Delirium: New Ways to Understand and Manage It

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Self-Assessment Question 1

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 *initial* plan would be best here?

a. Assign a sitter (1:1), evaluate patient for antidepressant, provide supportive psychotherapy to address prolonged hospitalization
b. Assign a sitter (1:1), check urinalysis, do a chest x-ray, begin SSRI
c. Transfer to psychiatry for further care
d. Evaluate for a sitter (1:1), check urinalysis, do a chest x-ray, discuss with primary team

Self-Assessment Question 2

A 70 yo man with severe alcohol abuse and a history of severe withdrawals (including DTs on one occasion), hepatitis, MI x 2, prior chronic renal insufficiency and hypertension now admitted after drinking 2/5 of whiskey per day for 2 months along with an acute cellulitis, who is delirious and agitated on admission with elevated pulse (105, RRR) and blood pressure 160/95) His last drink was 2 days prior. 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 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 risk of use of benzos worsening patient's delirium vs likelihood that he is in a withdrawal state severe enough that benzos are warranted routinely regardless of his risk of worsened delirium due to addition of benzos.
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

Self-Assessment Question 3

Which medication used for pain puts patients at the highest risk for iatrogenic delirium given the most recent studies regarding neurotransmitters involved in delirium?

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

Self-Assessment Question 4

Which of these risk factors are most important in predicting delirium?

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

B. Frail patients often have poor diets, again due to poor mobility and loss of economic resources

C. Frail patients' baseline medical risk levels impact on the person's ability to mount a full and complex response to acute medical illness

D. Frail patients often cannot manage their complex set of medication and appointment schedules

E. All of the above

Self-Assessment Question 5

Question: Which is a good example of an inattentive patient?

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

Recognition: D-

- 33-95% of cases MISSED—either misdiagnosed as depression, psychosis, or dementia, or not appreciated at all
- Inouye, J Ger Psy and Neurol., 11(3) 1998
- Bair, Psy Clin N Amer 21(4)1998

How Big a Problem is This?

- DELIRIUM
- 10-40% Prevalence in acute settings
- 25-60% Incidence in acute settings*
- VS DEPRESSION
- 10% Primary care; 25% Acute settings
- * Inouye, J Ger Psy and Neurol., 11(3) 1998

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:Inpatient

Outcomes of Delirium: NH

- 801 hospitalized patients ≥ 70
- Among patients with multicomponent targeted intervention (Elder Life program, Inouye)

Severity of Delirium

- 104 institutionalized elderly (secondary analysis)
- Severity of delirium correlated with outcome
- Correlation with prior cognitive status
- Voyer 2007 J Clin Nurs 16:5

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**

Death?

- Prospective study of 2 cohorts of medical inpatients ≥ 65; 243 with prevalent or incident delirium, 118 without
- Adjusted HR 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 Predispose to Dementia?

- 203 patients >65 on a general medicine service (Halifax), no dementia at baseline
- 5.6% per year without delirium
- 18.1% per year WITH delirium
- Adjusted OR: (sex, age, comorbid illness)=5.97 (CI=1.83-19.54); P=0.0003
- Rockwood Age Ageing 1999 28(6)

Reversible? Not Necessarily…

- 325 Elderly patients ≥ 65 admitted to teaching hospital; pre-existing dementia included
- Six month followup study

- Levkoff, Arch Intern Med. 1992 152(2)

Resolution of *All* New Symptoms of Delirium

	Full Syndrome	Partial Syndrome
Discharge	4.0%	17.3%
3 Months	20.8%	42.4%
6 Months	17.7%	37.4%

Levkoff 1992

Delirium Resolution

- 393 pts ≥65 referred to post acute facilities after delirium episode
- Delirium resolved by 2 weeks→regaining of 100% prehospital functional level
- Slowly resolving delirium or recurrent delirium had intermediate return of function
- With no resolution of delirium, <50% of prehospital functional level was achieved
- Kiely et al.2006 J of Gerontology A

