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Delirium: New Ways to Understand and Manage It

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DELIRIUM IS NOT A PSYCHIATRIC DISORDER!! It is a *MEDICAL DISORDER*

Teaching Points

- Delirium, though common, is mostly missed or misdiagnosed
- It is always due to a medical condition or medication
- Delirium is linked with very poor outcomes, including increased risk of death, dementia, functional impairment, and institutionalization
- Understanding who is at highest risk is best way to avoid missing the diagnosis
- Delirium requires a multimodal/multidisciplinary approach involving stabilization of the environment, treatment of medical problems, attention to sleep and mobility, and improvement of awareness of the environment (glasses, hearing aids)
- Medications must be reviewed: always avoid anticholinergic medications and benzodiazepines whenever possible
- Most treatments involve basic metabolic or hematologic functions

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What's the Problem?

DELIRIUM:

- 10-40% Prevalence in acute settings
- 25-60% Incidence in acute settings
- Up to 87% incidence in ICU
- Compared with DEPRESSION:
- 10% Primary care; 25% Acute settings*

Inouye, 1998, J Ger Psy Neurol; Patel, 2009, Critical Care Med

Rates of Postoperative Delirium

- 9-13% overall in-hospital mortality
- AA Aneurysm repair: 41-54%
- CABG: 32-50%
- Peripheral Vascular: 10-48%
- Elective Orthopedic: 9-15%
- Hip Fracture: 52%

Rudolph et al, 2007 American J Med 120:9

Lundstrom et al. 2007 Aging Clin Exp Res 19:3

Outcomes of Delirium

- In most studies:
- Up to four times the length of stay
- 2-7x Rate of new institutionalization
- Single strongest predictor of in-hospital complications (UTI, falls, incontinence) (O'Keeffe,1997)
- Strong predictor of long term loss of function

Outcomes of Delirium in Nursing Homes (NH)

- 801 postdischarge patients (NH, or community based care) ≥ 70
- Patients who received multi-component targeted intervention to prevent delirium showed:
- → Significantly lower total costs
- → Shorter length of stay
- → Lower cost per survival day
- → 15.7% decrease in costs among those in nursing home settings (likely due to shorter length of stay)

Leslie 2005 JAGS 53(3)

Death?

- Prospective study of 2 cohorts of medical inpatients ≥ 65; 243 with prevalent or incident delirium, 118 without
- Adjusted Hazard Ratio for delirium =2.11 (CI=1.18-3.77) (age, marital status, comorbidity, clinical severity, acute physiology, baseline dementia, degree of institutionalization)
- Greater severity of delirium associated with higher mortality among non-demented

McCusker 2002 Arch Intern Med. 162:4

Does Delirium Predict Onset of Dementia?

- 203 patients >65 on a general medicine service (Halifax), no dementia at baseline
- During followup (median of 32.5 months), dementia was diagnosed in
  - 5.6% of those without delirium during index hospitalization
  - 18.1% of those with delirium during index hospitalization
- Adjusted OR: (sex, age, comorbid illness)=5.97 (CI=1.83-19.54); P=0.0003

Rockwood 1999 Age Ageing 28(6)

Cost of Delirium

- $38-152 B per year in US alone; comparable to cost of falls, DM
- In ICUs, episodes of delirium average 39% higher ICU costs and 31% higher hospital costs, after adjusting for age, comorbidity, severity of illness, degree of organ dysfunction, nosocomial infection, hospital mortality, and other confounders[2]
- In other work LOS largely accounted for this difference

1. Leslie 2008 Arch Internal Med 168(1)
2. Milbrandt 2004 Critical Care Medicine 32:4

What Really Happens In Delirium?

A cataclysmic breakdown of brain function"

– *"Hard Drive Crash"*

- On a cellular level, *serious disruption*, in a largely random manner, of the *most basic* processes that "run" brain neurons, with high risk of cell death
    - Hypoxia, dehydration, hypoglycemia, hypercalcemia, hypernatremia, infection, medications that disrupt essential neurotransmitter functions

Why Does it Happen in Older, Ill Patients?

- They have more deteriorated organ systems, resulting in less well integrated “inter-organ mechanics”
- They have less reserve (brain cells, pulmonary, cardiac, renal, hepatic function, etc) to make up for the losses or “hits”
- Homeostasis MUCH harder to maintain; systems far from equilibrium respond to smaller insults

Why is it Difficult to Recognize?

- Cognitive losses occur in a *spectrum* that varies according to diverse causes/patterns of functional losses in any given patient
- "Delirium" is just the "frank middle point"
- Thus, some of its manifestations may look like part of normal behaviors/conditions
    - (Especially with hypoactive delirium)

A Failing Grade for Recognition: D-

- 33-95% of cases are
  - -MISSED altogether or
  - -Misdiagnosed as
    - - depression
    - - psychosis
    - - dementia

Inouye, J Ger Psy and Neurol., 11(3) 1998
Bair, Psy Clin N Amer 21(4)1998

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Clinical Features of Delirium

- Acute or subacute onset
- Fluctuating intensity of symptoms
  - ***ALL*** SYMPTOMS FLUCTUATE…not just level of consciousness
  - Clinical presentation can vary within seconds to minutes
  - Can be very subtle
- Inattention – aka “human hard drive crash”

Attention

Most basic cognitive organizing function; underlies ALL other cognitive functions

- Not a static property: an active, selective, working process that should continuously adapt appropriately to incoming internal or external stimuli, primarily based in pre-frontal cortex with limbic, parietal, and brainstem contributions

Inattention

- A cognitive state that DOES NOT meet the requirements of the person's environment, resulting in a global disconnect: inability to fix, focus, or sustain attention to most salient concern
- Hypoattentiveness (difficulty moving from one topic to another) hyperattentiveness (rapidly flitting of attention without regard to importance of each event attended to
- Days of week backward, immediate recall are good bedside tests

Summary of Clinical Signs (1)

- Overall: GROSS DISTURBANCE OF ABILITY TO INTERACT WITH ENVIRONMENT
  - Poor executive function (poor insight, can't address own personal needs, can't plan and execute complex and rational behaviors, interpretation of and relationship with environment often impaired)

What Does This Look Like?

Active: Agitated, Wild or Irrational Behavior

OR

Quiet: “Fuzzy Interface”

Patient appears withdrawn, uninterested, does not ask questions, no effort to be heard/understood (distinctly ***dysfunctional*** in modern hospital setting…does not reflect insightful behavior)

Summary of Clinical Signs

- "Fuzzy interface" is actually an important diagnostic sign!
- Misdiagnosis: Examiner often *misinterprets or "normalizes"* such patient behavior, which results in failure to diagnose. Examples: examiner can't hear patient, room "too noisy", "I must just be tired", patient is "sleepy" or worn out from PT, etc.

