Delirium: What is it, and what do we (not) know about it?

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Plan

• Delirium: What is it?
  – Historical Perspective
  – Geriatric syndrome

• What do we (not) know about it?
  – Assessment and Diagnosis
  – Epidemiology
  – Mechanisms
  – Interventions
Delirium: What is it?

Historical perspective
Delirium: early descriptions

Celsus, 1st Century:

“Sick people, sometimes in a febrile paroxysm, lose their judgment and talk incoherently… when the violence of the fit is abated, the judgment presently returns…”
Synonyms:
Peer-reviewed literature

- Acute confusional state
- Acute mental status change
- Altered mental status
- Toxic/metabolic encephalopathy
- Sundowning
- Subacute befuddlement

Multiple names still cause confusion across disciplines

Francis et. al., JGIM, 1990
# Delirium Timeline

<table>
<thead>
<tr>
<th>Years</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>Delirium first appears in DSM 3</td>
</tr>
<tr>
<td>1980’s</td>
<td>Delirium research takes off</td>
</tr>
<tr>
<td>1990</td>
<td>Publication of the CAM</td>
</tr>
<tr>
<td>Early 1990’s</td>
<td>Publication--predictive models</td>
</tr>
<tr>
<td>Late 1990’s</td>
<td>Publication--intervention studies</td>
</tr>
<tr>
<td>2000’s</td>
<td>ICU Delirium, Long term effects</td>
</tr>
<tr>
<td>2010’s</td>
<td>First NIH P01, ADS founded, Several intervention trials launch</td>
</tr>
</tbody>
</table>
Articles Published on Delirium Per Year

- 1980-84
- 1985-89
- 1990-94
- 1995-99
- 2000-04
- 2005-09
- 2010-11
What is delirium in DSM5?

- Disturbance in attention and awareness (reduced orientation to the environment)
- Develops acutely and tends to fluctuate
- An additional disturbance in cognition, (e.g., memory deficit, language, visuoperceptual)
- Not better explained by a preexisting dementia
- Not in face of severely reduced level of arousal or coma
- Evidence of an underlying organic etiology or etiologies

*Used with permission. American Psychiatric Association, 2013*
Delirium

Geriatric Syndrome
Delirium = Acute brain failure

- Caused by exceeding reserve
- Under stress, brain is “weakest link”
  - In others, falls, U.I., may occur
- Multiple contributing etiologies
- Final common pathway of multiple mechanisms
Delirium → Geriatric Syndrome

Inouye, Kuchel et. al., JAGS, 2007
Delirium: ↑ Risk with Aging

- Stressor
- Compensation
- Reserve
- Normal Range
- Decompenstation
- DELIRIUM

YOUNG

OLD

Reserve
Delirium Assessment and Diagnosis

What we know
Delirium Measures

- CAM: Diagnostic Algorithm, Long CAM
- CAM-ICU (B-CAM)
- Symptom checklists: NEECHAM, DOS
- Delirium Severity Measures
  - DRS-98, MDAS, CAM-S

CAM Diagnostic Algorithm

- Feature 1: Acute change, fluctuating course
- Feature 2: Inattention
- Feature 3: Disorganized thinking
- Feature 4: Altered level of consciousness

Diagnosis of Delirium: requires presence of Features 1 and 2 and either 3 or 4.

Bedside Delirium Evaluation

- Patient Interview:
  - Symptoms: confusion, perceptual disturbances
  - Cognitive testing: orientation, attention
- Interviewer observations:
  - Altered Level of Consciousness
  - Psychomotor agitation, retardation
- Family/caregiver: time course, acuity
- CAM puts it all together
Phenomenology

- Psychomotor variants:
  - Hyperactive, Mixed: 25%
  - Hypoactive, normal: 75%

- Abnl LOC: Prevalence varies widely
  - Higher in ICU, PACU

- Hallucinations, delusions rare (~10%)

- Delirium superimposed on dementia
  - May account for 50% in some settings
What we don’t know

• Which assessments are best suited to which populations?
• Can we use modern measurement theory to improve assessment?
• How to implement case finding on a broad “population” level?
• How to improve documentation?
  – ICD-9 (10) billing codes, EMRs
  – Facilitate large scale QI efforts
Delirium Epidemiology

What we know
## Delirium Incidence/Prevalence

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence or Incidence</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Inpatients &gt; 70 yrs</td>
<td>Mixed (50:50)</td>
<td>30-40%</td>
</tr>
<tr>
<td>Major surgery &gt; 70 yrs</td>
<td>Incidence</td>
<td>15-25%</td>
</tr>
<tr>
<td>Hip Fx, CABG &gt; 65 yrs</td>
<td>Incidence</td>
<td>45-55%</td>
</tr>
<tr>
<td>Intensive Care Unit &gt; 18 yrs</td>
<td>Mixed</td>
<td>75-80%</td>
</tr>
<tr>
<td>Post-acute admits &gt; 70 yrs</td>
<td>Prevalence</td>
<td>15-20%</td>
</tr>
</tbody>
</table>

