Karishma Rao, MD

Dr. Karishma Rao is a clinical assistant professor within the Division of Neonatology at Children's Mercy, Kansas City. Her interests include NEC and BPD. It was during her Neonatology fellowship at Children's Mercy itself that she first developed an interest in neonatal pain and infant delirium. The concept of delirium in neonates is poorly understood at this time but she hopes to shed light on it as it gains some mainstream interest.
INFANT DELIRIUM

Karishma Rao, MD
Division of Neonatology, Children’s Mercy Hospital
Clinical Assistant Professor, UMKC SOM
OVERVIEW

• DEFINITION
• MECHANISM/PATHOPHYSIOLOGY
• PHARMACOKINETICS (PK)
• RISK FACTORS
• SIGNS AND SYMPTOMS
• ADVERSE OUTCOMES
• LITERATURE REVIEW
• MANAGEMENT
• TAKE HOME POINTS
DELIRIUM OR ACUTE BRAIN DYSFUNCTION

• Delirium is defined as an acute and fluctuating change in awareness and cognition

• In the setting of a medical illness

• Incidence of approximately 17% in the PICU setting

• Uncommonly recognized in the NICU

• It is a well known and prevalent problem in the adult intensive care units
### POSSIBLE CAUSES OF PEDIATRIC DELIRIUM

<table>
<thead>
<tr>
<th>Category</th>
<th>Possible Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Encephalitis, meningitis, urinary tract infection, pneumonia…</td>
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<tr>
<td>Withdrawal</td>
<td>Alcohol, barbiturates, benzodiazepines…</td>
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<tr>
<td>Acute metabolic</td>
<td>Electrolyte imbalance, hepatic or renal failure…</td>
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<tr>
<td>Trauma</td>
<td>Head injury, postoperative…</td>
</tr>
<tr>
<td>CNS pathology</td>
<td>Stroke, haemorrhage, tumour, seizure disorder…</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Anaemia, cardiac failure, pulmonary embolus…</td>
</tr>
<tr>
<td>Deficiencies</td>
<td>Vitamin B12, folic acid, thiamine…</td>
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<tr>
<td>Endocrinopathies</td>
<td>Thyroid, glucose, parathyroid, adrenal…</td>
</tr>
<tr>
<td>Acute vascular</td>
<td>Shock, vasculitis, hypertensive encephalopathy…</td>
</tr>
<tr>
<td>Toxic or drugs</td>
<td>Toxins, substance intoxication, medications (alcohol, anaesthetics, anticholinergics, narcotics etc.)</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>Arsenic, lead, mercurv…</td>
</tr>
</tbody>
</table>
MECHANISM OF DELIRIUM

- Hypoperfusion and inflammation which occurs during critical illness plays a role

- Alterations in cerebral blood flow, disordered cellular homeostasis also play a role

- Neural ischemia leads to
  - Cortical depression due to an inability to maintain ionic gradients
  - Imbalance in neurotransmitter synthesis, release and metabolism
  - Inability to eliminate neurotoxic by-products of metabolism

- Delirium is the end result of diffuse cerebral metabolic abnormality
MECHANISM OF DELIRIUM

• Delirium is the neurobehavioral manifestation of alterations in neurotransmission

• Delirium has been associated with
  • Excess/ deficiency of dopamine
  • Acetylcholine deficiency
  • Increased GABA

• Morphine has been shown to increase the release of dopamine

• Benzodiazepines and Propofol have a high affinity for GABAergic receptors
PK OF MORPHINE IN NEONATES

• In one study, infants aged 1-4 days showed longer elimination half lives than older pts (6.8 vs 3.9 hrs)

• Clearance in newborns was less than 1/3 of that found in older infants (Aged 1d – 10w) (6.3 vs 23.8 ml/min/kg)

• Infants and neonates make relatively more M-3-G vs M-6-G

• This combination of longer half life and low clearance in infants may explain prolonged duration of action of morphine in very young infants
PK OF MIDAZOLAM IN NEONATES

• Midazolam elimination is slower in infants compared to adults

• It is mainly eliminated by hydroxylation by CYP3A4 and CYP3A5 enzymes

• These enzymes surge in the liver in the first few weeks of life

• Hence neonates have longer half lives of midazolam and slower clearance

• Multiorgan failure and severity of disease lowers the clearance of midazolam
RISK FACTORS

• Age < 2 years

• Developmentally delayed children

• Preexisting medical condition

• Severity of illness affects metabolism and PK of drugs

• Mechanically ventilated patients

• Use of benzodiazepines, narcotics, corticosteroids
SIGNS & SYMPTOMS

- Irritability
- Impaired alertness
- Impairments of sleep-wake cycles
- Inability to focus or sustain attention