Summary of Clinical Signs

Cognitive Signs:

- Inattention,
- Disorganized, fragmented thought patterns,
- Poor memory
- Disorientation
- Depressed level of consciousness

Summary of Clinical Signs

- Affective Signs: Often not recognized as "part of delirium"
  - Lability
  - Anxiety (particularly premorbid)
  - Dysphoria
    - –60% dysphoric; 52% thoughts of death; 68% feel "worthless"

Farrell Arch Intern Med. 1995 155:22

Summary of Clinical Signs

- Perceptual Distortions
  - Hallucinations more often illusory/reflect misinterpretation of environmental cues than in psychosis
  - Interpretation of pain often faulty…over- and under-exaggeration

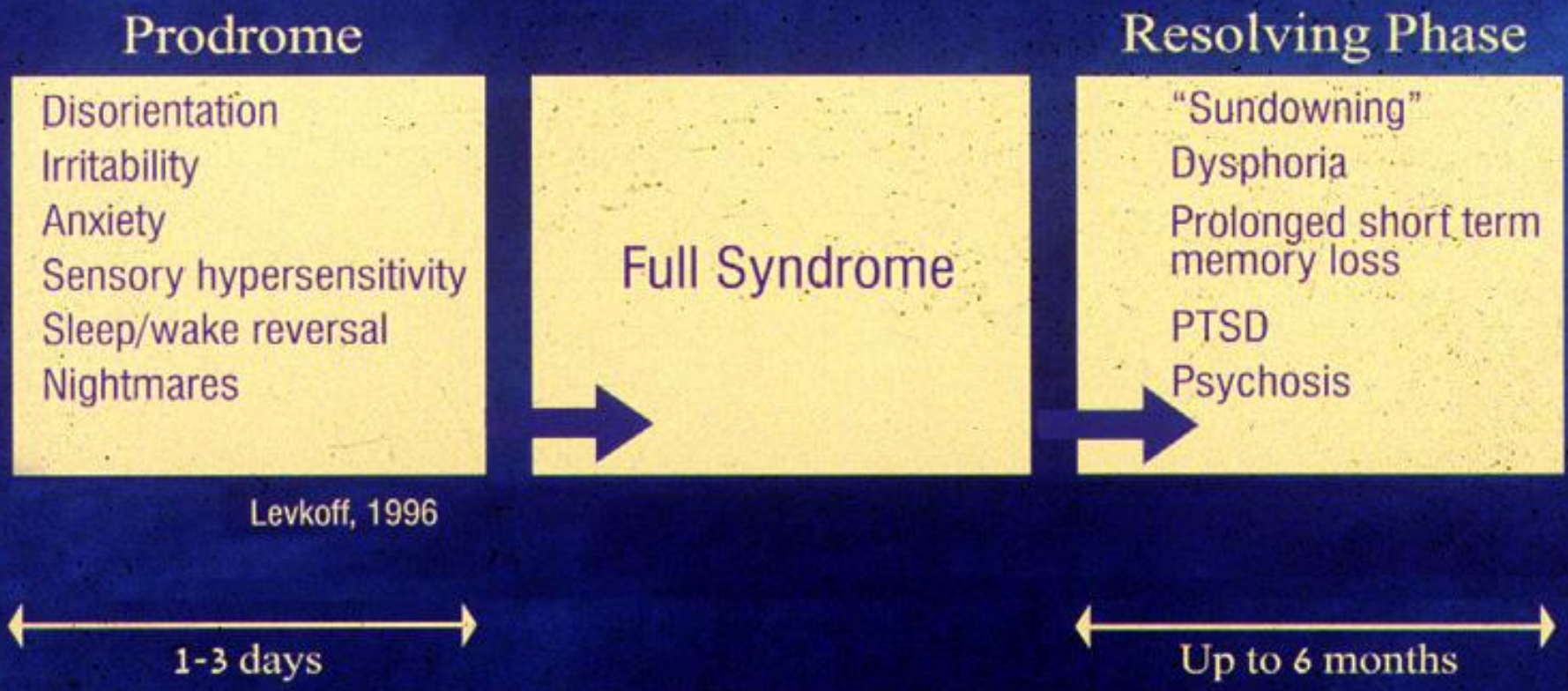
Summary of Clinical Signs

- Sensory and Motor Impairments
  - Erratic
  - Capacity to speak, hear, ambulate, swallow, etc.
  - ***All*** of these can vary ***within seconds***
  - Diagnostically very confusing
  - Wait for delirium to stabilize before final conclusions

Summary of Clinical Signs

- Behavioral signs:
  - Withdrawn, uncommunicative, unmotivated;
  - Impulsive, irrational, agitated, with chaotic activity;
  - But most are mixed in presentation
  - Both may have day/night reversal

Delirium: A Spectrum Disorder



Primary Differential: It is NOT Depression

- Quiet delirium:
  - Resembles depression: unmotivated, slow, withdrawn, undemanding; Up to 42% of cases referred for depression are delirious (Farrell, 1995)
  - Quiet delirium may be associated with worse outcomes (O'Keeffe 1999 Age Aging)
  - A *MAJOR* cause of poor recognition of delirium overall!

Misdiagnosis as Depression: Double Risk

- ***Risks of misdiagnosing delirium as depression:***

  A. May *overlook medical cause(s) of the delirium itself*

  B. May add an additional and inappropriate CNS active agent (antidepressant) prematurely

It is NOT Dementia

- *Abrupt onset* can help distinguish; dementia is a chronic condition
- *Level of attention* in demented patients is better and they are *less globally dysfunctional and chaotic*
- Prolonged or unresolvable delirium is basically a new dementia, however

Delirium "Trumps" Other Diagnoses!

- When a patient is delirious, ***no other psychiatric diagnosis can be made.*** This is critically important to the management of delirious patients, both to focus on the delirium and to avoid adding other medications. Keeping other diagnoses off the chart during delirium will greatly assist with this.
- The patient will need to be psychiatrically ***re-diagnosed*** after resolution of the delirium, which may have had a major impact on brain neurotransmitter systems that formerly supported a psychiatric illness such as depression, anxiety, bipolar disorder, etc.

How Do We Improve Delirium's Dire Outcomes?

