = 508	Precipitating factors (during hospitalization) Physical restraints Malnutrition >3 medications added in 24 h Bladder catheter Any iatrogenic event
Fisher, 1995[17]	Elective orthopedic patients, age ≥60, n = 80	Clock-drawing score ≥ 6 Male gender
Foy, 1995[20]	Medical patients, age ≥60, n = 418	Benzodiazepine use Age Hypoxia
Marcantonio, 1994[48]	Elective noncardiac surgery patients, >50 yrs, n = 1341	Age Alcohol abuse Cognitive impairment ASA class IV Abnormal sodium, potassium, glucose (preoperatively) Aortic aneurysm surgery Noncardiac thoracic surgery
Pompei, 1994[57]	Medical-surgical patients, age ≥70, n = 432	Cognitive impairment Comorbidity Depression Alcoholism
Inouye, 1993[33]	Medical patients, age ≥70, n = 281	Admission risk factors Vision impairment Severe illness Cognitive impairment High BUN/creatinine ratio
Jitapunkul, 1992[35]	Acute geriatric wards, age ≥60, n = 184	Dementia Infection
Schor, 1992[68]	Medical and surgical patients, age ≥65, n = 291	Age >80 y Chronic cognitive impairment Fracture on admission Neuroleptic or narcotic use Infection Male gender

ASA = American Society of Anesthesiologists.

routinely order bed rest or no activity in 26% of patient-days or minimal activity (e.g., bed to chair) in an additional 31% of patient-days.[41] Moreover, immobilizing devices (e.g., indwelling bladder catheters and physical restraints) can further contribute to the detrimental effects of immobilization. Indwelling bladder catheters are commonly used in hospitalized older patients—a rate of 50 per 196 patients (26%) in one study[30]—often without a clear medical indication, despite the well-documented association of these catheters with urinary tract infections, urosepsis, and delirium.[30,34,61] Dehydration and volume depletion as well as malnutrition during hospitalization (e.g., decline in weight, fall in serum albumin) are well-documented contributing factors to delirium.[30,69] Iatrogenic events include complications of diagnostic or therapeutic procedures, transfusion reactions, and bleeding resulting from over anticoagulation. Previous

Table 1. PROSPECTIVE STUDIES OF RISK FACTORS FOR DELIRIUM (*Continued*).

Study	Population, Age (y), and Sample Size (n)	Independent Predictors for Delirium
Williams-Russo, 1992[81]	Elective bilateral knee replacement patients, mean age 68, n = 51	Age Male gender Alcohol use
Francis, 1990[21]	Medical patients, age ≥ 70, n = 229	Abnormal sodium level Severe illness Chronic cognitive impairment Fever/hypothermia Psychoactive drug use Azotemia
Foreman, 1989[19]	Medical patients, age ≥ 60, n = 71	Hypernatremia Hypokalemia Hypotension Hyperglycemia Azotemia High number of medications High confusion rating by nurses High number of orienting items in environment Low number of social interactions
Rockwood, 1989[62]	Medical patients, age ≥ 65, n = 80	Age Dementia Unstable condition on admission
Rogers, 1989[64]	Elective hip or knee surgery patients, age ≥ 60, n = 46	Use of scopolamine, propranolol, or flurazepam
Gustafson, 1988[24]	Hip fracture patients, age ≥ 65, n = 111	Age Dementia
Williams, 1985[80]	Hip fracture patients, age ≥ 60, n = 170	Age Preoperative poor performance on cognitive testing Low preinjury activity level
Seymour, 1980[69]	Medical patients, age ≥ 70, n = 71	Dehydration score

BUN = Blood urea nitrogen.

studies have demonstrated that iatrogenic complications occur in 29% to 38% of older hospitalized patients.[4,61,71] In addition, rates of iatrogenic events rise strikingly with age, at least a three to five fold increase in older patients compared with younger patients.[9,23] Iatrogenic complications are an important precipitating factor for delirium.[30]

Insufficiency of any major organ system can precipitate delirium, particularly renal or hepatic failure, as well as other systemic diseases.[18,25,28,59,67,70] Both hypoxemia and hypercarbia may precipitate delirium. Occult respiratory failure has emerged as an increasing problem in elderly patients, often lacking the typical signs and symptoms of dyspnea and tachypnea[65] and readily missed by measuring oxygen saturation alone. Acute myocardial infarction or congestive heart failure commonly present as delirium or *failure to thrive* in an elderly patient, without the usual symptoms of chest pain or dyspnea.[65] Occult infection is a particu-

larly notable cause of delirium. Older patients frequently fail to respond to an infection with fever or leukocytosis, forcing clinicians to search patients carefully for signs of pneumonia, urinary tract infection, endocarditis, abdominal abscess, or infected joint.[18,25,59,65,70] A variety of metabolic disorders may contribute to delirium, including hypernatremia or hyponatremia, hypercalcemia, acid-base disorder, hypoglycemia and hyperglycemia, thyroid disorders, or adrenal disorders.[18,25,38,59,70] Drug and alcohol withdrawal are important, often unsuspected, causes of delirium in the elderly.[38,59,70] Environmental factors, such as unfamiliar environment and disruption of routines, sleep deprivation and fragmentation, frequent room changes, sensory overload, and sensory deprivation, may precipitate delirium in a vulnerable patient.[38,49,59] Psychosocial factors, such as depression, bereavement, pain, psychological stress, loss of independence, or lack of social supports, may also contribute to delirium.

