Supplementary Appendix

This appendix has been provided by the author to give readers additional information about their work.

Supplement to: Inouye SK. Delirium in Older Persons. N Engl J Med 2006;354:1157-65.

WEB-ONLY SUPPLEMENT
SUPPLEMENT TABLE 1. DIAGNOSTIC CRITERIA FOR DELIRIUM

Diagnostic and Statistical Manual (DSM-IV) Diagnostic Criteria [1]

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.

B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.

C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

ICD-10 Diagnostic Criteria [2]

For a definite diagnosis, symptoms, mild or severe, should be present *in each one* of the following areas:

a. impairment of consciousness and attention (on a continuum from clouding to coma; reduced ability to direct, focus, sustain, and shift attention);

b. global disturbance of cognition (perceptual distortions, illusions and hallucinations-- most often visual; impairment of abstract thinking and comprehension, with or without transient delusions, but typically with some degree of incoherence; impairment of immediate recall and of recent memory but with relatively intact remote memory; disorientation for time as well as, in more severe cases, for place and person)

c. psychomotor disturbances (hypo- or hyperactivity and unpredictable shifts from one to the other; increased reaction time; increased or decreased flow of speech; enhanced startle reaction);

d. disturbance of the sleep - wake cycle (insomnia or, in severe cases, total sleep loss or reversal of the sleep - wake cycle; daytime drowsiness; nocturnal worsening of symptoms; disturbing dreams or nightmares, which may continue as hallucinations after awakening);

SUPPLEMENT TABLE 1 (cont)

e. emotional disturbances, e.g. depression, anxiety or fear, irritability, euphoria, apathy, or wondering perplexity.

The Confusion Assessment Method (CAM) Diagnostic Algorithm* [3]

Feature 1. Acute onset and fluctuating course

This feature is usually obtained from a reliable reporter, such as a family member, caregiver, or nurse and is shown by positive responses to these 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 did it increase and decrease in severity?

Feature 2. Inattention

This feature is shown by a positive response to this question: Did the patient have difficulty focusing attention, for example, being easily distractible, or have difficulty keeping track of what was being said?

Feature 3. Disorganized thinking

This feature is shown by a positive response to this 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 this 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])?

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* The ratings for the CAM should be completed following brief cognitive assessment of the patient, for example, with the Mini-Mental State Examination. The diagnosis of delirium by CAM requires the presence of features 1 and 2 and of either 3 or 4.

SUPPLEMENT TABLE 2. CLINICAL FEATURES OF DELIRIUM (DETAILED VERSION)

Acute onset	Disturbance occurs abruptly, usually over hours to days, but onset over weeks described. Because the patient is often unable to provide an accurate history, a reliable informant is needed to ascertain the time course of onset.
Fluctuating course	Symptoms tend to come and go, or increase and decrease in severity over a 24-hour period. Lucid intervals are characteristic.
Inattention	Difficulty focusing, sustaining, and shifting attention. Patients are easily distracted, have difficulty maintaining conversation or following commands. Patients perform poorly on simple bedside tests of attention, such as digit spans and reciting months backwards.
Disorganized thinking	Manifested by disorganized or incoherent speech, reflecting abnormalities in form and content of thinking. Patients demonstrate rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching between subjects. Patients may be unable to make decisions, solve problems, or plan and sequence activities. Judgment and insight may be impaired.
Altered level of consciousness	Clouding of consciousness with reduced clarity of awareness of the environment. This is typically manifested by lethargy, where the patient is abnormally drowsy and difficult to keep aroused. The patient may also be hyperalert, vigilant, and unable to filter out environmental stimuli.

SUPPLEMENT TABLE 2 (cont)