- I. Improving recognition of delirium itself
- II. Focused multidisciplinary efforts
- III. Prevention: Recognition of *vulnerable* patients

1. Improving Recognition

- A. Clinical examination
- B. Nursing staff notes/observations
- C. Prediction by risk factors

A. Clinical Examination

- Clinical interview is often difficult to interpret alone, and it usually represents a small slice of patient's presentation and behavior during 24 hrs
- Active delirium is often not recognized; quiet ones are usually unrecognized or misdiagnosed.
- ICU presents additional problems given difficulty communicating with patients

Operationalizing Recognition of Delirium: The Confusion Assessment Method (CAM)

- Assesses:

  1) Acute onset and fluctuating course

  2) Inattention

  3) Disorganized Thinking

  4) Altered Level of Consciousness

  1 AND 2 necessary; and either 3 OR 4

Inouye 1990 Ann Intern Med 113:941

Widespread Acceptance

- CAM has become standard assessment tool (originally designed as a screening tool); often used with MMSE to obtain data for scoring

CAM ICU

- Based on CAM; widely used in intensive care settings; provides pictorial memory items and problem solving questions to avoid difficulty with communication

Ely 2001Crit Care Med 29(7)

Other Common Scales

- Cognitive Test for Delirium
- Delirium Rating Scale-98
- NEECHAM Confusion Scale
- Delirium Symptom Index
- Memorial Delirium Assessment Scale

B. Nursing's Contribution

- Much broader clinical exposure over 24 hour cycle
- Patient's interaction with challenges of environment and ability to problem solve much more readily assessed
- Fluctuations in clinical presentation are much more easily put into context

Nurses' Notes

- Review of 24 hour nurses' notes is *critical* to making the diagnosis in most cases—particularly with quiet delirium. Notes will more accurately reflect evidence of variable levels of orientation, cooperativeness, judgment, and behavior

Evidence: Nursing Chart Notations/Nursing Input

- Perez noted that physicians indicated possible delirium in only 34% of referrals, but non-psychiatric health personnel recorded signs of delirium in 93% of cases – with the first recording made most commonly by nurses.

Perez 1984 Intl J Psychiary in Med 14:3

Chart Notations/Nursing Input

- Chart Screening Checklist (Kamholz B, AAGP 1999)
- Composed of commonly charted behavioral signs (Sensitivity= 93.33%, Specificity =90.82% vs CAM)
- 97.3% of diagnoses of delirium can be made by nurses' notes alone using CSC
- 42.1% of diagnoses made by physicians' notes alone using CSC

C. Prediction by “Risk Factor Analysis”

- Helps “narrow the field” : must be specific, not just the usual compendium
- Inouye’s work critical in devising a two phase model—baseline (“predisposing”)risk (population of interest) and “last minute”precipitating factors (potentially treatable causes) that push the patient over the threshhold into delirium

Inouye 1999 Dement Geriatr Cog Disorder 10:5

Inouye: Risk Factor Study

- Inouye's initial study involved 281 patients in 2 cohorts, all over 70; 13 clinical variables were used; those involving relative risks of 1.5 or greater were used in the multivariable proportional hazards model.

Table 3. Predisposing Factors for Delirium (N = 107)

Risk Factor	*Adjusted Relative Risk (95% CI)*
Vision impairment	3.5 (1.2, 10.7)
Severe illness	3.5 (1.5, 8.2)
Cognitive impairment	2.8 (1.2, 6.7)
BUN/Cr ratio ≥18	2.0 (0.9, 4.6)

CI = confidence interval.

Adapted from Inouye et al.[10]

Table 5. Precipitating Factors for Delirium (N = 196)

Precipitating Factor	*Adjusted Relative Risk (95% CI)*
Use of physical restraints	4.4 (2.5–7.9)
Malnutrition	4.0 (2.2–7.4)
> 3 medications added	2.9 (1.6–5.4)
Use of bladder catheter	2.4 (1.2–4.7)
Any iatrogenic event	1.9 (1.1–3.2)

CI = confidence interval.

Adapted from Inouye and Charpentier.[9]

Table 8. Inter-relationship of Predisposing and Precipitating Factors in Development Cohort (N = 196)

Predisposing Factors Group	*Rate of Delirium (per 100 Person-days)**			
	Precipitating Factors Group			
	Low	*Intermediate*	*High*	*Total*
Low	0	0	0	0
Intermediate	0	3.2	13.6	1.6
High	1.4	4.9	26.3	5.6
Total	0.3	3.6	21.3	

*Corresponds with percentage of patients developing delirium per day.

Implications of Inouye's Risk Factor Model

- Thus, the population of interest in Inouye's model is that group of patients who have the most predisposing factors…who have vision impairment, severe illness, cognitive impairment, and BUN/Creatinine ratio $\geq$ 18

Highest Rates of Delirium

- …And in fact, the highest rates of delirium (per 100 person days) is found among those patients who have the highest concentration of predisposing factors; *they become delirious even when challenged with "low" levels of precipitating factors*

Similar Observation

- In the next slide, we see a similar pattern, although the risk factors are not broken into “predisposing and precipitating”…just overall burden of factors

Similar Pattern…

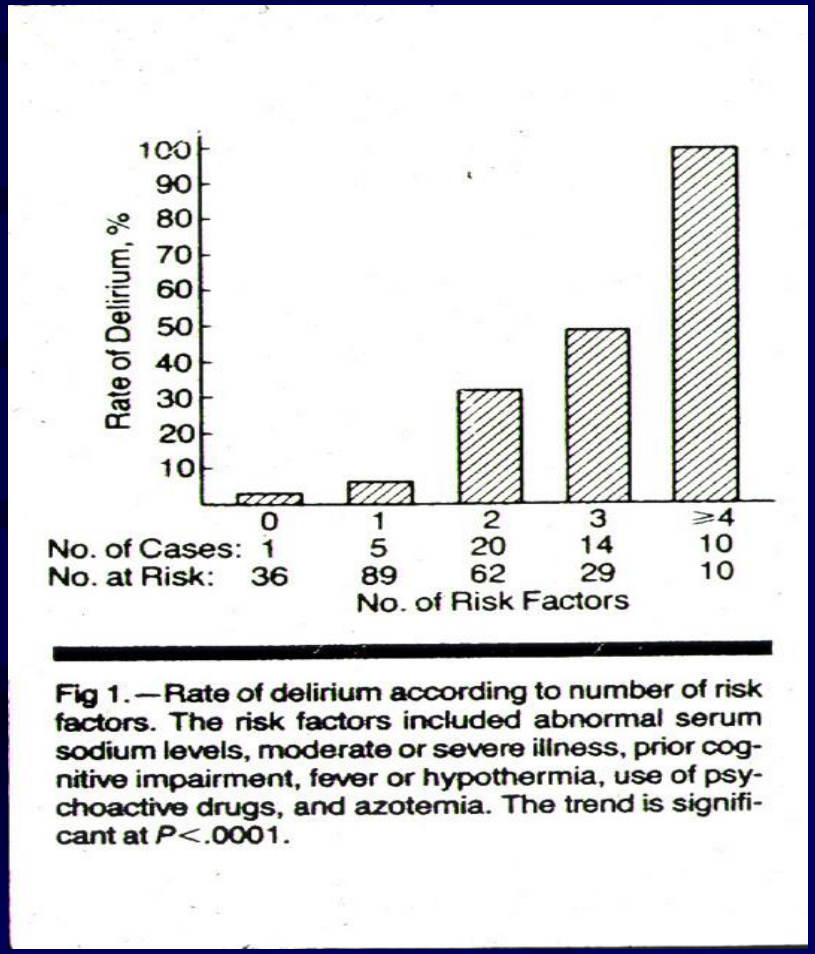


Fig 1.—Rate of delirium according to number of risk factors. The risk factors included abnormal serum sodium levels, moderate or severe illness, prior cognitive impairment, fever or hypothermia, use of psychoactive drugs, and azotemia. The trend is significant at $P<.0001$.