Drug Use and Delirium

Medications are the most common remediable cause of delirium—contributing to 40% of cases in previous studies.[29,30,38] Many different medications can lead to delirium; the most common are those with known psychoactive effects, such as sedative-hypnotics, narcotics, and medications with anticholinergic effects. Medications commonly associated with delirium are listed in Table 2. In previous studies, use of any psychoactive medication was associated with a 3.9-fold increased risk of delirium,[21] whereas use of two or more psychoactive medications was associated with a 4.5-fold risk.[30] Sedative-hypnotic drugs have been associated with a 3.0 to 11.7 fold increased risk of delirium,[20,48,64] narcotics with a 2.5 to 2.7 fold risk,[48,68,80] and anticholinergic drugs with a 4.5 to 11.7 fold risk.[24,64,68] In one study, benzodiazepine use caused 29% of delirium cases,[20] whereas 85% of patients on anticholinergic drugs in another study developed delirium.[24] All of these psychoactive medications are commonly prescribed during hospitalization. For instance, sedative-hypnotic drugs for sleep are prescribed for 46% to 66% of medical patients and 85% to 96% of surgical patients.[54,56]

The total number of medications prescribed as well as drug-drug and drug-disease interactions, increases with age, resulting in delirium as a leading untoward consequence.[50,72] Delirium is related to the number of medications prescribed.[19,30,40] Adding more than three medications during hospitalization increases the subsequent risk of delirium by at least fourfold.[30] The relative odds of an adverse drug reaction with cognitive impairment increases from 2.7 with two to three drugs prescribed, to 9.3 with four to five drugs, to 13.7 with six or more drugs.[40]

Although some delirium resulting from required medications is unavoidable, evidence indicates that many events may be preventable. A systematic review of 19 studies documented that 7% to 51% of psychoactive medications in elderly outpatients were inappropriately overused.[10] Owens et al[55] found that 73 of 215 (37%) of acutely ill hospitalized elderly patients were receiving one or more inappropriate medications. In a study of 416 consecutive hospital admissions,[44] inappropriate drug use was

Table 2. DRUGS ASSOCIATED WITH DELIRIUM

Sedative/hypnotics
Benzodiazepines (especially flurazepam, diazepam)
Barbiturates
Sleeping medications (chloral hydrate)
Narcotics (especially meperidine)
Anticholinergic drugs
Antihistamines (diphenhydramine, hydroxyzine)
Antiparkinsonian (benztropine, trihexyphenidyl)
Antispasmodics (belladonna, Lomotil)
Atropine/scopolamine
Heterocyclic antidepressants (amitriptyline, imipramine, doxepin)
Neuroleptics (chlorpromazine, haloperidol, thioridazine)
Cardiac
Antiarrhythmics (quinidine, procainamide, lidocaine)
Antihypertensives (β-blockers, methyldopa)
Digitalis glycosides
Gastrointestinal
H_2-antagonists (cimetidine, ranitidine, famotidine, nizatidine)
Metoclopramide (Reglan)
Miscellaneous
Anticonvulsants
Corticosteroids
Levodopa
Lithium
Nonsteroidal anti-inflammatory drugs
Nonprescription drugs
Cold/sinus preparations (antihistamines, pseudoephedrine)
Sleep aids (diphenhydramine, alcohol-containing elixirs)
Stay-awake preparations (caffeine)
Nausea/gastrointestinal (Donnagel, meclizine, H_2-antagonists, loperamide)

found in 161 (39%) of patients, including 48 patients with absolute contraindications to the drugs and 113 patients in whom the drugs were deemed unnecessary. Notably, 50% of all adverse drug events occurred in the group receiving inappropriate drugs. In a subsequent study of 4031 hospital admissions,[3] psychoactive medications accounted for 46% of preventable adverse drug events. Although *appropriateness* of prescribing was not assessed, this study documented that these patients were receiving an average of at least three psychoactive medications, that the use of these agents was discretionary, and that inappropriately high initial doses were often chosen. These studies provide strong evidence that inappropriate use and overuse of psychoactive medications are common in older patients and that delirium and other related adverse drug events may be preventable.

CLINICAL MANIFESTATIONS

The definition and diagnostic criteria for delirium continue to evolve. Standardized criteria for delirium appear in the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)* (Table 3).[2] These criteria are now being applied as a diagnostic standard. These criteria were developed based on consensus of experts, and their diagnostic sensitivity

Table 3. DIAGNOSTIC CRITERIA FOR DELIRIUM

DSM-IV Diagnostic Criteria[2]
Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention
Change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia
Disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
Evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiologic consequences of a general medical condition
Confusion Assessment Method (CAM)[32] Diagnostic Algorithm*
Feature 1. Acute onset and fluctuating course This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?
Feature 2. Inattention This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?
Feature 3. Disorganized thinking This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
Feature 4. Altered level of consciousness This feature is shown by any answer other than *alert* to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal], vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

*The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.

and specificity have not been established. The Confusion Assessment Method (CAM)[32] provides a simple, operationalized diagnostic algorithm (see Table 3), which is currently in widespread use as a delirium screening instrument. The sensitivity (94% to 100%) and specificity (90% to 95%) of the CAM algorithm as well as of each of its individual features have been assessed previously.[32]