Cost of Delirium

- $4-$16 Billion per year in US alone*
- 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**
- In other work LOS largely accounted for this difference
- * Inouye 1998 J Geriatr Psychiatry Neurol:11
- **Milbrandt 2004 Critical Care Medicine 32:4

Determining 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, hyperattentiveness
- Days of week backward, immediate recall are good bedside tests

Summary of Clinical Signs

- 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)

Gross Disturbance

- “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
- Misdiagnosis: Examiner often *misinterprets such* patient behavior as their own: Examiner can’t hear patient, room “too noisy”, “I must just be tired”, patient is “sleepy” or worn out from PT, etc.

Summary of Signs, con't

Cognitive Signs:

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

Summary of Signs, con't

- 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 Signs, con't

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

Sensory and Motor Losses

- 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 Signs, con't

- 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

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!

This Misdiagnosis: Double Risk

- ***Risk***:

  Misdiagnosing delirium as depression:

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

- B. May add another CNS active agent (antidepressant)

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

How Do We Impact Outcomes?

- I. Improving Recognition
- 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

- Active deliriums are often recognized;
- Quiet ones…no; unrecognized or misdiagnosed
- But….clinical interview data still often remains unclear and usually represents a small slice of patient's presentation and behavior during 24 hrs
- ICU presents specific problem given difficulty communicating with patients

Operationalizing Recognition:CAM

- “Confusion Assessment Method”
- 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

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 observed
- Fluctuations in clinical presentation are much more easily put into context

Nurses' Notes

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

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, 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

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.

Comments on 3 Prior Slides

- Note the *nonlinear* relationship between risk of delirium and cumulative risk burden (predisposing and precipitating) as you proceed from upper left to lower right in Inouye's prior slide
- You can observe nearly the same interaction in the following slide, although it is not segregated by predisposing and precipitating factors (Francis 1990 J Gen Internal Med 5:1)

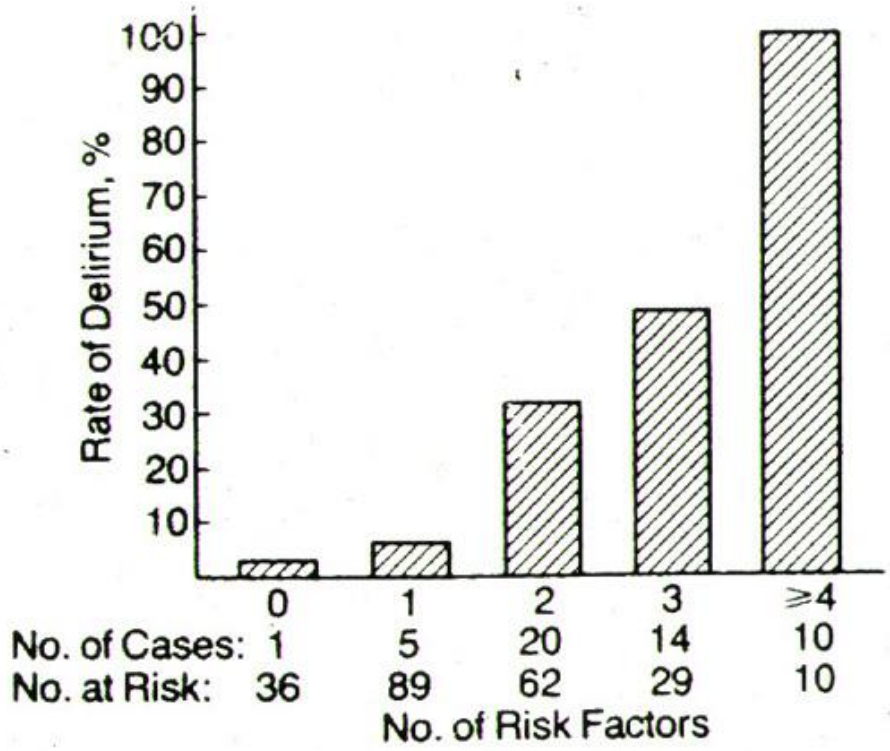

Fig 1.—Rate of delirium according to number of risk factors. The risk factors included abnormal serum sodium levels, moderate or severe illness, prior cognitive impairment, fever or hypothermia, use of psychoactive drugs, and azotemia. The trend is significant at $P<.0001$.