Francis 1997: JAGS 45(2):247-8.

The Caveat

- Every "risk factor" study actually lists a different assortment of factors…..so:
- *Specific* risk factor(s) must be less important than the burden of factors needed to overcome the patient's limited resilience, biological reserve, and (fragile) equilibrium…in a dose-dependent fashion. The more frail the patient, the less impact is required to precipitate a ***disequilibrated*** state (such as delirium or a fall.)

The Corollary

- The LESS FRAIL the patient, the MORE risk factors are needed to make them delirious
- Implication: *Do not settle for trivial medical complications as answers for causes of delirium in relatively healthy patients!*

Frailty

- The concept of frailty has been invoked to identify individuals who are not just disabled but are *approaching, at risk for,* disequilibrium and deterioration
- 61% of frail patients in acute decompensation present with *delirium*

Jarrett 1995 Arch Int Med

Implications of Frail Patients in Disequilibrium

….these are patients who are broadly vulnerable, for whom “fixing one thing” will not do; they remain vulnerable at least through the course of delirium and often afterwards….generally with the length of recovery proportional to the degree of baseline frailty and size of impact of stressors.

How Do States of Global Vulnerability Develop?

- Age associated decrease in homeodynamism (decrease of dynamic range of physiological solutions, redundant systems, or “reserves”)
- Loss of dendritic branching, loss of variability of heart rate, decrease of latency, amplitude and range of EEG frequencies, trabecular loss in bone, etc.
- Too little variation=less ability to adapt

Lipsitz, L . Loss of Complexity and Aging. JAMA 1992

Age and Reduced Reserves

- Redundant numbers/circuits exist at birth
- Neurons can increase metabolism to produce more transmitters to compensate
- Terminals are able to increase in size and take over function of lost terminals, and receptors can increase their sensitivity
- BUT, with aging, these compensatory systems wane….and become exhausted

Disequilibrium, etc

- Evidence from other biosystem investigations that at about 70% loss of function or reserve there is an abrupt break with a homeodynamic state
- Result is an unstable, unpredictable system with significant vulnerability
- States “far from equilibrium” characterized by large reaction to small insults

Bortz WM “The Physics of Frailty” JAGS 1993

Que Cheng-Li “Equilibrium, Homeostasis and Complexity” Annales CRMCC 1998

The Relationship Between Frailty and Delirium

…. for many patients with delirium, it seems to be best to think about it as a manifestation of frailty. Older adults are frail when they have several, interacting medical and social problems that give rise to a loss of redundancy in their homeostatic capacity and, thus, an inability to withstand stress. In other words, they need most of their physiologic components and most of their environmental supports at or near maximum capacity to get through the day. When one component goes awry, the equilibrium of this complex system fails, and the system's highest-order functions (staying upright, maintaining focused cognition) fail first. This is why delirium and falls…. are common among frail elderly people when they become ill, even with seemingly trivial illnesses. This is why their apparent causes are so protean. This is why their outcomes are so poor, and why successful management requires a multidisciplinary approach.

Rockwood 2002 CMAJ 167(7)

Graphic Image of Frailty

- In the following slide, note the great difference between Barthel's scores (measures of ADL, which are a proxy for medical burden) between frail elderly (bottom row) and well elderly (top row) before, during, and after hospitalization.
  →*Frail patients living in the community are as deteriorated as well patients upon acute admission to the hospital.*

Frailty

(Jarrett,P,Arch Intern Med. 155:1995)

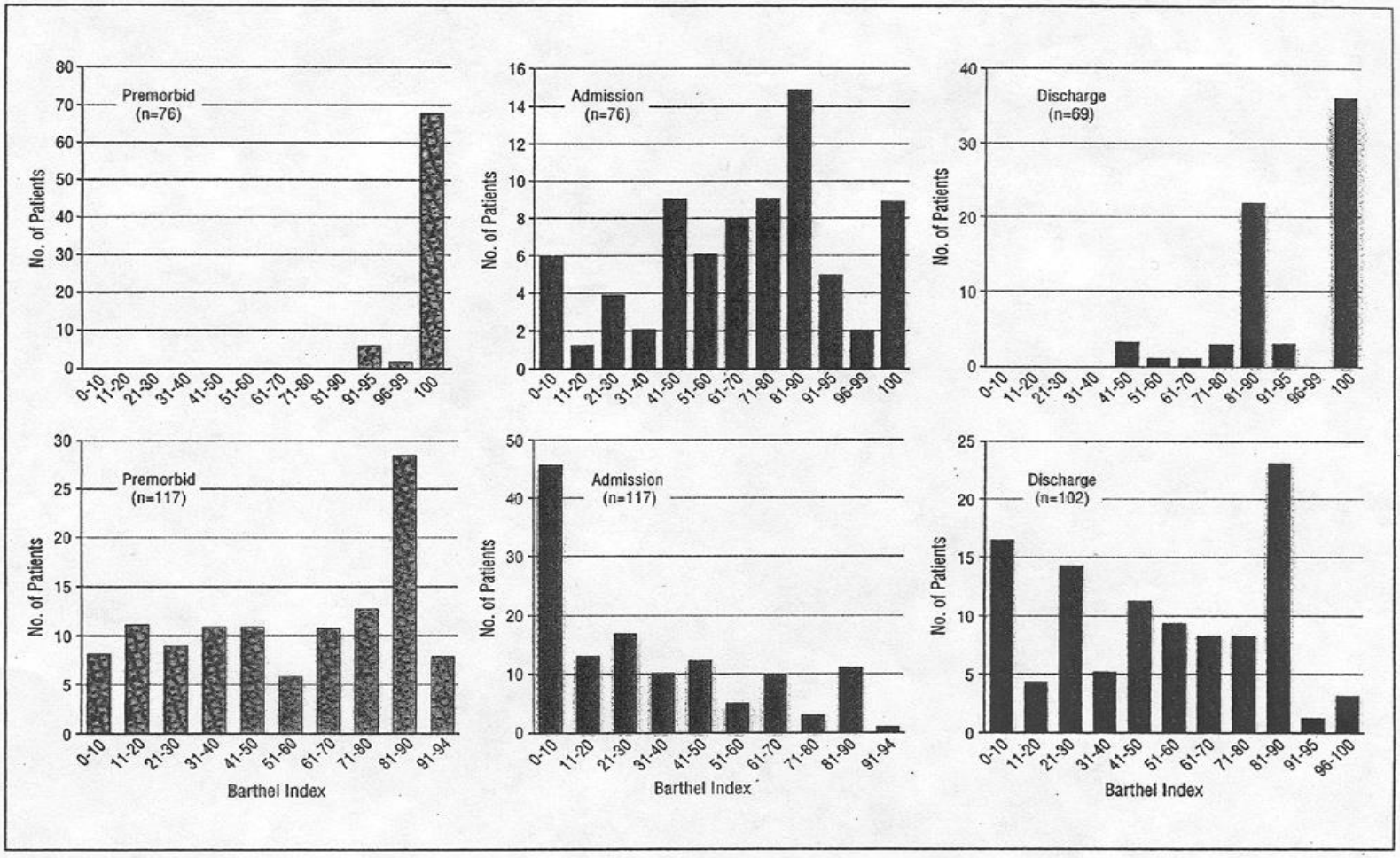


Figure 1. *Distribution of Barthel Index scores before admission, at admission, and at discharge for the well elderly (top) and for the frail elderly (bottom).*

Impact

- Loss of “internal complexity” found in delirium→ need for caregiving environment to respond in increasingly complex and protective ways.

