Delirium in the Intensive Care Unit
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Objectives

- Describe delirium, its prevalence, pathophysiology, and risk factors
- Describe the impact delirium has on patient outcomes
- Demonstrate how to use validated tools to monitor for delirium
- Understand how to treat delirium both pharmacologically and non-pharmacologically
- Describe the risks associated with antipsychotic therapy

What is Delirium?
Comes from the Latin word delirare, to “derail,” “to go off the plowed track”

Types of Delirium

Patient Factors
- Age
- Comorbidities
- HTN
- Cognitive Impairment
- Dementia
- Alcoholism
- Genetics
- Apolipoprotein E4 phenotype

Acute Illness*
- Mechanical ventilation
- Hypoxia
- Metabolic disturbances/Electrolyte imbalance
- Sepsis/Acute infections
- Withdrawal syndromes
- Seizures
- Head trauma/intracranial lesions
- Coma**

Environment
- Medications
- Sleep deficits
- Restraint use/immobilization

*HTN, dementia, alcoholism, and a high severity of acute illness are positively and significantly associated with delirium
** Coma is an independent risk factor for delirium in ICU patients

Prevalence
- 20-50% of non-intubated ICU patients
- 60-80% of ICU patients receiving mechanical ventilation
- Often present on admission
- More common in patients >65 years of age
- Remains unrecognized in 66-84% of patients
  - Attributed to other disease states
  - Treated as an expected occurrence
  - Not routinely assessed in most ICUs
  - Often missed due to fluctuating nature and variable presentation

Risk Factors for Delirium

Types of Delirium

Disorganized Thinking OR Altered Level of Consciousness
Inattention
Acute Confusional State
Fluctuating Mental Status

References
Pathophysiology

- Global brain dysfunction
- Patients with delirium have been found to have:
  - Alterations in cerebral blood flow and metabolism
  - Brain atrophy, lesions, ventricular enlargement
- Multifactorial
- Inflammation and cytokine release
- Hypoperfusion
- Imbalance in the synthesis, release, and inactivation of neurotransmitters
  - GABA, Dopamine, Acetylcholine, Serotonin


Prolonged Length of Stay

Delirious patients spend median of 10 days longer in the hospital
- 2-fold increased risk of staying in the hospital for each day spent in delirium
  - HR 1.2

Increased Mortality

- 3-fold increased risk of 6-month mortality
- 1.5 increased risk of death for each day spent in delirium
  - HR 1.1

Increased Health Care Costs

- 40% relative increase in ICU and total hospital costs

Delirium Contributes to Long-term Cognitive Impairment

- Delirious ICU patients were found to be nine times more likely to have cognitive impairment at discharge than non-delirious patients
- Delirium may lead to or accelerate development of dementia
- Delirium tends to persist in patients discharged from the hospital and ICU
- Only about 4% of patients have full resolution of symptoms before discharge from the hospital
- 40% of those patients had a full recovery 6 months later


Consequences Associated with Delirium

- Self-extubation
- 3-fold higher re-intubation rate
- Increased distress/anxiety for patients, families, caregivers
- Increased nosocomial Pneumonia
Monitoring Delirium in the ICU

- Recommended by the Society of Critical Care Medicine in all ICU patients (+1B)
- Validated monitoring tools
  - Confusion Assessment Method for the ICU (CAM-ICU)
  - Intensive Care Delirium Screening Checklist (ICU-DSC)

CAM-ICU

- Adapted from the original Confusion Assessment Method for use in ICU patients
- It has a sensitivity of 76-80% and specificity of 96%
- Four feature assessment
  1) Acute onset of mental status changes or a fluctuating course
  2) Inattention
  3) Disorganized thinking
  4) Altered level of consciousness
- Delirium is present when features 1 and 2 and either 3 or 4 are positive

CAM-ICU

- The Intensive Care Delirium Screening Checklist (ICDSC) is a validated screening tool for delirium in the ICU
- It has a sensitivity of 74-80% and a specificity of 75-82%
- It is based on DSM-IV criteria and features of delirium
- It is an 8 point scale that is to be completed based on data from each entire shift or from the previous 24 hours
- A score ≥4 indicates delirium