Main Observations*

- Every “risk factor” study actually lists a different assortment of factors…..so:
- It does not appear to be the *specific* risk factor(s) that is/are important…it is that there are *enough* to overcome the patient’s resilience, biological reserve, and (fragile) equilibrium…in a dose-dependent fashion. It is a continuum: the more frail the patient, the less of an impact is required to push them over the edge into a ***disequilibrated*** state (such as delirium or a fall.)

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

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**
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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

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- “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. (It might also be why systematic assessment of mobility and balance could be a better indication of recovery from delirium than assessment of cognition.)

Rockwood 2002 CMAJ 167(7)

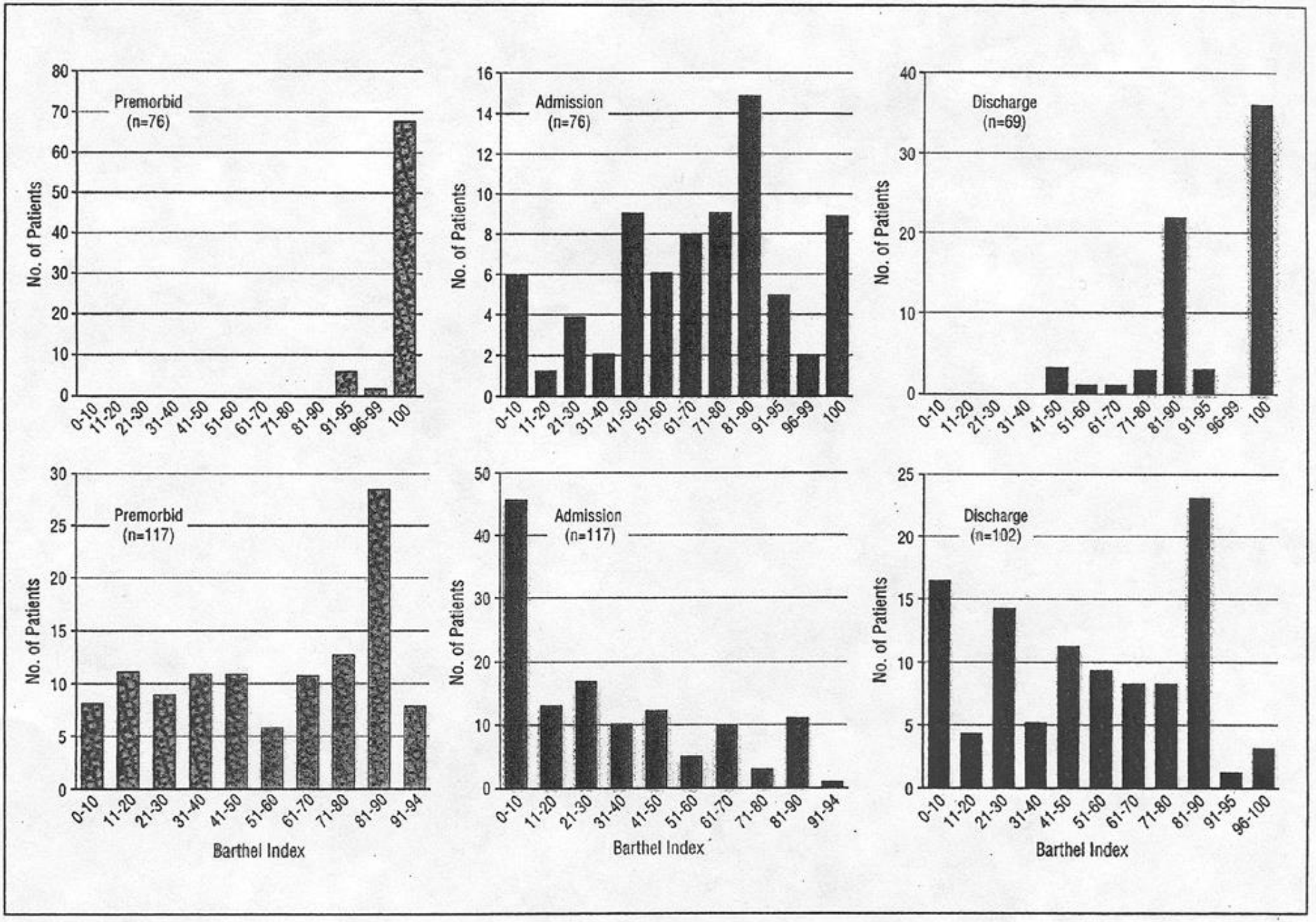

Figure 1. *Distribution of Barthel Index scores before admission, at admission, and at discharge for the well elderly (top) and for the frail elderly (bottom).*

Physiological Factors..?

- Sarcopenia (>50% in “old old”) atherosclerosis, cognitive impairment, malnutrition (decline in serum cholesterol)
- Precursors: Pain, delirium, depression, DM, anorexia, inactivity, fear of falling

- Morley 2002

On the Other Hand

- If enough variables are considered (say, 40), the specific ones do not matter. It is the number…that predicts "higher likelihood" of frailty
- Deficits=frailty; not age
- Less variability in health factors in later age; "all are sick"; less is needed to perturb
- Rockwood 9/07

How Frequent? How to Measure?

- 7% community dwellers (Fried, 2001)
- Obstacle course/hip abduction strength, semi-tandem part of Romberg, coordination on pegboard test (Brown 2000)
- One leg standing test (Vellas, 1997)
- TAG: “Timed up and go”: rise from chair, walk 3 meters, sit down. >4.5 seconds carrying glass of water=frail (Lundin-Ollsson)

Impact

- Incontinence restricts social activity, as does gait difficulty; → osteopenia and fractures, etc
- Does a loss of "internal complexity"→ need for world to respond in more complex 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: 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 J Gerontology 61 2006

Pathophysiology