Implications for Delirium

- “Diffuse vulnerability” can account for the ‘multiple pathways’ to delirium
- In fact, delirium may be the FIRST SIGN of an underlying medical disorder (sometimes the ONLY sign)
- But it’s more than just a signal: as we’ve seen above, it has an independent impact on outcomes

LOWERING Risk: Education?

- Each yr of completed education associated with .91 lower odds of delirium
- Individuals with 7 years of education had 1.6 fold increased odds of delirium compared to those with 12 years

Jones et al. J Gerontology 2006

Pathophysiology: Basic Problem

- Diverse etiologies: metabolic, perfusion-based, medication-related, structural lesions ALL result in same general phenomenon, implying that they all somehow feed OUT through the same neural circuit that determines this complex of behaviors

Prefrontal Cortex as "CEO"

- Prefrontal Cortex is ~ "CEO": consolidates polymodal sensory information with limbic (amygdala, anterior temporal regions, thalamus, cingulate gyrus, hippocampus) inputs, and which enables focusing attention *in on* matters most relevant and *away from* "distractions"

3 Models of Pathophysiology

- SEPSIS (inflammation)
- ARDS (oxidative stress)
- NEUROTRANSMITTER IMBALANCE
  (often associated with inflammation and oxidative stress)

Principles Of Neuronal Function

- Membrane potential/depolarization →neurotransmission
- Maintenance of membrane potential as well as cell integrity depend on *availability of ATP*
- ATP generation occurs in the mitochondria and requires adequate glucose and oxygen

1. A Principal Pathway: Oxidative Stress

- Includes ANY source of ischemia (low cardiac output, impaired pulmonary function, low hgb/hct, low oxygen saturation, anemia, ARDS, etc).
- →Rapid depletion of ATP
- →Depolarization of cell membrane
- → Ca++ influx, imbalance of neurotransmitters
- → Remodelling at all neuronal levels, including decreased synaptic transmission, cell death

Oxidative Stress

- Oxidative stress also → reactive oxygen and nitrogen species
- Free radical generation is *particularly* harmful to brain
  - Large lipid content of myelin
  - High rate of oxidative metabolism
  - Low antioxidant capacity

ARDS

- 78-100% have neurocognitive impairments at 1 year post ARDS, 47% at 2 years, 25% at 6 years
  - Average impairment was below 6th percentile of normal distribution
  - Significantly different from comparable, non-ARDS patients

- Hopkins RO et al. Am J Respir Crit Care Med 1999 160
- Rothenhausler HB et al. Gen Hosp Psychiatry 2001 23
- Hopkins RO et al. Am J Respir Crit Care Med 2005 171
- Marquis K et al. Am J Respir Crit Care Med 2001 161

2. Inflammation: *Evidence?*

Therapeutic and investigational uses of interleukins induce symptoms of delirium

- LPS peripheral challenge→impaired working memory, memory consolidation
- Cytokine dysregulation→neuronal injury
  - Necrosis
  - Altered neurotransmission
  - Activation of CNS microglia

Getting Into the CNS

- Il6, TNFα, IL1B can move from periphery to CNS
    - Direct neural pathways (primary autonomic afferents)
    - Transport across BBB
    - Circumventricular region/BBB non-continuous
- TNFα can persist for months in CNS (vs hours to days in periphery); associated with CNS microglial activation and *further* cytokine release
- Gradient from dementia to delirium of TNFα (amount, rate of cognitive decline)

CNS *Augmentation* of Systemic Inflammation

- CNS Microglia: Rapid proliferation/secretion of inflammatory mediators (cytokines, chemokines, proteases), free radicals
    - Weaken astrocytic tight junctions
    - Impair neuronal function
    - Microglia respond differently to a stimulus if other stimuli precede , coexist, follow the stimulus

Primed Microglia: Worst of All

Primed Microglia:

- Pre-existing neurodegeneration
- Aging

- In setting of neurodegeneration and repeated immunological challenges
  - Exacerbate neuronal dysfunction proportional to severity of underlying pathology
  - Accelerate disease in a cumulative manner

Impact of Aging and Primed Microglia

- PRIMED Microglia have exaggerated responses to subsequent challenges quite separate from degree of peripheral inflammation
- *This may be why the healthy 30 year old does NOT become delirious when she has PNA or a UTI!*

- Field, Campion, et al. Brain, Behavior and Immunity 2010 S

Immunosenescence

- Weaker adaptive immunity
- *But 2-4x increase in baseline circulating inflammatory mediators (cytokine, acute phase reactants)*
- Loss of synaptic density and plasticity, dendritic branching
- Overall, an increased inflammatory environment in aged brain

Sepsis

- The most common non-cardiac cause of critical illness
- Health and Retirement Survey: ongoing, community dwelling, 27,000+
- *Observational, prospective,*1194 patients; mean age 76.9
- Survivors of severe sepsis: OR of 3.34 →moderate to severe CI (OR 3.34; 95% 1.53-7.25); associated functional impairments
- NON-sepsis acute hospitalizations NOT associated with development of moderate-severe CI

- Iwashyna TJ et al.JAMA 2010 304

Sepsis

- Sequelae: severe functional limitations, depression, caregiver time, SNF placement, mortality

Inflammation: *Evidence*?