Fluctuation of symptoms
SIGNS & SYMPTOMS

"Impossible to sedate" Developmental Regression

Refractory agitation

Inability to console by usual caregivers Reduced eye contact with the usual caregiver
ADVERSE OUTCOMES

• Increased unplanned extubations

• Longer duration of mechanical ventilation

• Prolonged hospital stays

• Developmental delays

• Strongly and independently associated with increased mortality
A case of infant delirium in the neonatal intensive care unit

L.E. Edwards\textsuperscript{a}, L.B. Hutchison\textsuperscript{b}, C.D. Hornik\textsuperscript{c}, P.B. Smith\textsuperscript{a}, C.M. Cotten\textsuperscript{a} and M. Bidegain\textsuperscript{a,*}

\textsuperscript{a}Department of Pediatrics, Division of Neonatology, Duke University Medical Center, Durham, NC, USA
\textsuperscript{b}Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA
\textsuperscript{c}Department of Pharmacy, Duke University Medical Center, Durham, NC, USA
• 6 month old, born at 32 weeks, 4.7 kg male infant

• Required cardiac catheterization for evaluation of pulmonary hypertension

• Unable to extubate after the procedure

• 9 days later he was noted to have persistent agitation and was started on a versed gtt

• By day 19 he was on a fentanyl drip, midazolam drip, precedex drip

• Scheduled gabapentin, phenobarbital, methadone and diazepam
• He was noted to have purposeless movements like head shaking and arm waving

• No consistent eye contact, stopped visually tracking, did not respond to mother’s voice

• Child psych was consulted on day 19 due to concern for delirium

• Infant was diagnosed with delirium

• Primary recommendation was to wean deliriogenic medications, preferably versed gtt

• Enteral risperidone was also started
Detection and Management of Delirium in the Neonatal Unit: A Case Series

Alan Greves, MBChB, MD,* Chani Traube, MD,* Gabrielle Silver, MD*
ARE INFANTS IN THE NICU AT HIGHER RISK FOR DELIRIUM?
MANAGEMENT OF DELIRIUM

• Screen and monitor for signs and symptoms of delirium

• Identify and remove causative factors

• Environmental interventions by nursing and family

• Decrease deliriogenic medications like benzos, opiates

• Consider psychiatry consult and antipsychotic medications
CAPD

- Cornell Assessment of Pediatric Delirium
- It is an observational screening tool
- Assess critically ill children of all ages for delirium
- It has not been formally tested in a NICU population
- But has been validated in neonates and infants
RASS Score ____ (if -4 or -5 do not proceed)

Please answer the following questions based on your interactions with the patient over the course of your shift:

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the child make eye contact with the caregiver?</td>
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<tr>
<td>2. Are the child's actions purposeful?</td>
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<tr>
<td>3. Is the child aware of his/her surroundings?</td>
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<tr>
<td>4. Does the child communicate needs and wants?</td>
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</table>