ICU-DSC

- Inattention
  - Difficulty in following a conversation or instructions. Easily distracted by external stimuli. Difficulty in shifting focus
- Disorientation
  - Any obvious mistake in time, place, or person
- Hallucination, delusion, psychosis
  - The unequivocal clinical manifestation of hallucination or of behavior due to hallucination or delusion such as grabbing at a non-existent object
- Psychomotor agitation or retardation
  - Hyperactivity requiring the use of additional sedative drugs or restraints in order to control potential dangerousness such as pulling out lines or foppishness or psychomotor slowing
- Inappropriate speech or mood
  - Disorganized or incoherent speech. Inappropriate display of emotion related to events or situation
- Sleep/wake cycle disturbance
  - Sleeping less than 4 hours or waking frequently at night or sleeping most of the day
- Symptom fluctuation
  - Fluctuation of symptoms over 24 hours or from shift to shift

ICU-DSC

- PATIENT EVALUATION

<table>
<thead>
<tr>
<th>PATIENT EVALUATION</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>DAY 4</th>
<th>DAY 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness*</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
</tr>
<tr>
<td>Inattention</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Disorientation</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Hallucination - delusion - psychosis</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Psychomotor agitation or retardation</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sleep/wake cycle disturbance</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Symptom fluctuation</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>TOTAL SCORE (0-8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* A: no response
  B: response to intense and expanded stimulation (loud voice and pain)
  C: response to mild or moderate stimulation
  D: normal wakefulness
  E: exaggerated response to normal stimulation
Case Study #1

- GG is a 65 yof admitted with acute respiratory failure. She lives on her own, is active in church, and still drives a car. You walk into the room and she looks at you immediately. She appears anxious as she is being ventilated with Bipap. Her arms are restrained and she is pulling at them to get her Bipap mask off.
  - Lowest RASS in the previous 24 hours -2 (SAS 3)
  - Highest RASS in the previous 24 hours +2 (SAS 6)
  - Current RASS is?

Case Study #2

- KM is a 80 yom successfully weaned from the ventilator and extubated post abdominal surgery. He is alert and calm and all sedation has been stopped this am. Last evening he had periods of agitation with a documented RASS of -1 to +3 (SAS 3-7). He lives with family due to physical limitations but is cognitively intact.
  - What is the current RASS?

Case Study #3

- JS is a 65 yof 2 days post-op for emergent abdominal surgery. She is on the ventilator, eyes closed, does not open eyes to verbal stimuli, but does respond to physical stimuli. She is receiving midazolam and fentanyl and has been off of paralytics for 24 hours. She has been RASS -5 to -2 (SAS 1-3) over the past 24 hours. She does not follow any commands. Prior to admission she had just retired from her teaching job.
  - What is her current RASS?
Case Study #4

CC is a 78 yof admitted with a heart failure exacerbation that you have been caring for over the past several days. She lives at home and cares for her husband. She has been RASS -1 to 0 and ICU-DSC negative for the past 48 hours. She is calm in the morning and greets you by saying “How do you think I look?” You exchange pleasantries about how she is doing today.

What is her current RASS?

Case Study #4

- Calm and knows she is in the hospital
- No hallucinations or delusions
- Can sleep when left alone
- Expresses concern about her situation
- CAM-ICU
  - Answers 2 questions correctly
  - Follows commands
  - Gets 6 letters and 5 pictures correct
- Does CC have delirium?

Managing Delirium

- Treat underlying cause
- Risk factor modification
- Non-pharmacologic therapy
  - Early mobilization (+1B)
  - Promoting sleep (+1C)
- Pharmacologic therapy

Risk Factor Modification

Orientation
- Orient to person, place, and time
- Encourage communication
- Cognitively stimulate
- Provide visual and hearing aids
- Have familiar objects in the room
- Attempt consistency in nursing staff

Environment
- Allow television only during day
- Non-verbal music
- Sleep hygiene: Lights off at night, on during day
- Ambulate and mobilize early and often
- Remove catheters and restraints
- Discontinue delirigenic medications

Clinical Parameters
- Maintain systolic blood pressure >90 mmHg
- Maintain oxygen saturations >90%
- Treat underlying metabolic derangements and infections
- Treat pain

Medication Management

- Limit exposure to delirigenic medications
- GABA-mimetics, anti-cholinergics, etc.