- Much of this discussion adapted from Paula Trzepacz, M.D. (lecture presentation at University of Michigan, 2004)
- Animal studies are primary basis for this work (Trzepacz, Van der Mast)

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 *out of* "distractions" to focus attention…is this a place to investigate for etiology of delirium?

Prefrontal Cortex

- Layer 3 is a huge association/abstraction/EF area, takes very long time to develop (past adolescence (!))…and a main area of decline in Alz patients…delirium in this group found associated with significant declines in Layer 3, which is also very rich in acetylcholine

Neurochemical Findings:Most Useful Theories*

- *Decrease in acetylcholine;*
- *Increase in dopamine (ECT, opiates, cocaine…);*
- *OR imbalance between these systems*
- Others….glutamate, gaba pathways, immune mediators…less unifying in explanation

Acetylcholine*

- A primary neurotransmitter associated with arousal, learning, memory, attention, and sensory GATING at the thalamus
- Anticholinergic levels associated with increased agitation, slower EEG patterns, delirium (which may reverse with agonists)
- Decreases in acetylcholine associated with decrease in MMSE

Genesis of Acetylcholine

- Krebs/CAC: glucose and oxygen as substrates produce ATP as well as AcetylCoA, which is a precursor
- In hypoxic states, we know that AcChol is decreased and DOPA is increased
- With aging, synthesis of AcChol is decreased, but acetylcholinesterase activity is not decreased…net loss

Serotonin*

- Synthesis dependent on availability of tryptophan
- BUT→Both ***increased*** serotonin (such as in hepatic encephalopathy) and ***decreased*** serotonin (such as in alcohol w/d) in brain have been associated with delirium

Inflammatory Hypotheses

- Tissue injury and inflammation increase cytokine activity, alter BBB, and alter NT function/release
- Cytokines (interleukins—IL1, IL2, IL6, IF-alpha,TNF) are released from glia under stressful circumstances (such as surgery, acute illness)

Inflammatory Hypotheses, con't

- Cytokines affect hormonal regulation and neurotransmitter regulation—especially decrease in DOPA and norepinephrine and increase in AcChol
- Treatment with cytokines may cause dose dependent cognitive, emotional, and behavioral disturbances, such as delirium

Neuroimaging

- Little done; a number of SPECT studies
- 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 2006 J Gerontology A 61

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

Why Might UTI Predispose?