The cardinal features of delirium include its acute onset and inattention. Establishing the acuity of onset requires accurate knowledge of the patient's baseline cognitive functioning. Acquiring this information can sometimes require the additional effort of finding a reliable informant, such as a family member, caregiver, or nurse. Moreover, the course of delirium usually fluctuates, with symptoms tending to come and go or increase and decrease in severity over a 24-hour period. Lucid intervals are characteristic and can be misleading to the clinician. Inattention is defined as difficulty focusing, maintaining, and shifting attention. Delirious patients appear easily distracted by extraneous stimuli, have difficulty maintaining conversation and following commands, and may perseverate with an answer to a previous question. On objective testing, they may have difficulty with simple repetition tasks, digit spans, and reciting months backwards. Other key features include a disorganization of thought, which is usually a manifestation of underlying cognitive or per-

ceptual disturbances, and altered level of consciousness (typically lethargy, with reduced clarity of awareness of the environment). Although not cardinal elements, other features frequently associated with delirium include disorientation, cognitive deficits (e.g., memory impairment, aphasia), psychomotor agitation or retardation, perceptual disturbances (e.g., hallucinations, illusions, or misinterpretations), paranoid delusions, emotional lability, and sleep-wake cycle reversal.

Clinically, delirium can present in either a hypoactive or hyperactive form. The hypoactive form of delirium, characterized by lethargy and reduced psychomotor activity level, is the most common form in older persons. This form of delirium often is unrecognized and is associated with a poorer overall prognosis. The hyperactive form of delirium, in which the patient is agitated, often vigilant, and hallucinating, is rarely missed. Patients can fluctuate between the hypoactive and hyperactive forms.

DIAGNOSIS AND ASSESSMENT

Delirium remains a clinical diagnosis,[29] based on careful bedside observation and history taking from reliable informants. A high degree of clinical astuteness is required for evaluation of delirium in hospitalized older patients. Identifying the underlying multifactorial contributors to the delirium is of critical importance because many of these factors are treatable and if untreated may result in substantial morbidity and mortality. Because the potential contributors are innumerable, the search requires clinical judgment combined with a thorough medical evaluation. The process is made more challenging by the frequently nonspecific, atypical, or muted presentation of the underlying illness in older persons.[65] In fact, delirium is commonly the only presenting sign of underlying life-threatening illness, such as pneumonia, urosepsis, or myocardial infarction, in the geriatric population.

The first step in evaluation should be establishing the diagnosis of delirium through cognitive assessment and determining any acute change from the patient's baseline level of cognitive functioning. Because cognitive impairment is often inapparent during routine conversation, brief cognitive screening tests, such as the Mini-Mental State Examination, is recommended. Attention should be further assessed with simple tests, such as a forward digit span (inattention indicated by inability to repeat five digits forward) or reciting the months backwards. The cornerstone of the evaluation of delirium is a comprehensive history and physical examination. The history should be targeted toward establishing the patient's baseline cognitive functioning and the course of any mental status change as well as obtaining clues about potential precipitating factors, such as recent medication changes, intercurrent infections, or medical illnesses. The physical examination must include a detailed neurologic examination for focal deficits and a careful to search for signs of head trauma, occult infection, or other acute medical process.

A difficult challenge in the differential diagnosis of delirium is distinguishing dementia, a long-standing confusional state, from delirium

alone or delirium superimposed on dementia. The differential diagnosis is crucial, however, because delirium may represent an acute medical emergency. These two conditions are differentiated by the acute onset of symptoms in a delirium (dementia is much more insidious) and impaired attention and altered level of consciousness associated with delirium. Disorientation and memory impairment may be present with both conditions and may be absent in delirium. Thus, these features are not useful in differentiating delirium and dementia. Other differential diagnoses include depression and nonorganic psychotic disorders. Although paranoia, hallucinations, and affective changes can occur with delirium, the key features of acute onset, inattention, altered level of consciousness, and global cognitive impairment assist with the recognition of delirium. At times, the differential diagnosis can be quite difficult—particularly with an uncooperative patient or when an accurate history is unavailable. Because of the potentially life-threatening nature of delirium and its high occurrence rate in the hospitalized population, it is prudent to manage the patient in these cases as having delirium and to search for underlying precipitants (e.g., intercurrent illness, metabolic derangements, drug toxicity) until further information can be obtained.

Review of the medication list, including over-the-counter medications, is a high-yield procedure and should be carried out in every case. Medications with psychoactive effects should be removed or minimized whenever possible. In the elderly, these medications may cause psychoactive effects even at dosages and measured drug levels that are within the *therapeutic range*. When these medications cannot be removed, dosage reductions or substitution of less toxic alternatives should be considered. The side effects and potential interactions of all current drugs should be reviewed. Finally, chronic medication and alcohol use should be carefully reviewed to evaluate for any potential withdrawal effects.