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<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
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<tbody>
<tr>
<td>5. Is the child restless?</td>
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<tr>
<td>6. Is the child inconsiderable?</td>
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<td>7. Is the child underactive—very little movement while awake?</td>
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<tr>
<td>8. Does it take the child a long time to respond to interactions?</td>
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TOTAL
<table>
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<tr>
<th></th>
<th>NB</th>
<th>4 weeks</th>
<th>6 weeks</th>
<th>8 weeks</th>
<th>28 weeks</th>
<th>1 year</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Does the child make eye contact with the caregiver?</strong></td>
<td>Fixates on face</td>
<td>Holds gaze briefly</td>
<td>Holds gaze</td>
<td>Follows moving object/caregiver past midline, regards examiner’s hand holding object, focused attention</td>
<td>Holds gaze. Prefers primary parent. Looks at speaker</td>
<td>Holds gaze. Prefers primary parent. Looks at speaker</td>
<td>Holds gaze. Prefers primary parent. Looks at speaker</td>
</tr>
<tr>
<td><strong>2. Are the child’s actions purposeful?</strong></td>
<td>Moves head to side, dominated by primitive reflexes</td>
<td>Reaches (with some discoordination)</td>
<td>Reaches</td>
<td>Symmetric movements, will passively grasp handed object</td>
<td>Reaches with coordinated smooth movement</td>
<td>Reaches and manipulates objects, tries to change position, if mobile may try to get up</td>
<td>Reaches and manipulates objects, tries to change position, if mobile may try to get up and walk</td>
</tr>
<tr>
<td><strong>3. Is the child aware of his/her surroundings?</strong></td>
<td>Calm awake time</td>
<td>Awake alert time</td>
<td>Increasing awake alert time</td>
<td>Facial brightening or smile in response to nodding head, frown to bell, coos</td>
<td>Strongly prefers mother, then other familiar. Differentiates between novel and familiar objects</td>
<td>Prefers primary parent, then other familiar, upset when separated from preferred caretakers. Comforted by familiar objects especially favorite blanket or stuffed animal</td>
<td>Prefers primary parent, then other familiar, upset when separated from preferred caretakers. Comforted by familiar objects especially favorite blanket or stuffed animal</td>
</tr>
<tr>
<td><strong>4. Does the child communicate needs and wants?</strong></td>
<td>Cries when hungry or uncomfortable</td>
<td>Cries when hungry or uncomfortable</td>
<td>Cries when hungry or uncomfortable</td>
<td>Cries when hungry or uncomfortable</td>
<td>Vocalizes /indicates about needs, e.g. hunger, discomfort, curiosity in objects, or surroundings</td>
<td>Uses single words, or signs</td>
<td>3-4 word sentences, or signs. May indicate toilet needs, calls self or me</td>
</tr>
<tr>
<td>NB</td>
<td>4 weeks</td>
<td>6 weeks</td>
<td>8 weeks</td>
<td>28 weeks</td>
<td>1 year</td>
<td>2 years</td>
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<tr>
<td>5. Is the child restless?</td>
<td>No sustained awake alert state</td>
<td>No sustained calm state</td>
<td>No sustained calm state</td>
<td>No sustained calm state</td>
<td>No sustained calm state</td>
<td>No sustained calm state</td>
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</tr>
<tr>
<td>6. Is the child inconsolable?</td>
<td>Not soothed by parental rocking, singing,</td>
<td>Not soothed by parental rocking, singing,</td>
<td>Not soothed by parental rocking, singing,</td>
<td>Not soothed by usual methods e.g. singing,</td>
<td>Not soothed by usual methods e.g. singing,</td>
<td>Not soothed by usual methods e.g. singing,</td>
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<tr>
<td></td>
<td>feeding, comforting actions</td>
<td>feeding, comforting actions</td>
<td>feeding, comforting actions</td>
<td>holding, talking</td>
<td>holding, talking</td>
<td>holding, talking, reading (May tantrum, but</td>
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<td></td>
<td>can organize)</td>
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<td>7. Is the child underactive — very little movement while awake?</td>
<td>Little if any flexed and then relaxed state</td>
<td>Little if any reaching, kicking, grasping</td>
<td>Little if any purposeful grasping, control</td>
<td>Little if any play, efforts to sit up, pull</td>
<td>Little if any more elaborate play, efforts</td>
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<tr>
<td></td>
<td>with primitive reflexes (Child should be</td>
<td>(still may be somewhat discoordinated)</td>
<td>of head and arm movements, such as pushing</td>
<td>up, and if mobile crawl or walk around</td>
<td>to sit up and move around, and if able to</td>
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<tr>
<td></td>
<td>sleeping comfortably most of the time)</td>
<td></td>
<td>things that are noxious away</td>
<td></td>
<td>stand, walk, or jump</td>
<td></td>
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</tr>
<tr>
<td>8. Does it take the child a long time to respond to interactions?</td>
<td>Not making sounds or reflexes active as</td>
<td>Not making sounds or reflexes active as</td>
<td>Not kicking or crying with noxious stimuli</td>
<td>Not babbling or smiling/laughing in social</td>
<td>Not following simple directions. If verbal,</td>
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<td></td>
<td>expected (grasp, suck, moro)</td>
<td>expected (grasp, suck, moro)</td>
<td></td>
<td>interactions (or even actively rejecting an</td>
<td>not engaging in simple dialogue with words or</td>
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<td>interaction)</td>
<td>jargon</td>
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</table>
CAPD SCORE $\geq 9$

- Evaluate for delirium
- Modify the environment
- Consider discontinuing medications that can cause delirium
- Treat underlying illness
- If it persistent, consider a trial of antipsychotic medications
ENVIRONMENTAL INTERVENTIONS

• Can prevent and help manage delirium in those that do need pharmacological treatment

• Establish daily routines and schedules

• Promote good sleep hygiene

• Control light and noise in the room

• Promote a familiar environment
PHARMACOLOGICAL MANAGEMENT

• Most importantly, decrease deliriogenic medications like benzos and opiate infusions