- Alzheimer's Disease
  - Acute systemic inflammatory events were associated with a 2x increase in cognitive decline over 6 months, increased TNFα levels
  - If prior high TNFα levels, 4x increase

Trial: Peripheral Inflammatory Impact on CNS Microglia

- Mice with early stage neurodegeneration (ME7 prion disease, with synaptic loss, and primed microglia in HC) compared with normal mice
- Task was separable from a systemic response to inflammation: a “pure” memory task in T and Y mazes

Murray, Sanderson, Barkus, Cunningham et al. Neurobiology of Aging 2010

Trial, con't

- Bacterial endotoxin injected; effects on working memory analyzed at 3-8 hours
  - Normals: no impact
  - ME7: decreased working memory

Trial, con't

- Degree of peripheral inflammation was not critical in result
  - *At 1 hour, ME7 animals actually had less peripheral TNFα than normals*
- Normals: CNS TNFa subsided within 2-4 hours
- CNS TNFa in ME7 animals continued to increase inflammatory products over 4 hours
- Higher HC transcription of proinflammatory cytokine genes than in normals

3. Neurotransmitter Dysfunction: Dopamine

- States of hypoxia are associated with
  - Massive increases in production due to upregulated tyrosine hydroxylase (increased Ca++)--up to 500x in striatal ischemia
    - Also, positive feedback loop to TH from increased firing of DOPA neurons
  - Toxic metabolites of DOPA→decreased activity of COMT (Ca++ influx)
  - *Excess extracellular DOPA→further Ca++ influx*

Acetylcholine

- *Synthesis* very sensitive to hypoxia and *transmission* is very sensitive to metabolic abnormalities, especially O2 and glucose levels

- A suppressor of immune dysregulation

Acetylcholine ← → Inflammation

- Vagal stimulation→inhibits systemic inflammation
- Peripheral inflammation→significant reduction in choline acetyltransferase activity
- →Immune-mediated neuronal damage further compromises cells producing AcChol

Glutamate

- Extracellular concentrations increased by Ca++ influx seen in hypoxia, dopamine excess
- In presence of high levels of dopamine, activity is magnified (independently increases activity of NMDA receptor)
- Activates NMDA receptors→ cell damage, delirium, death

- Bokesch P.M., Izykenova G.A., Justice J.B., et al: NMDA receptor antibodies predict adverse neurological outcome after cardiac surgery in high-risk patients. *Stroke* 37. (6): 1432-1436.2006

How Do We Explain Fluctuation?

- The structures supporting consciousness and brain function are intact initially; it is the *metabolic environment* that changes
- This is consistent with huge proportion of cases being peripheral in source, NOT central
- → In this context, fluctuation→sign of recoverability of potential function, *not pathology*

Summary: Feet of Sand

- Cognitive impairment due to delirium is mostly likely associated with disturbances of the *most basic substrates and cellular functions*
  - Impaired oxygenation (blood loss, pulmonary disease)
  - Infection/inflammation (UTI, Pneumonia)
  - Medications, especially those that affect vital, basic pathways such as maintenance of cell integrity and synthesis, availability, and degradation of NT
  - Disturbances of Na, Calcium, critical to cellular function
  - Obscure CNS causes are in the *distinct minority*

Prevention?

- Increase acetylcholine availability/activity
    - Cholinomimetic drugs
    - Vagal nerve stimulation
    - Direct nicotinic receptor ligands
- Inhibitors of microglial activation (minocycline) or of cytokines
- Haloperidol?? IL-RA levels (protective cytokine) increased by haloperidol
- ABCDE Program of early mobilization and early weaning trials in ICU

- *Van Gool, deBeek, Eikelenboom*, Systemic Inflammation and Delirium: When Cytokines and AcChol Collide, Lancet 2010
- *Simone, Tan*, the Role of Inflammation in the Pathogenesis of Delirium and Dementia in Older Adults, CNS Neuroscience and Therapeutics 2010
- *Vasilevskis, Pandharipande et al*. A Screening, Prevention, and Restoration Model for Saving the Injured Brain in ICU Survivors Crit Care Med 2010 38

Neuroimaging

- Among the limited studies, SPECT findings are notable
- Frontal and parietal areas (likely right sided) and basal ganglia are areas of some consensus
- Delirium is likely associated with reduced blood flow and recovered blood flow after delirium resolves

Alsop et al The role of neuroimaging in elucidating delirium pathophysiology, *J Gerontol A Biol Sci Med* 61(12): 1287-93 2006

Interventions:What's Available Now

- Delirium is complex and rates increase with level of comorbidity, so interventions must be multi-focused
- Currently the "gold standards" include multicomponent interventions
- Increasingly, multidisciplinary interventions using risk factor targeting are being reported

Inouye ,1999 NEHM 340(9), Marcantonio 2001 JAGS 49:5, Pitkala 2006 J Gerontol A Biol Sci Med Sci. 61(2)I

Limits of Multicomponent Interventions

- There is a fine line between interventions that result in favorable outcomes (decreased LOS, in-hospital mortality, decreased incidence, decreased outpatient function/placement) and evidently equally dedicated ones that do not.

Limits, con't

- Why?
- Some groups used geriatric specialists or delirium specialists to diagnose; more accurate?
- Some were more comprehensive than others in application of the interventions
- Some were initially guided by identification of risk factors
- Some provided more staff training
- Some provided dedicated "delirium rooms" with more specialization
- *Not enough "head to head" comparisons…yet!*

Does Identification and Management of Specific Risk Factors Make a Difference?

- In theory, yes; but focusing on some may mean less attention to others
- Principal foci: Restraints, indwelling bladder catheters, BUN/Creat ratio, visual impairment, severe baseline medical morbidity, dementia, malnutrition
- And, cost-intensive

An Multidisciplinary Intervention Program That Works

- "Hospital Elder Life Program" (HELP)
- *Classic* initial study demonstrating *decreased incidence*, LOS, days of delirium

- Inouye SK et al. A multicomponent intervention to prevent delirium in hospitalized older patients. NEJM 1999 (340)

Elder Life Program

- 852 patients >70, general medicine
- Interventions addressed cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration
- Multiple community and international replications
- Inouye 1999 NEJM 340(9)

Results of Multicomponent Intervention Trial

	Control	Intervention
Incidence of delirium	15.0%	9.9% (matched odds 0.60, 95% confidence interval)
Days of delirium	161	105 (p=0.02)

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Multicomponent Trial

- Cost per patient, $327; per case of delirium prevented, $6,341 (however, volunteers were used)
- Severity not different
- Rate of recurrence not different
- PREVENTION is best strategy
- PREVENTION IS POSSIBLE

Interdisciplinary Comprehensive Care: Another "Gold" Standard

- Prospective, Randomized, Blinded, 126 patients ≥ 65; Intensive geriatric consultation v. usual care
- 77% adherence to recommendations
- Recs: Adequate CNS Oxygenation, F/E Balance, Pain, Reduce medication burden,B/B Regulation, Nutrition, Early mobilization, Prevention of Medical Complications, Environmental Orientation/Stimuli, Treatment of Agitation with Low Dose Neuroleptics

Marcantonio 2001 JAGS 49:5

Hip Fracture Trial Results

	Interv	Usual	P	RR
Incident Delirium	32%	50%	.04	.64
Severe Delirium	12%	29%	.02	.40

Adj OR (dementia,ADL impairment)

Incident Delirium	0.60 (NS)
Severe Delirium	0.40 (NS)

Hip Fracture Trial

- Hip fracture patients who did NOT fulfill CAM criteria for delirium, but who had *some symptoms* of delirium (subsyndromal) had outcomes *similar to, or even worse than*, those with mild delirium

Outcomes of Delirium after Discharge

- Unfortunately, multidisciplinary interventions have *not* had a significant impact on survival, cognitive status, or institutionalization at 6 months and there are few reports at 12 months
- Is this due to the limited, inhospital intervention?