For the laboratory assessment, there is no standard approach, and the evaluation must be tailored to the individual situation, requiring substantial clinical judgment. An astute history and physical examination, review of medications, targeted laboratory testing, and search for occult infection should be adequate to identify the majority of potential contributors to the delirium. Further testing should be tailored to the situation. In patients with preexisting cardiac or respiratory diseases or with related symptoms, an electrocardiogram or arterial blood gas determination may be indicated. The need for cerebrospinal fluid examination, brain imaging, or electroencephalography remains controversial. Overall, these tests are probably indicated in fewer than 10% of delirium cases, and the clinical yield for these procedures is low.[14,51] Clearly, cerebrospinal fluid examination is needed for the febrile delirious patient when meningitis or encephalitis is suspected. Brain imaging should be reserved for patients with new focal neurologic signs, with history or signs of head trauma, or without another identifiable cause of the delirium. The electroencephalogram, with its false-negative rate of 17% and false-positive rate of 22% for distinguishing delirious and nondelirious patients, has a limited role and is most useful to detect occult seizure disorder and to differentiate delirium from nonorganic psychiatric disorders.[36,58,75]

TREATMENT

Nonpharmacologic Approaches

In general, nonpharmacologic approaches to treatment should be used whenever possible and are successful for symptom management in most patients. Nonpharmacologic management of symptoms is indicated for every delirious patient,[5] including presence of family members, orienting influences, use of sitters, transferring a disruptive patient to a private room or closer to the nurse's station (for increased supervision). Interpersonal contact and communication are of vital importance, using reorientation strategies, simple instructions and explanations, and frequent eye contact. Patients should be involved in their care and allowed to participate in decision making as much as possible. Eyeglasses and hearing aids should be worn to reduce sensory deficits. Mobility, self-care, and independence should be encouraged as much as possible; physical restraints should be avoided because of their well-established adverse effects of immobility and increased agitation, their questionable efficacy, and their potential to cause injury. Attention must be paid to minimize the disruptive influences of the hospital environment. Clocks and calendars should be provided to assist with orientation. Room and staff changes should be kept to a minimum. A quiet environment with low-level lighting is optimal for the delirious patient. Perhaps the most important intervention is to allow an uninterrupted period for sleep at night. This requires coordination of nursing and medical procedures, such as medications, vital signs, intravenous fluids, and treatments. Unit-wide changes may be needed to ensure a decreased noise level at night, including hallway noise and conversations. Nonpharmacologic approaches for relaxation, including music, relaxation tapes, and massage, can be highly effective for management of agitation in delirious patients.

Pharmacologic Approaches

Pharmacologic approaches to treatment should be reserved for patients with severe delirium, when the delirium symptoms may result in the interruption of needed medical therapies (e.g., intubation, intravenous lines) or may endanger the safety of the patient or other persons. The clinician must be aware, that there is no ideal drug for treatment of delirium symptoms; any choice may further cloud mental status and obscure efforts to follow the course of the mental status change. Thus, any drug chosen should be given in the lowest dose for the shortest time possible. In the absence of any comparative efficacy data, the drug choice is usually dictated by the required route of administration and adverse effects profile. Neuroleptics are the preferred agents of treatment, with haloperidol and thioridazine representing the most widely used agents in this class. Haloperidol has less risk of orthostatic hypotension and anticholinergic side effects than thioridazine and is available in parenteral form; however, it has a higher rate of extrapyramidal side effects and acute dystonias. If

parenteral administration is required, intravenous use results in rapid onset of action with short duration of effect, whereas intramuscular use has a more optimal duration of action. The increased sedative properties of thioridazine are often beneficial in agitated patients. The elixir form of thioridazine can assist with oral or nasogastric routes of administration. The recommended starting dose is haloperidol 0.5 to 1.0 mg orally or parenterally or thioridazine 10 to 20 mg orally, then repeating the dose every 20 to 30 minutes after vital signs have been rechecked until sedation has been achieved. The end point should be an awake but manageable patient. The average older patient who has not previously been treated with neuroleptics should require a total loading dose of no more than 3 to 5 mg of haloperidol or 50 to 100 mg of thioridazine. Subsequently a maintenance dose of one half of the loading dose should be administered in divided doses over the next 24 hours, with tapering doses over the next few days.

Benzodiazepines are not recommended for the first-line treatment of delirium because of their tendency to cause oversedation, exacerbation of the confusional state, and brief duration of peak effects. They remain the drugs of choice for treatment of withdrawal syndromes from alcohol and sedative drugs. Lorazepam is the preferred agent of this class, with its favorable half-life (10 to 15 hours), lack of active metabolites, and availability of parenteral form.

OUTCOMES AND PROGNOSIS

Studies of delirium outcomes published since 1970 are summarized in Table 4. Delirium is consistently associated with poor outcomes at hospital discharge and longer-term follow-up ranging from 1 month to 2 years, including increased mortality, prolonged length of hospital stay, increased rates of nursing home placement, and functional and cognitive decline. Although delirium is clearly associated with poor prognostic outcomes, it remains unclear whether the delirium itself independently contributes to the poor prognosis or whether the delirium simply serves as a marker identifying patients with poor baseline prognostic features, such as severe illness and comorbidity, dementia, functional impairment, or advanced age. Many of the previous studies did not adequately control for these potential confounders.