Inouye et. al., Ann Int Med, 1993; Marcantonio et. al., JAMA, 1994; Marcantonio et. al., JAGS, 2000; Ely et. al., JAMA, 2004; Marcantonio et. al., JAGS, 2010
Delirium Risk Model

Predisposing factors:
- advanced age
- pre-existing dementia
- other CNS diseases
- functional impairment
- multiple comorbidities
- multiple medications
- imp. vision/hearing

Precipitating factors:
- new psychoactive med
- acute medical problem
- exacerbation of chronic medical problem
- stroke
- surgery
- pain

Inouye et. al., JAMA, 1996
Implications of Risk Model

• More baseline vulnerability, less acute precipitants needed
• Acute precipitants rarely in the CNS
• “Law of Parsimony” rarely applies:
  – There is rarely a single cause of delirium
  – C/w geriatric syndrome
## Validated Clinical Prediction Rules

<table>
<thead>
<tr>
<th>Population</th>
<th>Risk Stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Medicine</td>
<td>18X low-high</td>
</tr>
<tr>
<td>Non-cardiac surgery</td>
<td>22X low-high</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>10X low-high</td>
</tr>
<tr>
<td>Cardiac Surgery</td>
<td>5X low-high</td>
</tr>
</tbody>
</table>

Marcantonio et. al., JAMA, 1994, Rudolph et.al., Circulation, 2009
Outcomes after Delirium
Short Term Outcomes

- Nosocomial complications: RR=2-5
- In-hospital death: RR=2-20
- Increased LOS: 2-5 days
- Post-acute facility placement: RR=3-5

*Adjusted for age, sex, cognitive impairment, functional impairment, comorbidity, admitting diagnosis

Marcantonio et. al, JAMA, 1994 and others
Long term outcomes

Meta-analysis showed delirium was independently* associated with:

- Mortality for up to 2 years
- Institutionalization for up to 14 months
- New dementia for up to 4 years

*Adjusted for age, sex, cognitive impairment, functional impairment, comorbidity

Witlox et. al., JAMA, 2010
Costs

- Delirium → $60,000 incremental costs per patient over subsequent 12 months
- Translates to over $100 billion annually
- Most of these costs after hospitalization
- Increasing importance in ACO era

Leslie, Marcantonio et. al. Medical Care, 2008
Relationship to long term cognition
TRACS: Thinking and Recovery after Cardiac Surgery--Delirium, Cognition

Saczynski, Marcantonio et. al., NEJM, 2012
RANK-USA: Cognition 12 mos. after ICU

Pandharipande et. al, NEJM, 2013
What we don’t know

- Can we implement risk factor models at “point of care” to impact outcomes?
- Can we further improve risk stratification with biomarkers, genes, or imaging?
- What are the mechanisms by which delirium is linked to long term outcomes?
- What is the true relationship between delirium and dementia?
Delirium Mechanisms

What we know
Schematic of Delirium Mechanisms

Maldonado, Am J Geri Psych, 2013
Major Mechanistic Models

- Neuro-inflammation
- Neuro-aging (homeostenosis)
- Neuro-endocrine (aberrant stress)
- Neurotransmitter dysregulation
- Oxidative stress
- Sleep/wake dysregulation (melatononin)
- Network disconnectivity

Maldonado, Am J Geri Psych, 2013
Neuroinflammation Hypothesis

Marcantonio et al. JAMA, 2012
Neurotransmitter Hypothesis (simplified)

Treatment: ↑ Acetylcholine
- Reduce Anti-cholinergics
- Pro-cholinergic drugs

Treatment: ↓ Dopamine
- Reduce dopaminergic drugs
- Antipsychotics

Dopamine

Acetylcholine

Delirium
Animal Models

• Necessary to advance basic research
• Several models now developed
• Delirium: “sickness behavior syndrome”

Cons/Caveats:
• Can we truly replicate delirium in an animal?
• Is it possible to create a single model for such a complex syndrome?
• Need to consider issues of aging
What we don’t know

• Of all the postulated mechanisms, are some more prevalent/pertinent?
• Can we match mechanisms to delirium phenotypes?, to patients?
• Can we create animal models that inform the human condition?
• Given its complexities, can a coherent picture of the “whole elephant” emerge?
Delirium Interventions