- Barrington's nucleus: a pontine structure that regulates pelvic visceral function (signals ascending noradrenergic paths that awaken us from sleep to relieve ourselves…)
- Has major reciprocal connections with serotonergic nuclei such as raphe, locus ceruleus……..

Interventions:What's Available Now*

- Delirium rates increase with level of morbidity, so interventions must be multi-focused
- Currently somewhat effective "gold standards" include multicomponent interventions (Inouye 1999 NEHM 340(9), Marcantonio 2001 JAGS 49:5, Pitkala 2006 J Gerontol A Biol Sci Med Sci. 61(2)

What's Available Now, con't*

- Prophylactic low dose haloperidol may reduce duration and severity of delirium with decreased LOS in hip fracture patients (Kalisvaart 2005 J Am Geriatr Soc. 53(10)
- Overall, only one has decreased incidence of delirium (Inouye 1999 NEJM 340(9), but severity, duration, and length of hospital stay are more frequently achieved.

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?

Outcomes of Delirium: NH

- 801 hospitalized patients ≥ 70
- Among patients with multi-component targeted intervention ("Elder Life" program), no impact on % needing long term care
- BUT, lower total costs, shorter LOS, lower cost per survival day (15.7% savings) among those receiving intervention
- Leslie 2005 J Am Geriatr Soc 53:3

Interdisciplinary Comprehensive Care: One "Gold" Standard*

- Prospective, Randomized, Blinded, 126 patients $\geq$ 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, con't

- 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

What Guidance Do We Have?*

- Cases involving moderate risk are more amenable to alterations in course of delirium (Inouye S 1998 NEJM 340(9); partial syndromes present risk also (Marcantonio 2001 JAGS 49:5)
- Increased severity predicts worse outcome (McCusker 2002 J Arch Int Med 162(4)
- Once delirium develops, it is harder to impact (Inouye 1999 NEJM 340(9)

So, to Practicalities….*

- 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

Precipitating Risk Factors: Systemic, Basic,*not* CNS*

- 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

Precipitating Risk Factors: Systemic, *not* CNS, con't*

- Any new medical event (MI, PE, CHF, hip fracture, orthopedic injury)
- Pain (especially at rest)
- Alcohol/benzodiazepine withdrawal
- Use of restraints
- Dehydration, Malnutrition
- New interventions/tests: Intubation, surgery (particularly orthopedic/vascular), biopsy, BM transplant, neuroimaging

Goals of Treatment*

- 1) EARLY intervention and screening for most common factors, taking med history into account
- 2) Maintain VIGILANCE (vulnerability appears to correlate with length of recovery)
- 3) 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 Prolongs Itself

- 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

Ways that Delirium Prolongs Itself, con't

- 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

- Medications are not used for disease modification so much as to modify ***behavior***
- Very few placebo controlled, randomized, double blinded trials published

Medication Trials

- Liptzin, in a sample of younger old, cognitively intact patients undergoing elective joint replacement surgery that donepezil was not helpful with delirium prevention or cholinesterase inhibitors were not helpful with delirium resolution or prevention (Liptzin B 2005 Am J Ger Psychiatr 13(12)

Medication Trials, con't

- 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 53(10)

Medication Trials con't

- One pilot study (randomized, placebo controlled, double blinded) of 12 patients $\geq$ 45 undergoing spinal surgery, demonstrated that no patients (0/9) receiving 900 mg/day of gabapentin for 3 days postoperatively developed delirium; 5/12 on placebo+opiates did develop delirium.
- Opium sparing effect? Leung 2006 Neurology 67(7)

