Abstracts Accepted for an Oral Presentation at the 2019 Annual Meeting of the American Delirium Society

Monday June 17, 2019

10:30-11:30am Delirium in the Neurologically Injured
Moderators: T. Fong and E. Kimchi

The predisposing and precipitating factors for delirium in an observational cohort of 1,487 neurological patients

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Objective: To examine the interaction and impact of predisposing and precipitating factors for delirium in neurological patients
Methods:

Methods: In this observational cohort study, 1,487 patients admitted to the neurology service were included, 356 patients with delirium and 1,131 without delirium. The relevant neurological disorders and medical /- related clusters were assessed with multiple regression analyses evaluating their interactions and impact on delirium.

Results: The delirious patients were older, multimorbid, more cognitively and functionally impaired, their hospitalization was prolonged and institutionalization at discharge more frequent. The most relevant predisposing factors were: frailty (OR 10.02, CI 4.59-21.91, $p<0.001$), substance use disorders (OR 4.29, 2.30-7.98, $p<0.001$), advanced age (OR 3.51, CI 2.46-5.01, $p<0.001$), dementias or degenerative disorders (OR 2.52, CI 1.44-4.42, $p<0.001$), and transfers from institutions (OR 1.88, CI 1.32-2.69, $p=0.001$). Demyelinating disorders did not predispose to delirium. The most relevant precipitating factors were: meningitis (OR 22.93, CI 1.41-373.41, $p=0.028$), acute renal failure (OR 9.68, CI 1.09-85.72, $p=0.041$), intracranial hemorrhages (OR 3.69, CI 2.11-6.41, $p<0.001$), sepsis-related disorders (OR 3.41, CI 1.07-10.91, $p=0.039$), epilepsies (OR 3.26, CI 2.27-4.68, $p<0.001$), and decubital ulcers (OR 3.21, 1.10-9.34, $p=0.032$). Notably, pneumonia, cystitis or electrolyte imbalances were not relevant to delirium in acute neurological illness.

Conclusions: Delirium in acute neurological inpatients was dependent on age and age-related cognitive and functional impairments, in addition to acute neurological and medical disorders.

Deconstructing Post-Stroke Delirium in a Prospective Cohort of Patients with Intracerebral Hemorrhage

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Objective: Post-stroke delirium is associated with worse outcomes, yet is likely underdiagnosed due to the challenges of disentangling delirium symptoms from underlying neurological deficits. We aimed to

determine the prevalence of individual delirium features and the frequency with which they could not be reliably assessed in a cohort of patients with intracerebral hemorrhage (ICH).

Methods: Consecutive patients admitted with ICH received daily assessments for delirium by an expert clinician, all of which included the Confusion Assessment Method for the ICU (CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC), a focused bedside cognitive exam, chart review, and nurse interview. We characterized individual symptom prevalence and established delirium diagnoses using DSM-5 criteria, then compared performance of the CAM-ICU and ICDSC with reference-standard diagnosis.

Results: We performed 257 assessments for delirium on 60 patients (mean age 68.0 [SD 18.4], 62% male, median ICH score 1.5 [IQR 1-2]), of whom 55% had delirium. Symptom fluctuation (61% of all assessments), impaired arousal (37%), psychomotor changes (46%), and sleep-wake disturbances (46%) had a high prevalence and were never rated â€œunable to assessâ€ (UTA), while inattention (36%), disorganized thinking (18%), and disorientation (27%) were also common but were often UTA (32%, 44%, and 43% of assessments, respectively), most frequently due to aphasia (present in 32% of patients). As the ICDSC may be positive without the presence of symptoms that require verbal assessment, it was more accurate (Sensitivity=77%, Specificity=97%) than the CAM-ICU (Sensitivity=41%, Specificity=88%) relative to the DSM-5-based reference standard. Allowing non-verbal visual- and auditory-based assessments of attention decreased the frequency of UTA assessments to 11%.

Conclusions: Delirium is common after ICH, but reliance on verbal interaction with patients may confound its assessment and lead to underdiagnosis. The ICDSCâ€™s inclusion of non-verbal features makes it more accurate than the CAM-ICU, but novel tools specifically designed for patients with neurological deficits may be warranted.

Prescribing patterns relative to delirium recognition in stroke patients

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Objective: Delirium affects 13-48% of patients with stroke, but medication prescribing practices have not been previously described in this population. We studied prescribing patterns relative to delirium recognition at a tertiary care stroke center.

Methods: Clinical data and medication administrations were identified from electronic medical records of patients admitted to the stroke unit between 1/2017 and 2/2018. Patients were screened for delirium every shift by RNs using a modified Confusion Assessment Method (mCAM). Medications were compared between those who ever (mCAM+, n=535) and those who never (mCAM-, n=905) had a positive mCAM.

