Phenotyping Delirium: Current Evidence and Future Directions

Presenters: Emily Bowman, BSc, PhD and Kelly Toth, PhD, RN

Time	Section
02:20	**Introduction of Emily Bowman and Kelly Toth**
04:10	**The Delirium Subtyping Initiative (Emily Bowman)**

04:47	**Background**
	• Lipowski quote
	  o Came up with delirium framework of: hypoactive, mixed, and hyperactive delirium
	• Delirium Characterizations
	  o Categorized as present or absent
	  o Psychomotor subtype (hypoactive, hyperactive, mixed, no subtype)
	  o Severity of symptoms
	• More accurate classification is required

06:10	**Current Literature**
	• Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study (Girard and colleagues)
	  o Published in 2018
	  o Characterized based on the insult (hypoxic, septic, metabolic, sedative-associated)
	• Association between components of the delirium syndrome and outcomes in hospitalized adults: a systematic review and meta-analysis
	• Reduced level of arousal and increased mortality in adult acute medical admissions: a systematic review and meta-analysis
	• Assessment and report of individual symptoms in studies of delirium in postoperative populations: a systematic review (Emily's work)
	  o 10 most reported symptoms: inattention, disorientation, psychomotor agitation/retardation, hallucination, memory impairment, speech/language, altered level of consciousness, sleep/wake cycle disturbance, perceptual disturbance, fluctuation
	  o Other symptoms fell into the other category (maybe most traumatic symptoms)
	  o Highlights lack of standardization
	• Refining Delirium: a transtheoretical model of delirium disorder with preliminary neurophysiologic subtypes
	• Delirium Disorder
	• An interdisciplinary reappraisal of delirium proposed subtypes
	• There's been more interest in figuring out the pathophysiology of delirium (diagram)
	• Increased interest in biomarkers (a lot of heterogeneity in the results)
	• Phenotyping new to delirium, but not new overall and has been done in other fields

09:49	**The Problem** • Delirium research increasing over last 20 years • Understanding of pathophysiology is low • Delirium is common

10:13	**Phenotypes and subphenotypes of delirium: a review of current categorizations and suggestions for progression**
	• Definitions
	  o Phenotypes: all have delirium (based on clinical features)
	  o Subphenotypes: red (in diagram) all have delirium and a shared risk factor (ex: sepsis)
	  o Endotypes: red all share a mechanism (ex: neuroinflammation)
	  o Treatable traits: characteristics targeted by an intervention
	• Upside down triangle diagram demonstrating the above definitions

11:18	**Delirium Subtyping Initiative Steering Committee (diversity—25 people)**

	• Aim of initial meeting was to reach consensus on:
	  o Methods for selecting primary outcomes to be considered/recorded in delirium diagnosis
	  o Definitions for subtyping
	  o Which clinical and biomarker features should be considered with most importance
	• Discuss ideas on:
	  o How to update and validate new subtypes
	  o What we can learn from previous subtyping works
	  o A plan to conquer logistical challenges in data sharing and combination

12:58	**Session 1-Clinical Features**
	• Problems
	  o Indexical approach- DSM-5-TR is a partial picture
	  o Delirium normally recorded as a binary outcome
	  o How to define and operationalize core feature, e.g. inattention
	  o Boundaries between clinical syndromes, e.g. Delirium and dementia, can be indistinct
	  o Variability in outcomes assessment make study comparison difficult- even in similar populations
	  o Currently defined by clinical features only
	  o How to describe those unable to engage with delirium assessment? Possible/probable delirium?
	  o Is the number of delirium symptoms predictive of outcomes?
	• Recommendations
	  o Operationalization of features must be standardized across studies for combination and comparison of results
	  o Delirium subtyping methods should consider including all "delirium-spectrum syndromes"
	  o Delirium screening should involve a patient's level of communication and reasoning
	  o Creation of distinct research and clinical criteria should be considered
	• Future Aims
	  o Robust collection of individual, routine and well-classified clinical features
	  o Delirium identification and severity assessment tools for all medical settings and communicative abilities
	  o Consistent collection of clinical feature data and biomarker data in both clinical and research settings

15:50	**Session 2- Refinement and Validation**
	• Problems
	  o Potentially limited translatability of statistical clustering methods into clinical practice (imputation)
	  o Categories of clinical and biomarker features are not consistently measured
	  o Subtyping success requires establishing validation and methods for regular updates
	• Recommendations
	  o Use of large datasets incorporating clinical and biomarker variables
	  o Analysis of similar and different cohorts, with caution, for understanding variability and validity
	• Future Aims
	  o Application of cluster analysis techniques (e.g. latent class analysis)
	  o Data complexity and feature quality should dictate clinical phenotypes
	  o Methods used must be replicable and easily understood
	  o Strong phenotypes must be discrete, consistent, reproducible, validated and clinically useful
	  o Multivariable phenotyping and prognostic enrichment needed to identify groups of patients with specific treatment responses or treatable traits

17:22	**Session 3- Methods for handling data & statistics**

	• Problems
	  o Heterogeneity in medical setting, clinical features, demographics, precipitants, insults, cognition, and outcomes
	  o Transiency, patient multimorbidity and treatment response
	  o Ensuring ease of data sharing
	  o Variability in data records and thresholds used
	  o Potential differences between hypothesis driven studies and data/sample driven studies
	• Recommendations
	  o Large multicenter studies should collect data using repeated, frequent and standardized measures of clinical features
	  o Data-driven phenotypes must incorporate clinical applicability to become a knowledge-based phenotype
	• Future Goals
	  o Data collection (notes and samples) must be robust, consistent, and statistical protocols shared among all
	  o Operationalization and standardization of all recommendations
	  o A universally translatable language within which we are collecting data based on a framework
	  o Newly identified subtypes must be standardized and validated
	  o Reconvening of the delirium subtyping initiative in 1-2 years for progress updates and review of goals