• Optimize pain and sedation while weaning benzo and opiate infusions

• Consider consulting clinical pharmacology

• Indications for considering antipsychotic medications
  • When the patient is distressed by the symptoms
  • The symptoms impose a safety concern/ device dislodgement
  • Or if symptoms are impeding advancement of medical care
# ANTIPSYCHOTIC MEDICATIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Forms Available</th>
<th>Frequencies of Adverse Effects</th>
<th>Cardiac Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Age 5–16 years, 0.5 mg–2.5 mg/day, divided into two to four doses; maximum dosage: &lt;20 kg, 1 mg/day, 20–45 kg, 2.5 mg/day, &gt;45 kg, 3 mg/day</td>
<td>Oral (tablets, orally disintegrating tablets, solution), intramuscular (depot)</td>
<td>&gt;30%: weight gain; &gt;10%: sedation, agitation, extrapyramidal side effects (akathisia/parkinsonism &gt; dystonia); anticholinergic effects, hyperglycemia, hyperlipidemia, orthostasis; &lt;2%: skin reactions, blood dyscrasias; seizures, hepatic impairment</td>
<td>Abnormal ECG, &gt;2%; QTc prolongation, &lt;2%; tachycardia, &gt;10%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Age 13–17 years, 2.5–10 mg/day; dosing every 12–24 hours; recommended maximum, 20 mg/day</td>
<td>Oral (tablets, orally disintegrating tablets), intramuscular</td>
<td>&gt;30%: sedation, anticholinergic effects, weight gain, hyperlipidemia, hyperglycemia; &gt;10%: insomnia, agitation; 2%–10%: extrapyramidal side effects (akathisia &gt; dystonia/parkinsonism); &gt;2%: orthostasis, hepatic impairment; &lt;2%: skin reaction, blood dyscrasia, seizure</td>
<td>Abnormal ECG, &lt;2%; QTc prolongation, &lt;2%; tachycardia, &lt;2%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Age 10–17 years, 12.5–400 mg; dosing every 12–24 hours (usually 12 hours); recommended maximum, 750 mg/day</td>
<td>Oral (tablets; immediate release, extended release)</td>
<td>&gt;30%: sedation, anticholinergic effects, hyperglycemia; &gt;10%: agitation, orthostasis, weight gain, hyperlipidemia; &gt;2%: extrapyramidal side effects (akathisia &gt; parkinsonism/dystonia), hepatic impairment; &lt;2%: seizure, skin reaction (no data for rate of blood dyscrasias with quetiapine)</td>
<td>Abnormal ECG, &lt;2%; QTc prolongation, &lt;2%; tachycardia, &gt;2%</td>
</tr>
</tbody>
</table>
TAKE HOME POINTS

• Critically ill infants and children are at high risk for delirium

• PK of sedatives and analgesics in infants is different and contributes to increased risk

• Delirium is an under recognized clinical entity in the NICU

• Increased awareness of delirium as a differential and screening for it is critical

• Earlier identification and treatment can minimize associated morbidities and mortality
THANK YOU!

Questions?
• Delirium and Mortality in Critically Ill children: Epidemiology and Outcomes of Pediatric Delirium; Traube, Silver. Critical Care Medicine 2017.


• Pediatric Delirium and Associated Risk Factors: A Single Center Prospective Observational Study; Silver G, Traube C, Gerber L. Pediatric Critical Care Medicine 2015.


• Pediatric Delirium, A Practical Approach, Scheiveld et al, IACAPAP Textbook of Child and Adolescent Medical Health

• Atypical Antipsychotic Medications to Control Symptoms of Delirium in Children and Adolescents; Turkel et al. Journal of Children and Adolescent Psychopharmacology 2012.


• CHOP Pediatric Delirium Pathway.
REFERENCES

• Cornell Assessment of Pediatric Delirium: A Valid, Rapid, Observational Tool for Screening Delirium in the PICU; Traube, Silver et al. Critical Care Medicine 2014.

• Sequestration of drugs in the circuit may lead to therapeutic failure during ECMO; Shekar et al Journal of Critical Care 2012.

• The ECMO PK Project: an incremental research approach to advance understanding of the pharmacokinetic alterations and improve patient outcomes during ECMO; Shekar et al BMC Anesthesiology 2013.

• Medicating patients during ECMO: The case is building; Dzierba; Critical Care 2017.


• Pharmacokinetic changes in patients receiving ECMO. Shekar et al. Journal of Critical Care 2012.

• Determinants of Drug Absorption in Different ECMO Circuits*; Wildschut; Intensive Care Medicine 2010.


• Groves A. Pediatrics. 2016;137(3):e200153369

• Brahmbhatt K. Pediatrics 2016;137(3):e20151940