A large-scale epidemiologic study[31] involving 727 patients across three sites addressed this issue by examining the independent contribution of delirium to hospital outcomes, after controlling for age, gender, dementia, illness severity, and baseline functional status. This study documented that delirium was an important independent prognostic determinant of hospital outcomes at discharge after controlling for potential confounders, including new nursing home placement (adjusted odds ratio [OR] for delirium = 3.0; 95% confidence interval [CI] = 1.4 to 6.2), death or new nursing home placement (OR = 2.1; 95% CI = 1.1 to 4.0), and functional decline (OR 3.0; 95% CI = 1.6 to 5.8). Similarly, at 3-month follow-up, delirium remained an important independent prognostic

determinant after controlling for confounders, including new nursing home placement (OR = 3.0; 95% CI = 1.5 to 6.0), death or new nursing home placement (OR = 2.6; 95% CI = 1.4 to 4.5), and functional decline (OR = 2.7; 95% CI = 1.4 to 5.2). Although delirium was associated with increased mortality, a relatively infrequent outcome event, the results were not statistically significant (OR = 1.6; 95% CI = 0.8 to 3.2).

Although delirium has long been considered a transient, reversible condition, studies on the duration and persistence of delirium symptoms provide evidence that delirium may be much more persistent than previously believed. This long persistence of delirium, greater than 30 days in many cases, undoubtedly contributes to poor long-term outcomes. In one study, only 20% of patients—many of whom had baseline cognitive impairment—resolved all delirium symptoms at 6-month follow-up.[42] A prolonged transitional phase after delirium, including abnormalities of cognition, affect, or behavior, appears to be quite typical.[45] Moreover, recurrent episodes of delirium are common.

Taken together, these studies provide substantial evidence that delirium does contribute to detrimental outcomes in the long-term and that these effects persist far beyond the identified acute episode. In addition, delirium appears to have greater adverse effects in patients with underlying cognitive impairment. The long-term deleterious effects are most likely related to the duration, severity, and underlying cause(s) of the delirium as well as the vulnerability of the host. Not all of the etiologic contributors to delirium are reversible (e.g., prolonged hypoxemia or hypoglycemia, structural neurologic lesions), and it may not be possible to alter the patient's baseline vulnerability or to remove the noxious insults. Future studies are greatly needed to establish better the independent long-term effects of delirium in larger samples and to determine whether delirium itself leads to permanent neurologic damage.

PREVENTION

Primary prevention, that is, preventing delirium before it occurs, is the most effective strategy to reduce delirium and its attendant complications. Controlled trials of delirium prevention are currently underway, but the results are not yet available. The risk factors for delirium have been well defined, as described earlier. Preventive strategies should address these important delirium risk factors (both predisposing and precipitating factors). Table 5 indicates well-documented delirium risk factors and potential preventive interventions for each risk factor. These risk factors were selected because current evidence supports both the clinical relevance and the potentially remediable nature of each risk factor with practical interventions.

On a larger scale, preventive efforts for delirium also require system-wide changes to educate physicians and nurses to improve recognition and heighten awareness of the clinical implications; encourage cognitive assessment of all elderly hospitalized patients; provide incentives to change practice patterns that lead to delirium (e.g., immobilization, use

Table 4. STUDIES ON DELIRIUM PROGNOSIS

Reference	Population	Delirium Outcomes					Adequate Control for Confounders?
		LOS	Nursing Home	Death	Functional Decline	Cognitive Decline	
Inouye, 1998[31]	Medical-surgical patients, 3 hospitals, n = 727	↔	↑	↑	↑	—	Yes
O'Keefe, 1997[53]	Acute geriatric unit, n = 225	↑	↑	↔	↑	—	Yes
van Hemert, 1994[77]	Psychiatric consultations, n = 519	—	—	↑	—	—	Partial
Marcantonio,1994[49]	Elective surgical patients, n = 1341	↑	—	↑	↔	—	Yes
Murray, 1993[53]	Medical-surgical patients, n = 325	—	—	—	↑	—	Yes
Levkoff, 1992[42]	Medical-surgical patients, n = 325	↑	↑	↔	—	—	Yes
Francis, 1992[22]	Medical patients, n = 229	—	—	↔	↑	↑	Yes
Williams-Russo, 1992[81]	Elective orthopedic patients, n = 51	↔	—	—	↔	—	No
Brannstrom, 1991[8]	Hip fracture patients, n = 35	—	—	—	↑	—	No

Francis, 1990[21]	Medical patients, n = 229	↑	↑	↔	↔	↔	Partial
Rockwood, 1990[63]	Medical patients, n = 80	↑	—	—	—	—	No
Koponen, 1989[39]	Psychogeriatric unit, n = 70	—	—	—	↑ (dementia group only)	↑	No
Magaziner, 1989[47]	Hip fracture patients, n = 814	—	—	↑	—	—	No
Rogers, 1989[64]	Elective orthopedic patients, n = 46	↔	—	—	↑	—	Partial, matching
Gustafson, 1988[24]	Hip fracture patients, n = 111	↑	↑	↑	↑	—	No
Levkoff, 1988[43]	Medical-surgical patients, n = 1285	↑	—	↑	—	—	No
Thomas, 1988[73]	Medical patients, n = 133	↑	—	↑	—	—	No
Fields, 1986[16]	Medical patients, n = 116	↑	↑	↔	—	—	Partial
Rabins, 1982[60]	Psychiatric consultations, n = 73	—	—	↑	—	—	No
Hodkinson, 1973[20]	21 geriatric units, n = 588	—	—	↑	—	—	No

LOS = Length of hospital stay; ↔ = no effect or not statistically significant; ↑ = significantly increased rate of outcome in delirium group; — = outcome not examined.