Cognitive deficits	Global or multiple deficits in cognition are typical. Disorientation to time and place are common; disorientation to person is present in more severe cases. Memory deficits for immediate and short-term memory are typical, with preserved remote memory. Language functions are often abnormal, with tangential or slurred speech, paraphasias, and word-finding difficulty progressing to aphasia in severe cases.
Perceptual disturbances	Significant perceptual disturbances occur in up to 30% of delirious patients. Initial changes include distortions with abnormalities in the perception of size of objects (macropsia, micropsia), shape, position, movement, or derealization. Illusions are frank misinterpretations of environmental stimuli (such as mistaking a pile of laundry for a person, or hallway sounds for gunshots). Both visual and auditory hallucinations occur with delirium; tactile hallucinations are less common. The perceptual disturbances may be frightening to patients and may result in significant behavioral disturbances.
Psychomotor disturbances	Delirium demonstrates three psychomotor variants: hyperactive, hypoactive, and mixed. In the hyperactive form of delirium, the patient is agitated (i.e., restless, picking at clothing, tapping fingers, making frequent changes of position), often vigilant and hallucinating. In the hypoactive form of delirium, the patient has a markedly decreased level of motor activity (i.e., sluggishness, staring into space), often lethargic or passive. Patients may alternate between the hyperactive and hypoactive subtypes.

SUPPLEMENT TABLE 2 (cont)

Altered sleep-wake cycle	Sleep cycle disturbances are characteristic. Daytime drowsiness, nighttime insomnia, fragmented sleep, or complete sleep-cycle reversal are typical with delirium.
Emotional disturbances	Emotional disturbances are common, manifested by intermittent and labile symptoms of fear, anxiety, depression, irritability, apathy, anger, or euphoria. Paranoid delusions may occur.

SUPPLEMENT TABLE 3

A PROPOSED RESEARCH AGENDA TO EXPLORE DELIRIUM AND THE INTER-RELATIONSHIP OF DELIRIUM AND DEMENTIA

Epidemiology

- Diagnosis of delirium: What is the sensitivity, specificity, clinical yield and cost-effectiveness of various evaluation approaches to delirium? What is the optimal diagnostic approach?
- Long-term follow-up studies of delirious patients: Does delirium itself lead to permanent cognitive impairment? How often does delirium lead to mild cognitive impairment or dementia?
- Delirium superimposed on dementia: Does delirium alter the trajectory of cognitive decline in patients with dementia?
- Cognitive reserve capacity/recovery from delirium: Are there factors that assist in cognitive recovery after delirium, such as educational level, exercise, health habits, medications (e.g., cholinesterase inhibitors)?
- Genetic factors: Are there genetic determinants of the risk of development of delirium, or lack of recovery from delirium? What is the role of APOE-ε4?
- Identification of high-risk populations: Does delirium exert its maximal detrimental effects only in certain high-risk subgroups? Or high-risk settings (e.g., post-operative, intensive care)?
- Impact of delirium: What are the economic and societal costs associated with delirium and delirium superimposed on dementia?

Pathophysiology

- Neuroimaging, neuropsychological, and neuropathological studies: Does delirium lead to permanent neurological sequelae?
- Structural and functional imaging methods: Do preexisting abnormalities (e.g., white matter hyperintensities, volume losses) or functional changes predict the development of delirium, as well as longer-lasting cognitive decline?
- Amyloid imaging: Does degree of amyloid pathology correlate with the risk of delirium or the likelihood of recovery from delirium?
- Animal models: Are there pathologic changes after induced delirium (e.g., general anesthesia) in normal and dementia models?
- Laboratory, electrophysiologic, or neuroimaging markers: Can we identify markers that will assist in diagnosis of delirium? Can we identify markers for delirium that is likely to lead to chronic cognitive impairment or dementia?

- Behavioral manifestations: What is the underlying pathophysiology of behavioral manifestations of delirium (e.g., hyperactive vs. hypoactive form)? Do genetic factors or neuroreceptor subtypes play a role?

Prevention and Treatment

- Prevention of delirium: Does prevention of delirium with proven non-pharmacologic intervention strategies mitigate or abate future cognitive decline?
- Treatment of delirium: Randomized trials to evaluate treatment strategies for delirium in cognitively normal and in dementia patients (e.g., nonpharmacologic approaches, cholinesterase inhibitors, dopamine antagonists, anti-inflammatory agents, anti-platelet agents, lipid-lowering agents, antioxidant or neuroprotective drugs). Will early recognition and treatment of delirium mitigate or abate subsequent cognitive decline?

REFERENCES:

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington DC: American Psychiatric Association, 1994.
2. World Health Organization. The ICD-10 classification of mental and behavioural disorders. Diagnostic criteria for research. Geneva: WHO, 1992;57-9.
3. Inouye SK, Van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: The Confusion Assessment Method. A new method for detection of delirium. Ann Intern Med. 1990; 113: 941-948.