19:40	**<u>Latent Class Analysis- Methods</u>** • Generate hypothesis → data set-up→ estimate models→ evaluate models→ interpret optimal model • Graph of PoDB results from latent class analysis (it was regardless of delirium status) • 2 subphenotypes of PoDB participants
23:02	**<u>Advances in Delirium Phenotyping: The Old and The New (Kelly Toth)</u>**
23:25	**<u>What's Ahead?</u>** • Pharmacologic management of delirium in the ICU • Established approaches in delirium heterogeneity • New approaches in delirium heterogeneity

23:43	**<u>Pharmacologic management of delirium in the ICU</u>**
	• Clinical trials to identify pharmacologic treatments for delirium
	  o Several studies have tried, heterogeneity and have yield neutral results (why?: No true mechanistic target for delirium, heterogenous syndrome)
	• Current approach to delirium clinical trials
	  o Different predisposing factors contribute to delirium: infection, sedation, hypoxia, brain injury, inflammation
	  o Then syndrome of delirium is used as the randomization criteria
	  o Have seen no difference in average treatment effect between the intervention and control groups
	• Clinicians tend to use medications for delirium management
	  o Haloperidol is the most common medication (used mostly for treatment rather than prevention), but no evidence that it reduces a patient's delirium

25:25	**<u>Established approaches in delirium heterogeneity</u>**
	• Delirium in the ICU is identified through clinician assessment often by the CAM-ICU or Intensive Care delirium Screening Checklist
	• Psychomotor delirium subtypes (hypoactive, hyperactive, mixed)
	  o Have prognostic utility→ can predict worst outcomes; mixed delirium do have worse outcomes including mortality
	  o Not considered in the evidence-based recommendations for delirium
	• Clinical risk factor-based delirium subtypes (based on hypothesized insult)

	○ Hypoxic, Septic, Metabolic, Sedative-Associated, Unclassified ○ Common for patients to classify into more than 1 subtype ▪ Sedative-associated delirium was most common • Historical limitations to delirium subtyping: ○ Require clinician observation, often co-occur, might be too simple to capture full heterogeneity of delirium, currently do not influence treatment decisions
28:13	**<u>New approaches in delirium heterogeneity</u>** • Discover latent heterogeneity through data driven subtyping • Example of how this can be done in delirium (diagram) ○ Multidimensional data available in the ICU (vital signs, clinical exam, biomarkers, EEG, Imaging) ○ Can do data driven subtyping in a machine-learning method to identify treatable traits and then randomizing based on those treatable traits • Data-Derived Subtypes of Delirium ○ Identify data-derived delirium subtypes ○ Compare with delirium subtypes derived through other methods ○ Compare short- and long-term outcomes ○ Methods: ▪ Secondary analysis of Brain-ICU and Mind-ICU prospective cohort studies ▪ Latent class analysis • Data from first delirium identification (CAM-ICU) • Model variables: baseline, clinical, and treatment characteristics • Primary fit evaluation: Bayesian information criterion elbow method ▪ Comparison with: clinical subtypes, psychomotor subtypes, acuity subtypes ▪ Unadjusted comparisons of short- and long-term outcomes ○ Results: ▪ Table of patient characteristics ▪ Latent class analysis: model fit (graph) ▪ Heat map of clinical profile differences among the 4 classes • Class 1: more propofol, fewer opioids, higher SpO2 (better oxygen saturation) • Class 2: more hypotensive, worse kidney impairment • Class 3: more hypoxic, higher troponin, younger, higher BMI • Class 4: more ventilator days pre-delirium, deeper sedation, more benzodiazepines, opioids, worse live function, lactate ▪ Comparison with clinical phenotypes • All clinical subtypes appeared in data driven subtypes, but not really a meaningful representation of them • New data driven subtypes revealed additional heterogeneity unexplained by the clinical risk factor-based subtypes alone ▪ Comparison with psychomotor subtypes • No association between psychomotor subtypes and data driven subtypes ▪ Comparison with acuity subgroups • Fewer patients from data-driven class 2 in SOFA Quartile 1 • Patients from all SOFA quartiles in all data-driven subtypes ▪ Hospital Outcomes • Looked at delirium- or coma-free days by classes • Days of coma among subtype (class 4 highest) • Days of delirium among subtypes (class 4 highest)

	▪ Mortality • 30-day mortality (class 2 had the greatest) ▪ Long-Term Outcomes • Cognition: clinically significant cognitive impairment did affect all data driven delirium subtypes, but did not differ in delirium severity at 3 or 12 months
38:19	**Take Home Message** • We identified four data-driven delirium subtypes that were different from prior subtyping approaches • Class 2 (hypotensive, kidney impairment) had greatest mortality • Class 4 (benzodiazepines, liver dysfunction) had longest duration of delirium and coma • Significant cognitive impairment affected the overall sample but no statistically significant differences between subtypes
38:49	**What's Next?** • External validation • Heterogeneity of treatment effect • Examine influence of additional domains (detailed profiling of delirium: possible dimensions—acute or pre-delirium) • Evaluate trajectories of subtypes • Prospective identification of delirium subtypes
40:26	**Questions and Answers**