Table 5. DELIRIUM RISK FACTORS AND POTENTIAL INTERVENTIONS

Risk Factor	Interventions	Examples
Cognitive impairment	Therapeutic activities program	Cognitive-stimulating activities, including current events, reminiscence, word games, crafts.
	Reality orientation program	Orientation board, providing day's schedule, reorienting communication
Sleep deprivation	Noise reduction strategies	Silent pill crushers, vibrating beepers, eliminating hallway conversations at night
	Adjusting patient's schedule to allow uninterrupted period of sleep	Rescheduling medications, tests, procedures, vital signs and nursing activities
Immobilization	Early mobilization	Ambulation or active range-of-motion exercises 3-times/d
	Minimizing immobilizing equipment	Reducing indwelling bladder catheters, physical restraints. Use of long oxygen tubing, portable oxygen tanks for mobility
Psychoactive medications	Restricted use of as-needed sleep and psychoactive medications	Sedative-hypnotics, narcotics, anticholinergic medications. Reduce dosage, substitute less toxic alternatives
	Nonpharmacologic protocols for management of sleep and anxiety	Provision of glass of warm milk or herbal tea, relaxation tapes, music and massage
Vision impairment	Provision of vision aids	Eyeglasses, magnifiers, special lighting
	Provision of adaptive equipment	Large illuminated phone dials, large-print books
Hearing impairment	Provision of amplifying devices	Bedside portable amplifiers (Radio Shack listenator)
	Repair of hearing aids	Provide batteries; instruct in proper use. Wax disimpaction
Dehydration	Early recognition and volume repletion	Encourage oral or intravenous fluids

of sleep medications, bladder catheters, and physical restraints); and create systems that enhance high-quality geriatric care (e.g., geriatric expertise, case management, clinical pathways, and quality monitoring for delirium). Because incident delirium—occurring during hospitalization—often results from hospital-related complications or inadequate care, its rate can be used as a quality marker for hospital care. With its common occurrence, its frequently iatrogenic nature, and its close linkage to the processes of care, delirium serves as an invaluable means to examine quality of hospital care and provides an opportunity for overall improvement.

CONCLUSIONS

Delirium is a common, serious problem for hospitalized older patients. Moreover, it is a problem that will likely continue to increase with the aging of the US population. Recognition of delirium may be difficult and requires cognitive assessment and knowledge of the clinical course of mental status changes. Delirium is usually of complex, multifactorial

etiology, involving an interrelationship of baseline vulnerability and precipitating factors. Adequate treatment of delirium often involves addressing these multiple, cumulative factors simultaneously. Delirium is associated with poor outcomes and long-term prognosis, including prolonged length of hospital stay, nursing home placement, functional and cognitive decline, and death. Nonpharmacologic approaches for delirium management are recommended. Pharmacologic management (i.e., with major tranquilizers) should be reserved for patients who pose a danger to themselves or others. Many cases of delirium may be preventable through a targeted risk factor approach, with avoidance of factors contributing to delirium, such as disorienting influences, sleep deprivation, immobilization, psychoactive medications, dehydration, and sensory impairment. With appropriate preventive measures, the substantial morbidity and mortality associated with delirium may be reduced.

ACKNOWLEDGMENT

The author thanks Ms. Robbin Bonnano for assistance in manuscript preparation. This work is dedicated to the memory of Bradley Inouye and Jane Krieger.

References

1. American Association of Retired Persons and the Administration on Aging: A profile of older Americans: 1995. Washington, DC, American Association of Retired Persons, 1995
2. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 4. Washington, DC, American Psychiatric Association, 1987
3. Bates DW, Cullen DJ, Laird N, et al: Incidence of adverse drug events and potential adverse drug events: Implications for prevention. JAMA 274:29, 1995
4. Becker PM, McVey LJ, Saltz CC, et al: Hospital-acquired complications in a randomized controlled clinical trial of a geriatric consultation team. JAMA 257:2313, 1982
5. Beresin EV: Delirium in the elderly. J Geriatr Psychiatry Neurol 1:127, 1988
6. Bergman K, Eastham EJ: Psychogeriatric ascertainment and assessment for treatment in an acute medical ward setting. Age Ageing 3:174, 1974
7. Black DW, Warrack G, Winokur G: The Iowa record-linkage study: II. Excess mortality among patients with organic mental disorders. Arch Gen Psychiatry 42:78, 1985
8. Brannstron B, Gustafson Y, Norberg A, et al: ADL performance and dependency on nursing care in patients with hip fractures and acute confusion in a task allocation care system. Scand J Caring Sci 5:3, 1988
9. Brennan TA, Leape LL, Laird NM, et al: Incidence of adverse events and negligence in hospitalized patients. N Engl J Med 324:370, 1991
10. Brook RH, Kamberg CJ, Mayer-Oakes A, et al: Appropriateness of acute medical care for the elderly: An analysis of the literature. Health Policy 14:225, 1990
11. Cameron DJ, Thomas TI, Mulvihill M, et al: Delirium: A test of the Diagnostic and Statistical Manual III criteria on medical inpatients. J Am Geriatr Soc 35:1007, 1987
12. Chisholm SE, Deniston OI, Igrisan RM, et al: Prevalence of confusion in elderly hospitalized patients. J Gerontol Nurs 8:87, 1982
13. Creditor MC: Hazards of hospitalization of the elderly. Ann Intern Med 118:219, 1993
14. Dunne JW, Leedman PJ, Edis RH: Inobvious stroke: A cause of delirium and dementia. Aust N Z J Med 16:71, 1986
15. Fields SD, Mackenzie DR, Charlson ME, et al: Cognitive impairment: Can it predict the course of hospitalized patients? J Am Geriatr Soc 34:579, 1986
16. Fields SD, Makenzie CR, Charlson ME, et al: Reversibility of cognitive impairment in medical inpatients. Arch Intern Med 146:1593, 1986