What we know
Delirium Prevention
Homeostenosis: Implications for Prevention

- Stressor
- Compensation
- Reserve
- Normal Range
- Decompenstaion

YOUNG
- Reserve

OLD
- DELIRIUM
Reduce Stressors

Stressor

Reserve

Normal Range

Compensation

YOUNG

Reserve

OLD
Increase Reserve

Reserve

Stressor

Compensation

Normal Range

YOUNG

Reserve

OLD

Stressor

Compensation
## Multicomponent Prevention

<table>
<thead>
<tr>
<th>Approach</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>HELP</td>
<td>Targeted 6 Delirium Risk Factors</td>
</tr>
<tr>
<td></td>
<td>Reduced delirium by 40%</td>
</tr>
<tr>
<td></td>
<td>Disseminated (&gt;100 centers)</td>
</tr>
<tr>
<td>Proactive Consultation</td>
<td>10 Modules targeting Delirium Risk</td>
</tr>
<tr>
<td></td>
<td>Reduced delirium by 36%</td>
</tr>
<tr>
<td>Patient Centered Care</td>
<td>Care: task allocation → individualized</td>
</tr>
<tr>
<td></td>
<td>Reduced delirium duration, LOS</td>
</tr>
</tbody>
</table>

Inouye et. al. NEJM, 1999, Rubin et. al. JAGS 2011, Marcantonio et. al. JAGS, 2001, Lundstrom et. al., JAGS, 2005
# Single Component Prevention

<table>
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<tr>
<th>Approach</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics (low dose)</td>
<td>Mixed (benefit/harm)</td>
</tr>
<tr>
<td>Dementia Drugs</td>
<td>No benefit</td>
</tr>
<tr>
<td>Reducing sedation, surgery</td>
<td>Preliminary benefit</td>
</tr>
<tr>
<td>Reducing sedation, ICU</td>
<td>Benefit</td>
</tr>
<tr>
<td>Blood transfusion, Hgb=10</td>
<td>No benefit</td>
</tr>
</tbody>
</table>

Summary of Prevention

• Multifactorial strategies work
  – Multiple small interventions yield big results
  – Key: fidelity to intervention program
  – Little ongoing work in this area (why?)

• Single component interventions
  – ↓ drugs: effective
  – Other single mechanism targets: mixed

• Little work: ↑ Reserve
Delirium Treatment and Rehabilitation
## Multicomponent Treatment (Acute)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic detection of delirium, Specialized care</td>
<td>Trend toward quicker cognitive improvement</td>
</tr>
<tr>
<td>Comprehensive Geriatrics Assessment, Specialized Management</td>
<td>Reduced delirium severity and duration</td>
</tr>
<tr>
<td>“Delirium Room”</td>
<td>Reduced use of sedating meds; equally safe outcomes</td>
</tr>
</tbody>
</table>

Single Component (Drug) “Treatment”

- What (and who) are we treating?
- Existing literature:
  - Antipsychotics pref. to benzodiazepines (most cases)
  - Atypicals: equivalent to haloperidol
  - Reduced delirium severity: hyperactive → hypoactive?
- New placebo controlled trials:
  - Several ongoing, primarily in the ICU
  - First just published: “haloperidol did not modify duration of delirium in critically ill patients”

Lacasse et. al., Ann Pharm, 2006; Multiple Cochrane systematic reviews; Page, et. al. Lancet Resp Med, 2013
## Commonly used drugs (all “off label”)

<table>
<thead>
<tr>
<th>Drug/Route</th>
<th>Starting Dose</th>
<th>Sedation</th>
<th>EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol PO, IV</td>
<td>0.25-2 mg</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Risperidone PO, IV</td>
<td>0.25-2 mg</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine PO, SL, IM, IV</td>
<td>2.5-10 mg</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Quetiapine PO</td>
<td>12.5-50 mg</td>
<td>++++</td>
<td>+</td>
</tr>
</tbody>
</table>

Marcantonio, Ann Int Med, 2011
Delirium Rehabilitation

• Substantial fraction of delirium persists
• Even if resolved, cognitive deficits persist
• Goal of programs:
  – Assess delirium perpetuating factors and eliminate as possible
  – Cognitive rehabilitation
  – Physical rehabilitation
• Several trials ongoing in post-acute and outpatient settings
What we don’t know

• How can we more effectively disseminate proven multifactorial strategies?
  – Adding effective single component interventions
• Can we design/test new interventions?
  – to improve reserve?
  – for delirium rehabilitation?
• Can we create research networks to facilitate testing of complex interventions?
• How do we get delirium on the radar screen of large healthcare organizations?
U13 Conference Sessions

• Delirium as a Geriatric Syndrome
  – Parallels to Sleep, Voiding Dysfunction
• Psychoneuroimmunology
• Delirium and dementia: same or different?
• Delirium in vulnerable older adults: frailty, multi-morbidity, anesthesia
• Interventional research
U13 Conference Structure

• Large groups:
  – 20 minute talks
  – 5 minutes for questions

• Discussion time: large and small group

• Mentoring program

• Make connections: move the field forward