Early and Occupational Therapy in Mechanically Ventilated, Critically Ill Patients

- Early mobilization protocol reduced the median number of days with ICU delirium by half
- Current Guidelines recommend to pursue early mobilization to reduce the incidence and duration of delirium (+1B)

Limitation of Delirium's Impact on Lives of Patients in ICU

- Early mobilization protocol reduced the median number of days with ICU delirium by half
- Current Guidelines recommend to pursue early mobilization to reduce the incidence and duration of delirium (+1B)
**Optimize the quantity and duration of sedatives and analgesics to reduce the incidence of coma**
- Use of protocol driven sedation
- Use of validated sedation scales (RASS, SAS)
- Treat pain first (analgo-sedation)
- Using intermittent doses vs. continuous sedation
- Daily interruption of sedation or targeting light levels of sedation

**Opioids**
- Conflicting data
- Untreated pain associated with delirium
- Guidelines RECOMMEND IV opioids to treat non-neuropathic pain (+1C)

**Propofol**
- No significant relationship has been found
- GABA-mimetic
- Guidelines SUGGEST using over benzodiazepines for continuous sedation in non-delirious patients (+2B)

**Dexmedetomidine**
- Alpha2-agonist with sedative and analgesic properties
- May reduce the prevalence and increase delirium-free days
- May reduce time to extubation
- Guidelines SUGGEST using over benzodiazepines for continuous sedation in delirious and non-delirious patients (+1B)
- Does not provide deep sedation
- Expensive $400-1000/day
- Has not been compared to analgesia first sedation

**Antipsychotics should not be used to prevent delirium in ICU patients (-2C)**
- There is no published evidence that haloperidol reduces the duration of delirium in ICU patients (no evidence)
- Atypical antipsychotics may reduce the duration of delirium in ICU patients, but this needs to be validated in sufficiently powered studies (C)
- Antipsychotics are not recommended in patients at risk for torsades de pointes (-2C)

**Use of Dexmedetomidine as a Sedative and Analgesic Agent in Critically Ill Adult Patients: A Meta-analysis**

**Effect of Dexmedetomidine on Risk of Delirium**

**Haloperidol**
- Limited to case reports and anecdotal evidence
- Butyrophenone antipsychotic agent
- Competitively blocks central dopaminergic receptors
- Onset IV: 5-30 minutes
- Long half-life (18-54 hours)
- Loading regimen
  - Double the dose every 15-20 minutes
  - Give 100% of the total dose divided q6h
- Taper the dose over several days
- Baseline and daily QTc recommended (Hold if >500)
Randomized, double-blind, placebo-controlled trial
n=142
Haloperidol 2.5 mg IV q8h vs. NS placebo
All mechanical ventilated patients whether they were delirious or not
Randomized within 72 hours
Treated for 14 days unless discharged from the ICU or had two consecutive CAM-ICU negative screenings

Primary Outcome: Median Delirium and Coma-Free Days
- Haloperidol (0-10)
- Placebo 6 (0-11)
RR = 0.48 (0.08 to 1.21) p=0.53
No difference in the proportion of patients with resolution over time (Figure)
Trend towards reduced need for sedatives with haloperidol

Atypical Anti-Psychotics
- Olanzapine
- Quetiapine
- Ziprasidone
- Risperidone
- Clozapine
- Aripiprazole

Efficacy and Safety of Quetiapine in Critically Ill Patients with Delirium:
- N=36
- ICU-DSC positive patients, with a prn order for Haloperidol were randomized to:
  - Quetiapine 50mg Q12H or matching placebo
  - Titrated daily by 50mg Q12H to a maximum of 200mg Q12H if at least one dose of Haloperidol received

Time to First Resolution of Delirium
- Quetiapine: 1 (0-5.3) days
- Placebo: 4.5 (2-7) days
Efficacy and Safety of Quetiapine in Critically Ill Patients with Delirium:
A Prospective, multicenter, randomized, double blind, placebo-controlled pilot study
Critical Care Medicine 2010 38(2):249-27

- Safety
  - No difference between groups:
    - QTc prolongation
    - Extrapyramidal symptoms
    - Side effects due to Quetiapine
    - 5 episodes of somnolence
    - 1 episode of hypotension

Safety of Antipsychotic Therapy

- Extrapyramidal effects due to D2 blockade
  - Haloperidol>Atypicals
  - Atypicals have higher 5-HT2:D2 blockade
  - Greater with oral haloperidol vs. intravenous
  - Higher concentrations of the pyridium metabolite
- Orthostatic hypotension
  - α1-adrenergic antagonism
- Haloperidol>clozapine>quetiapine>risperidone>olanzapine
- Antihistamine
  - Clozapine and quetiapine are most sedating
- Anticholinergic
  - Olanzapine>quetiapine > risperidone, ziprasidone, haloperidol