17. Fisher BW, Flowerdew G: A simple model for predicting postoperative delirium in older patients undergoing elective orthopedic surgery. J Am Geriatr Soc 43:175, 1995
18. Flint FJ, Richards SM: Organic basis of confusional states in the elderly. BMJ 2:1537, 1956
19. Foreman MD: Confusion in the hospitalized elderly: Incidence, onset and associated factors. Res Nurs Health 12:21, 1989
20. Foy A, O'Connell D, Henry D, et al: Benzodiazepine use as a cause of cognitive impairment in elderly hospital inpatients. J Gerontol Med Sci 50A:M99, 1995
21. Francis J, Martin D, Kapoor WN: A prospective study of delirium in hospitalized elderly. JAMA 263:1097, 1990
22. Francis J, Kappor WN: Prognosis after hospital discharge of older medical patients with delirium. J Am Geriatr Soc 40:601, 1992
23. Gillick MR, Serrell NA, Gillick LS: Adverse consequences of hospitalization in the elderly. Soc Sci Med 15:1033, 1982
24. Gustafson Y, Berggen D, Brannstrom B, et al: Acute confusional states in elderly patients treated for femoral fracture. J Am Geriatr Soc 36:525, 1988
25. Guze SB, Cantwell DP: The prognosis in "organic brain" syndromes. Am J Psychiatry 120:878, 1964
26. Guze SB, Daengsurisri S: Organic brain syndromes: Prognostic significance in general medical patients. Arch Gen Psychiatry 17:365, 1967
27. Henker FO: Acute brain syndromes. J Clin Psychiatry 40:117, 1979
28. Hodkinson HM: Mental impairment in the elderly. J R Coll Physicians Lond 7:305, 1973
29. Inouye SK: The dilemma of delirium: Clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. Am J Med 97:278, 1994
30. Inouye SK, Charpentier PA: Precipitating factors for delirium in hospitalized elderly persons: Predictive model and interrelationship with baseline vulnerability. JAMA 275:852, 1996
31. Inouye SK, Rushing JT, Foreman MD, et al: Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. J Gen Intern Med 13:234–242, 1998
32. Inouye SK, Van Dyck CH, Alessi CA, et al: Clarifying confusion: The Confusion Assessment Method: A new method for detection of delirium. Ann Intern Med 113:941, 1990
33. Inouye SK, Viscoli CM, Horwitz RI, et al: A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 119:474, 1993
34. Inouye SK, Wagner DR, Acampora D, et al: A controlled trial of a nursing-centered intervention in hospitalized elderly medical patients: The Yale Geriatric Care Program. J Am Geriatr Soc 41:1353, 1993
35. Jitapunkul S, Pilloy I, Ebrahim S: Delirium in newly admitted elderly patients: A prospective study. QJM 83:307, 1992
36. Johnson JC: Delirium in the elderly. Emerg Med Clin North Am 8:255, 1990
37. Kay DWK, Norris V, Post F: Prognosis in psychiatric disorders of the elderly: An attempt to define indicators of early death and early recovery. J Ment Sci 120:129, 1956
38. Koponen H, Partanen J, Paakkonen A, et al: EEG spectral analysis in delirium. J Neurol Neurosurg Psychiatry 52:980, 1989
39. Koponen H, Stenback U, Mattila E, et al: Delirium among elderly persons admitted to a psychiatric hospital: Clinical course during the acute stage and one-year follow-up. Acta Psychiatr Scand 79:579, 1989
40. Larson EB, Kukull WA, Buchner D, et al: Adverse drug reactions associated with global cognitive impairment in elderly persons. Ann Intern Med 107:169, 1987
41. Lazarus BA, Murphy JB, Colletta EM, et al: The provision of physical activity to hospitalized elderly patients. Arch Intern Med 151:2452, 1991
42. Levkoff SE, Evans DA, Liptzin B, et al: Delirium: The occurrence and persistence of symptoms among elderly hospitalized patients. Arch Intern Med 152:334, 1992
43. Levkoff SE, Safran C, Cleary PD, et al: Identification of factors associated with the diagnosis of delirium in elderly hospitalized patients. J Am Geriatr Soc 36:1099, 1988
44. Lindley CM, Tully MP, Paramsothy V, et al: Inappropriate medication is a major cause of adverse drug reactions in elderly patients. Age Ageing 21:294, 1992
45. Lipowski AJ: Delirium: Acute Confusion States. Oxford University Press, Oxford, 1990