Approaches to Medication*

- For agitation
- Avoid benzodiazepines, trazodone, benadryl
- Provide **safe** prns
- LOW DOSE NEUROLEPTICS
  - Quetiapine 25 mg po bid prn: →*Some very valuable efficacy noted recently in diminishing syndrome itself*
  - Risperidone 0.25-0.5 po bid prn
  - Haloperidol 0.25-0.5 po bid/IM
  - Avoid olanzapine; too anticholinergic

Very Effective: IV Haldol

- Haldol IV:QTC>440, Normal K+, Under 40 mg/day
  - » Risk: Hypotension, Fatal Ventricular Arrythmias which (per case reports) appear most common >40 mg/day
  - » ***Drip*** is easiest to titrate; start (.25 mg/hr), SLOW titration; rarely need >40 mg/day
  - » Often prolongs QTc; patients MUST be monitored
  - » Some studies: up to 900/day/rare EPS

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

Sedating Agents, con't

--Propofol

--IV general anesthetic with sedative/hypnotic properties at lower doses

--1-2 minute onset; 26-32 hr half life; 5-80 ug/kg/min (>80, cardiac arrest adults)

-- Hypotension (esp with initial bolus) bradycardia, elevated pancreatitic enzymes

-- Very rapid reawakening (11-13 minutes)

→ YOU CAN TAPER IT with better result

-- May contribute less to delirium than benzos

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!**

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, con't

- 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.

Summary

- 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 deliruim, 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

Self-Assessment Question 1

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 *initial* plan would be best here?

a. Assign a sitter (1:1), evaluate patient for antidepressant, provide supportive psychotherapy to address prolonged hospitalization
b. Assign a sitter (1:1), check urinalysis, do a chest x-ray, begin SSRI
c. Transfer to psychiatry for further care
d. Evaluate for a sitter (1:1), check urinalysis, do a chest x-ray, discuss with primary team

Best Answer: d
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.

Self-Assessment Question 2

A 70 yo man with severe alcohol abuse and a history of severe withdrawals (including DTs on one occasion), hepatitis, MI x 2, prior chronic renal insufficiency and hypertension now admitted after drinking 2/5 of whiskey per day for 2 months along with an acute cellulitis, who is delirious and agitated on admission with elevated pulse (105, RRR) and blood pressure 160/95) His last drink was 2 days prior. What first approach would you ake?

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 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 risk of use of benzos worsening patient's delirium vs likelihood that he is in a withdrawal state severe enough that benzos are warranted routinely regardless of his risk of worsened delirium due to addition of benzos.

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

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 its 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 is vital in determining whether this relatively frail, ill man should have the additional deliriogenic risk from the addition of benzos for 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.*

Self-Assessment Question 3

Which medication used for pain puts patients at the highest risk for iatrogenic delirium given the most recent studies regarding neurotransmitters involved in delirium?

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

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

Self-Assessment Question 4

Which of these risk factors are most important in predicting delirium?

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

B. Frail patients often have poor diets, again due to poor mobility and loss of economic resources

C. Frail patients' baseline medical risk levels impact on the person's ability to mount a full and complex response to acute medical illness

D. Frail patients often cannot manage their complex set of medication and appointment schedules

E. All of the above

Best answer: E

Self-Assessment Question 5

Question: Which is a good example of an inattentive patient?

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

Best answer is (d);

A. Impulsive question asking in the absence of other signs of delirium is non conclusive
B. This patient may in fact be delirious, but his otherwise intact awareness of his environment weighs somewhat against it. He may have just received some sedating medication. A fuller clinical picture is needed to r/o delirium.
C. Sudden bursts of affect are not unusual in delirium, but in and of itself, this patient may simply be upset about their amputation
D. This patient is having difficulty focusing her/his attention on an issue of clear importance to her/him, and then appears to have a depressed level of consciousness