Safety of Antipsychotic Therapy

- QTc prolongation
  - Dose related
  - Cardiac disease appears to predispose
  - Reported most with haloperidol and ziprasidone
- Neuroleptic Malignant Syndrome
  - All agents <1%

Safety of Antipsychotic Therapy

- Medication Reconciliation/Safe discharge
  - Discontinue or taper once delirium resolves
- Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances
  - JAMA 2005 meta-analysis
    - 15 randomized placebo-controlled trials
    - 3353 patients received study drug
    - 1757 patients received placebo
    - OR 1.54 (p=0.02)

When Delirium is Present.......

- Toxic situations
- Hypoxia/hypercarbia
- Infection, inflammation, immobility
- Non-pharmacologic therapy
- K+ or other electrolyte abnormalities

DR.DRE

- Diseases
- Drug Removal
- Environment

Tips for Implementing Delirium Screening in the ICU

- Multi-disciplinary
  - “Delirium Champions”
  - ICU leadership and nurse buy-in
- Use a validated screening tool
  - CAM-ICU or ICU-DSC
- Identify and address barriers
  - Perceived difficulty in using tools and assessing intubated patients
  - Time constraints
Tips for Implementing Delirium Screening in the ICU

- Use multifaceted approach to train clinicians
  - Didactic instruction, videos, online resources
  - Case studies
  - One-on-one teaching
  - Compliance metrics
  - Follow-up training for feedback and reinforcement
- Incorporate into interdisciplinary rounds and documentation systems
- Small changes at a time or plan-do-study-act cycles
- Develop a delirium management protocol/guideline

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URMC ICU Delirium Guideline

**Is the Patient Delirious (ICU-DSC positive (Score ≥4))?**

(See Delirium Assessment)

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Normal cognition, no change in mental status</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>Impaired concentration, restlessness, confusion</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Inappropriate behavior, agitation, difficulty in concentration</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Disorientation to person, place, time</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Disorientation to person, place, time</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Disorientation to person, place, time</td>
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<tr>
<td>6</td>
<td></td>
<td>Disorientation to person, place, time</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Disorientation to person, place, time</td>
</tr>
</tbody>
</table>

**URMC ICU Delirium Guideline**

1. DELIRIOGENIC MEDICATIONS
   - Consider stopping or substituting for:
     - Benzodiazepines
     - Anticholinergics
     - Corticosteroids
     - Promethazine
     - Metoclopramide
     - Diphenhydramine
     - H2 Antagonists

2. NON-PHARMACOLOGIC THERAPY
   - Orientation
     - Provide visual and hearing aids
     - Encourage communication and reorient patients
     - Have familiar objects in the room
     - Attempt consistency in nursing staff
     - Allow television during day with daily news
     - Non-verbal music
   - Environment
     - Sleep hygiene: Lights off at night, on during day
     - Control excess noise at night
     - Ambulate and mobilize early and often
   - Clinical Parameters
     - Maintain systolic blood pressure >90 mmHg
     - Maintain oxygen saturations >90%
     - Treat underlying metabolic derangements and infections

3. ANTIPSYCHOTIC THERAPY
   - While tapering or discontinuing sedatives, consider:
     - Haloperidol 5 mg IV/PO q6h, increase dose by 5 mg to max of 20 mg q6h
     - Quetiapine 50-400 mg/day PO divided twice daily
     - Olanzapine 2.5-20 mg/day PO divided once or twice daily
   - *Acute Delirium* Haloperidol 3-5 mg IV x1 for acute delirium (ICU-DSC positive and SAS of 6 to 7)
   - Double previous Haloperidol dose every 20 minutes until patient controlled or maximum dose of 40 mg is reached
   - Haloperidol maintenance dose is 25% of total dose given to control agitation every six hours
   - Monitor QTc daily if on a scheduled antipsychotic regimen
   - Hold if QTc >0.5 msec
   - Discontinue antipsychotics if high fever, QTc prolongation, or drug-induced rigidity occurs

Conclusions

- High prevalence of delirium in ICU patients
- Pathophysiology not completely understood
- Associated with worse outcomes
- Can persist and lead to long-term cognitive impairment
- All ICU patients should be screened for delirium
- Prevention is key
- Non-pharmacologic therapy should be treatment of choice
- Antipsychotic therapy can be used for hyperactive delirium
- Choice of agent and safety are uncertain