Results: Compared to mCAM- patients, mCAM+ patients were older (+5.83 years, $p<0.001$), had a greater odds of death (OR 1.80, $p=0.031$), 30-day readmission (OR 1.88, $p=0.003$), prolonged length of stay (+6 days, $p<0.001$), and higher median NIH Stroke Scales (mCAM+ 9, mCAM- 3, $p<0.001$). Antipsychotics were used more frequently in mCAM+ patients than mCAM- (OR 6.09, $p<0.001$). Quetiapine was prescribed most commonly (in 44.5% of mCAM+ patients) followed by haloperidol (in 30.5%). The rate of prescribing increased after first positive mCAM, atypicals (from 24.9% to 44.3%) more than typicals (from 18.3% to 21.1%).
Benzodiazepines were used more frequently in mCAM+ patients than mCAM- (OR 1.55, p=<0.001). However, this difference was not present prior to delirium recognition (OR 0.81, $p=0.06$). Lorazepam was

prescribed most commonly. Similarly, sleep aids were used more frequently in mCAM+ patients than mCAM- (OR 2.86, p<0.001), but not prior to delirium recognition (OR 0.99, p=0.916).

Conclusions: In a stroke unit, a nurse led delirium screening program identified a vulnerable patient population with prolonged healthcare utilization. There were high rates of antipsychotic, benzodiazepine, and sleep medication use, particularly in mCAM+ patients after delirium recognition. These findings emphasize the need for continued study of delirium management of stroke patients.

Effects of Neurologic Injury on Delirium Duration and Hospital and ICU Length of Stay

Kate Frost [1], Heidi Chen [1], Rameela Chandrasekhar [1], Chevis Shannon [2], Pratik Pandharipande [2], Heidi Smith [2]
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Objective: Delirium, or acute brain dysfunction, is prevalent among critically ill children, and is associated with longer intensive care unit (ICU) and hospital length of stay (LOS). Its effects in patients with neurologic injury is unknown. This investigation aimed to determine whether neurologic injury, defined as baseline developmental delay (DD) or ICU admission with an acute neurologic injury are independent risk factors for longer ICU and hospital LOS, and if delirium mediated any association.

Methods: Patients aged 6 months to 5 years in a tertiary-level Pediatric ICU underwent daily delirium assessments. Negative binomial regression determined the effect of neurologic injury on delirium duration. Cox proportional hazard regressions determined the impact of neurologic injury on ICU and hospital discharge. Delirium mediation was inferred by comparing the total (no delirium covariate), direct (delirium included as a covariate), and indirect effect of neurologic injury on outcomes. Models were adjusted for known confounders.

Results: Of 282 patients, 79 had baseline DD, 54 had acute neurologic injury, and 7 patients had both. ICU delirium prevalence in the general cohort was 45% (N=127). Both DD (p=0.008) and acute neurologic injury (p=0.056) were associated with longer delirium duration. DD was significantly associated with a lower likelihood of ICU discharge (hazard ratio, HR, 0.76 [95% confidence interval, 0.54-0.95]) and hospital discharge (HR 0.72 [0.50-0.90]), with delirium partially mediating these relationships. Acute neurologic injury trended towards lower likelihood of ICU discharge (HR 0.73 [0.53-1.00]), with partial delirium mediation, but no association with hospital discharge (HR 0.83 [0.61-1.17]).

Conclusions: Delirium partially mediates the associations between baseline DD and prolonged ICU and hospital LOS, and between acute neurologic injury and longer ICU LOS. Further study of at-risk patients and the possible impact of delirium management are necessary.

1:45-2:45pm NIDUS Session-1
Moderators: D. Fick and M. Avidan

Association between Components of the Delirium Syndrome and Mortality: A Systematic Review and Individual Patient Data Analysis
Zoë Tieges [1], Alasdair MacLullich [1]
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Objective: To determine how domains of the delirium syndrome each predict outcomes in hospitalised patients with delirium through (1) a systematic literature review and meta-analysis; and (2) an individual patient data (IPD) analysis from high-quality studies.

Methods: Study 1: We conducted a systematic review searching MEDLINE, EMBASE, PsycINFO, CINAHL, clinicaltrials.gov and the Cochrane Central Register of Controlled Trials (inception to May 2018). We included studies of delirium in acutely hospitalised adults that used validated delirium assessment tools, and reported associations between delirium components (arousal, inattention, psychotic features, etc.) and mortality. We performed random-effects meta-analysis. Study 2: IPD analysis from three studies comprising detailed assessment of delirium domains in older inpatients (Delirium Rating Scale-Revised 98, assessment of arousal, attention and global cognition) and 12-week mortality data. Logistic regression models were fitted adjusted for age, sex and dementia.