46. Lowy FH, Engelsmann F, Lipowski ZJ: Study of cognitive functioning in a medical population. Compr Psychiatry 14:331, 1973
47. Magaziner J, Simonsick EM, Kashner M, et al: Survival experience of aged hip fracture patients. Am J Public Health 79:274, 1989
48. Marcantonio ER, Goldman L, Mangione CM, et al: A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 271:134, 1994
49. Millar HR: Psychiatric morbidity in elderly surgical patients. Br J Psychiatry 138:17, 1981
50. Montamat SC, Cusack B: Overcoming problems with polypharmacy and drug misuse in the elderly. Clin Geriatr Med 8:143, 1992
51. Moses H, Van Kaden BA: Neurologic consultations in a general hospital: Spectrum of iatrogenic disease. Am J Med 81:955, 1986
52. Murray AM, Levkoff SE, Wetle TT, et al: Acute delirium and functional decline in the hospitalized elderly patients. J Gerontol A Biol Sci Med Sci 48:M181, 1993
53. O'Keefe S, Lavan J: The prognostic significance of delirium in older hospital patients. J Am Geriatr Soc 45:174, 1997
54. O'Reilly R, Rusnak C: The use of sedative-hypnotic drugs in a university teaching hospital. Ann Intern Med 142:585, 1990
55. Owens NJ, Sherburne NJ, Silliman RA, et al: The Senior Care Study: The optimal use of medications in acutely ill older patients. J Am Geriatr Soc 38:1082, 1990
56. Perry SW, Wu A: Rationale for the use of hypnotic agents in a general hospital. Ann Intern Med 100:441, 1984
57. Pompei P, Foreman M, Rudberg MA, et al: Delirium in hospitalized older persons: Outcomes and predictors. J Am Geriatr Soc 42:809, 1994
58. Pro JD, Wells CE: The use of the electroencephalogram in the diagnosis of delirium. Dis Nerv Syst 38:804, 1977
59. Purdie FR, Honigman B, Rosen P: Acute organic brain syndrome: A review of 100 cases. Ann Emerg Med 10:455, 1981
60. Rabins PV, Fistein MF: Delirium and dementia: Diagnostic criteria and fatality rates. Br J Psychiatry 140:149, 1982
61. Reichel W: Complications in the care of five hundred elderly hospitalized patients. J Am Geriatr Soc 13:973, 1965
62. Rockwood K: Acute confusion in elderly medical patients. J Am Geriatr Soc 37:150, 1989
63. Rockwood K: Delays in the discharge of elderly patients. J Clin Epidemiol 43:971, 1990
64. Rogers MP, Liang MH, Daltroy LH, et al: Delirium after elective orthopedic surgery: Risk factors and natural history. Int J Psychiatr Med 19:109, 1989
65. Rosenthal G, Steel K: Difference in the presentation of disease. *In* Hazzard WR, Andres R, Bierman EL, et al (eds): Principals of Geriatric Medicine and Gerontology, ed 2. New York, McGraw-Hill, 1990, p 212
66. Rosin AJ, Boyd RV: Complications of illness in geriatric patients in hospital. J Chron Dis 19:307, 1966
67. Roth M: The natural history of mental disorder in old age. J Ment Sci 101:281, 1955
68. Schor J, Levkoff SE, Lipsitz LA, et al: Risk factors for delirium in hospitalized elderly. JAMA 267:827, 1992
69. Seymour DG, Henschke RD, Cape T, et al: Acute confusional states and dementia in the elderly: The role of dehydration/volume depletion, physical illness and age. Age Ageing 8:137, 1980
70. Sirois F: Delirium: 100 cases. Can J Psychiatry 33:375, 1988
71. Steel K, Gertman PM, Crescenzi C, et al: Iatrogenic illness on a general medicine service at a university hospital. N Engl J Med 304:638, 1981
72. Stewart RB, Hale WE: Acute confusional states in older adults and the role of polypharmacy. Annu Rev Health 13:415, 1992
73. Thomas RI, Cameron DJ, Fahs MC: A prospective study of delirium and prolonged hospital stay: Exploratory study. Arch Gen Psychiatry 45:937, 1988
74. Trzepacz PT, Teague GB, Lipowski ZJ: Delirium and other organic mental disorders in a general hospital. Gen Hosp Psychiatry 7:101, 1985
75. Trzepacz TT, Brenner RP, Coffman G, et al: Delirium in liver transplantation candidates: Discriminate analysis of multiple tests variables. Biol Psychiatry 24:3, 1988
76. US Bureau of the Census: Statistical Abstract of the United States, ed 116. Washington, DC, U.S. Bureau of the Census 1996, p 165

77. van Hemert AM, van der Mast RC, Hengeveld MW, et al: Excess mortality in general hospital patients with delirium: A 5-year follow-up of 519 patients seen in psychiatric consultation. J Psychosom Res 38:339, 1994
78. Warshaw GA, Moore JT, Friedman SW, et al: Functional disability in the hospitalized elderly. JAMA 248:847, 1982
79. Weddington WW: The mortality of delirium: An underappreciated problem? Psychosomatics 23:1232, 1982
80. Williams M, Campbell EB, Raynor WJ, et al: Predictors of acute confusional states in hospitalized elderly patients. Res Nurs Health 8:329, 1985
81. Williams-Russo P, Urquhart BL, Sharrock NE, et al: Post-operative delirium: Predictors and prognosis in elderly orthopedic patients. J Am Geriatr Soc 40:759, 1992

Address reprint requests to

Sharon K. Inouye, MD, MPH
Yale University School of Medicine
Yale—New Haven Hospital
20 York Street, Tompkins 15
New Haven, CT 06504