What Other Guidance Do We Have?

- Cases involving moderate risk are more amenable to alterations in course of delirium[1] (partial syndromes present risk also)[2]
- Increased severity and persistence predict worse outcomes (3)
- Once delirium develops, it is harder to impact[4] →THUS PREVENTION AND EARLY INTERVENTION ARE MOST IMPORTANT!!

1. Inouye S 1998 NEJM 340(9); 2. Marcantonio 2001 JAGS 49:53;
3. McCusker 2002 J Arch Int Med 162; 4. Inouye 1999 NEJM 340(9)

So, to Practicalities….

- *For delirium in progress*, modified risk factor model helps recognition, helps focus treatment in all phases despite variability of evidence-based risk factors identified
- "Consensus" Baseline Risks:
  - Age
  - Cognitive Impairment
  - Multiple Medical Problems

Organization of Approach to Risk Factors

- 1st: Review basic metabolic/hematologic infectious, environmental causes and those related to acute medical events (see next few slides)
- 2nd : If no credible causes in 1st line, pursue full evaluation of patient's known medical problems
- 3rd: If no result from 1st and 2nd, pursue CNS workup (primary CNS causes other than CVA are very rare)

Precipitating Risk Factors: “First Pass”

- Infections – UTI, Pneumonia
- Metabolic – Hyper, hyponatremia; high BUN, low H/H, low 02 sats, high Ca++
- Medications (39%)– *Anticholinergics (diphenhydramine)*, Opiates (meperidine), Benzodiazepines (high dose/longer acting), Lithium, Antidepressants, High dose antipsychotics (>3 mg/d haloperidol equivalents), Steroids

First Pass, con't

- Pain
- Restraints
- Substance withdrawal
- Any new medical event (MI, PE, CHF, hip fracture, orthopedic injury)
- New (traumatic?) interventions/tests: Intubation, surgery (particularly orthopedic/vascular), biopsy, BM transplant, neuroimaging

Precipitating Risk Factors: 2nd Pass

- *Pursue any complications of the patient's underlying (baseline) medical problems that may not yet be obvious (viz, silent MI, DVT, etc)*

Precipitating Factors: 3rd Pass

- Basic head imaging—CT, MRI (very little gain unless there are focal signs)
- LP (again, surprisingly little gain without fever, focal signs)
- EEG
- Cerebrovascular review (MRA, vasculitis)
- Limbic Encephalitis

Goals of Treatment

- 1) EARLY intervention and screening for most common factors, taking med history into account
- 2) PRIMARY: *FIND REVERSIBLE FACTORS*!
- 3) Maintain VIGILANCE (vulnerability appears to correlate with length of recovery)
- 4) Maintain adequate behavioral control
  - Assists with preventing functional decline while in hospital
  - Less chance of complications while hospitalized (broken limbs, self extubation, aspiration, etc.)

Ways that Delirium Can Prolong Itself When Ignored

- Increased risk of aspiration→pneumonia
- Agitation→Risk of falls, breakage,restraints
- Altered perceptions of pain→ inadequate/increased use of opiates
- Poor oral intake→ dehydration, malnutrition, hyponatremia, uremia

Further Ways that Delirium Prolongs Itself

- Inactivity/prolonged bedrest→ decubiti, UTIs, phlebitis, poor conditioning, bony resorption (hypercalcemia)
- Impaired sensory awareness/poor communication→ poor reporting of new sources of pathology (pain, infection, etc)

Medication Considerations

- Historically, for behavior
- Newer pathophysiological theories may allow disease modification, however
- Will dopamine blockers prove particularly helpful with the excesses of dopamine found in delirium related to oxidative stress? (see slides 75-79)
- Will immune mediators have a role? (see slides 86-91)

Maldonado JR (2008): Crit Care Clin 24(4): 789-856.

Few Double-Blind, Placebo-Controlled, Randomized Trials

Few, and few replications, little consensus

- Benzodiazepines are to be ***avoided!!!***
- Antipsychotics are preferred; in general, avoid those with anticholinergic effects
- Effectiveness found for risperidone, olanzapine, quetiapine but not clear these are better than haloperidol
- Kim S 2010 Hum Psychopharmacol, Devlin J 2010 Crit Care Med

Classic Medication Trial

- Kalisvaart et al found that among elderly hip surgery patients at risk for delirium, preoperative use of haloperidol 1.5 mg/day in combination with the same dose up to 3 days after hip surgery, resulted in decreased *severity and duration* of delirium episodes, as well as the number of days of delirium, but *did not decrease the incidence* of delirium postop.

Kalisvaart KJ J Am Ger Soc 2005

Approaches to Medication In Agitated Delirious Patients

- ***Avoid benzodiazepines***, trazodone, benadryl
  - Lorazepam an independent risk factor for transition to delirium , even compared with fentanyl, morphine, and propofol in ICU patients [1]
- Provide safe prns
- *LOW* DOSE NEUROLEPTICS**
  - Risperidone 0.25-0.5 po bid prn (unless hx CVA)
  - Quetiapine 25 mg po bid prn
  - Haloperidol 0.25-0.5 po bid/IM
  - Haldol IV:QTC>440, Normal K+, Under 40 mg/day
    - » Risk: Hypotension, Severe Ventricular Arrythmias
    - » Drip is MOST effective, starting at very low dose

Pandharipande, Anesthesiology. 2006 Jan;104(1):21-6

•***NOTE: This regimen is provided by the author based on clinical practice; I have not found olanzapine useful for delirium. Low doses are much more appropriate than high.*

Sedating Agents in Critical Care Settings

- Analgesics and sedatives may help alleviate stress response in critically ill pts, improving outcomes as well as ability of staff to work effectively and safely with pts, as well as being essential (at times) for mechanical ventilation
- Agitation and anxiety may reflect physiological states such as pain, hypoxia, withdrawal
- Historical problems with midazolam (benzo) and propofol (gaba-ergic)

Dexmedetomidine: A Better Way?

- Alpha 2 adrenergic agonist
- 2-3 hour half life; easy to provide as IV infusion
- Negatives: Bradycardia, sinus pause, arrest
- Hypertension and hypotension (related to alpha 2 impacts)
- *Possible* decreased minute ventilation, response to CO2 challenge;
- Positives:
- Some analgesia
- Some anti-inflammatory impact
- ?Neuroprotective effect in ischemia?
- May address withdrawal from benzos, alcohol but peripheral alpha blockade may mask signs of sympathetic outflow

Environmental Factors*

- Frequent reorientation
- Moderate level of sensory stimulus
- Minimize caregiver changes
- Provide hearing aids, glasses
- Family available
- QUIET at night—avoid VS, meds, etc.
- Avoid Restraints
- **AMBULATE! Emphasize FUNCTION!**
- ***See appendix for full description

Delirium as a Symptom of Hospital Care

- "Delirium often results from hospital-related complications or inadequate hospital care and can be viewed as a symptom of broader problems in the delivery of hospital services."
- "…the incidence of delirium…can serve as a window on aspects of the quality of hospital care that are not currently measured"

Inouye S, et al., "Delirium: A symptom of how hospital care is failing older persons and a window to improve quality of hospital care", Am J Med 106:565-573, 1999

Example ….

- A 79 year old man with dementia, DMII, CAD, COPD, and acute renal failure but no other psychiatric history was admitted for pneumonia. After a 3 week hospital course complicated by delirium, hyponatremia, and UTI, he has been less agitated, more cooperative and more oriented for 2 days in association with decreased wbc and lessened oxygen requirements. You are consulted for acute suicidal ideation. What should you do?

Case #1 Discussion

- Delirium must be ruled out first here…it offers more morbidity than depression in this setting and this patient is very vulnerable to it. Suicidal ideation is common in delirium. Adding an antidepressant may worsen the picture—better to wait 2-3 days to r/o delirium, as that delay will not greatly impact treatment of depression anyhow. Mislabelling as depression may result in failing to search for the cause of the delirium.

Example #2

- A 59 year old man functional man with a lifetime history of bipolar disorder and no other medical comorbidities was initially treated 3 months PTA with lithium, valproate, and risperidone in slowly escalating doses. He has a 1 month history of steadily declining mental status, now being completely dependent in ADLs. He appears cognitively very slowed on admission, struggling with attention questions. Li+ level is 2.15. What do you do now?

Example #2 (2)

- Okay, lithium and risperidone are stopped and valproate is reduced to ¼ prior dose (500 mg/day). Over the next 10 days he improves only slowly and gradually.
- What do you do now?

Case #2 Discussion

- This relatively young, healthy patient should not have had such profound delirium, or such slow resolution, with just this one stressor (elevated Li+) based on risk factor analysis. Therefore, medical investigation proceeded further…head CT revealed gross atrophy that had not otherwise been apparent. Treatment course had to be fundamentally different! “Manic” symptom presentation one month before might have been first sign of dementia.

"Take Homes"

- Delirium is a severe illness with many negative consequences that is very ***rarely*** completely recoverable
- The most effective approach is ***prevention***, focusing on frail patients as the most important population of interest (less frail patients are more likely to recover)
- In the presence of delirium, your most important job is to identify and address ***treatable*** causes
- ***Always*** use very low dose neuroleptics, which may not modify disease but **will** allow behavioral control so the underlying causes can be addressed
- ***Always*** use environmental modifications
- New findings on pathophysiology may have real impacts on modifying the disease itself

Multiple Choice #1

A 70 yo man with a history of severe alcohol abuse, life-threatening withdrawals (including DTs on one occasion), hepatitis, MI x 2, prior chronic renal insufficiency and hypertension is admitted for treatment of an acute cellulitis. He has been drinking two fifths of whiskey per day for the past 2 months. On admission he is delirious and agitated, with elevated pulse (105, RRR) and blood pressure 160/95) His last drink was 2 days earlier. What first approach would you take?

A. Pt is high risk for severe withdrawal, which, given his baseline burden of illness and cellulitis, could complicate his medical recovery. Begin lorazepam at 2mg q 4 to prevent a serious withdrawal

B. Review medications and remove any with significant risk for delirium; review laboratories (comp, CBC, urinalysis) to assess overall risk factors for delirium; provide symptom triggered alcohol withdrawal regimen using lorazepam 2 mg q 2 hr prn P>110, BP >165/100

C. Interview the patient to determine whether he has any signs of delirium (inattention, fluctuation in any behavioral/affective/cognitive sphere), obtain history from collaterals re whether he has in fact been drinking recently, and to what extent; weigh the risk that benzos will worsen his delirium against the benefits they might have in treating alcohol withdrawal in his case.

D. Put patient on low dose beta blockers to control VS, treat other medical illnesses, provide symptom triggered lorazepam regimen (as above) for withdrawal prophylaxis, and put the patient into restraints to avoid having to use any CNS active agents

Multiple Choice #1

Best answer: C

This patient is already at a high risk for delirium based on his age and severe comorbidities, including renal insufficiency. Use of benzos for withdrawal must be carefully weighed against the risk of worsening his delirium.

B. Without adequate collateral history, providing a high dose prn regimen of potentially unnecessary benzos puts the patient at risk of worsened delirium. His elevated VS may reflect agitation or pain due to the cellulitis

C. Beta blockers most often mask the sympathetic outflow signs of withdrawal, which are vital to monitor in determining whether this relatively frail, ill man should be exposed to tthe additional deliriogenic risk from the addition of benzos for treatment of a withdrawal syndrome.

- →*Note that with additional trials of anticonvulsants for alcohol withdrawal, or dexmedetomidine for alcohol withdrawal delirium, benzos remain the standard of care.*

Multiple Choice #2

Which of the following medication used for the treatment of pain puts patients at the highest risk for iatrogenic delirium (in light of recent studies of neurotransmitter mechanisms involved in delirium)?

A. Tramadol
B. Gabapentin
C. Morphine
D. Nortriptyline

Best answer: (c), because morphine is BOTH anticholinergic and dopaminergic

Multiple Choice #3

Choose the answer which best describes the most important risk factors in predicting delirium in frail patients:

A. Frail patients often lack social support networks due to loss of mobility.

B. Frail patients often lack nutritious diets due to poor mobility and loss of economic resources

C. Baseline medical risk factors impair frail patients' response to the effects of additional acute medical illness.

D. Adherence to a medical treatment regimen may be poor in a frail patient with chronic medical conditions.

E. All of the above

Best answer: E

Multiple Choice #4

Which of the following is the best example of inattentiveness?

A. The patient interrupts the conversation to ask when he will be discharged.
B. The patient is oriented and aware of his recent medical problems but falls asleep during the conversation.
C. The patient suddenly bursts into tears when you are discussing his recent amputation.
D. The patient watches a fly buzzing on the ceiling while you are discussing the prognosis for his lung cancer, then falls asleep.

Multiple Choice #4

Best answer is (d);

A. Impulsive interruptions may or may not indicate inattentiveness.

B. Falling asleep may indicate inattentiveness, but further information would be needed to rule out other explanations such as recent administration of a sedating medication.

C. Sudden bursts of affect have a significant differential beyond inattention.

D. This patient seems distracted despite discussion of an issue of vital personal importance to him. In the context also of apparent drowsiness, the clinician should suspect the presence of delirium.

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