Results: Study 1: From 6,802 citations we included 5 studies (4,448 patients, 731 delirium). Meta-analyses showed higher mortality in patients with altered vs normal arousal (4 studies; pooled Odds Ratio (OR) 2.84, 95% Confidence Interval (CI) 2.20, 3.67) and impaired vs normal attention (3 studies; pooled OR 2.57, 95% CI 1.74, 3.80). Studies varied in risk of bias and quality. Study 2: We analysed data from 1,292 patients (278 delirium). Reduced arousal (Richmond Agitation-Sedation Scale score<0) was the strongest determinant of mortality (OR 3.13, 95% CI 1.91, 5.14, p<0.001), followed by impaired attention (months backward: OR 2.25, 95% CI 1.38-3.96, p<0.001) and delirium as a syndrome (OR 2.24, 95% CI 1.30, 3.86, p<0.004). No significant associations were found between psychotic features and mortality.

Conclusions: These findings indicate an association between key delirium components and mortality, particularly altered arousal. More high-quality studies are needed to estimate the risk of impairments in delirium domains whilst considering potential confounders including dementia diagnosis and illness severity.

A Telehealth Delirium Coaching Intervention for Family Caregivers of Community-Dwelling Older Adults with Dementia

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Objective: The purpose of this study is to develop and evaluate the feasibility of a telehealth coaching intervention for delirium prevention among family caregivers (FCs) of community-dwelling older adults with dementia.

Methods: This study used an explanatory mixed methods design in which survey data was augmented with semi-structured interviews. A purposive sample of 20 older adult dyads participated in the study. The intervention consisted of 6-weeks of telephone coaching sessions. FCs conducted daily delirium assessments and using the FAM-CAM. We employed correlations and GLM to investigate the relationships between variables and the outcomes.

Results: The model showed a statistically significant positive correlation between the Human Connection Scale and the SF-36 pretest domain of *general health* (r= .47, p= .04). There were statistically significant positive correlations between the Human Connection Scale and the SF-36 posttest domains of *physical functioning* (r= .54, p= .014) and *general health* (r= .76, p≤.001). There were a small not statistically significant positive changes in mean scores on each domain between the pre- and post-test scores on the SF-36; however, we believe that in this feasibility study the limited coaching time and small sample size contributed to the limited statistical power. The most impressive findings came from FCs identification of delirium using the FAM-CAM. These 20 patients had no diagnosed history of delirium but 6 of 20 (30%)

reported at least one episode of delirium. These helped diagnose unidentified UTIs. The qualitative analysis revealed that FGs found weekly coaching sessions beneficial and supportive.

Conclusions: While not statistically significant, many of the changes indicated a moderate effect. That combined with the strong results from the FAM-CAM suggests that coaching may have a meaningful impact on how we assess delirium in the community and warrants longer and larger coaching intervention studies.

The Association between Delirium Severity and Long-term Clinical Outcomes among Persons with and without Alzheimer's Disease and Related Dementias

Tammy T. Hshieh[1,2,3], Annie M. Racine[3], Tamara G. Fong[2,3,4], Eva M. Schmitt[3], Yun R. Gou[3], Richard N. Jones[3,5], Sharon K. Inouye[2,3,4]
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Objectives: The influence of delirium severity on adverse clinical outcomes in persons with and without ADRD remains uncertain. Our objective was to determine the association between delirium severity with clinical outcomes at one-month after hospital discharge among persons with and without ADRD.

Methods: Prospective cohort study of medical and surgical patients (N=352). Cognitive status, delirium and delirium severity were rated daily among hospitalized patients using brief cognitive testing, the Confusion Assessment Method (CAM) and CAM-Severity (CAM-S). ADRD status was determined by cognitive testing, chart review and expert consensus. Outcomes at one-month included any decline in Activities of Daily Living (ADL) from baseline, institutionalization, and mortality.

Results: Delirium incidence among persons with ADRD was 45% (38/45) and 19% (50/267) without ADRD - relative risk, RR 2.3 ($p<0.001$). ADRD patients (85/352, 24%) had higher peak CAM-S scores, mean difference 1.24 points (95% CI 0.83-1.65, $p<0.001$). Among persons with ADRD, the relative risk (RR) for adverse outcomes increased significantly with each standard deviation (SD=1.6) increase in peak CAM-S score: for mortality RR (95% CI) was 1.3 (1.1-1.5, $p=0.01$); and for nursing home placement RR was 1.4 (1.0-2.0, $p=0.04$). Among persons without ADRD, RR for nursing home placement was 1.4 (1.2-1.7, $p<0.001$); and RR was 1.2 (1.0-1.3, $p=0.01$) for ADL decline for each SD increase in peak CAM-S score. However, risk for mortality was not significantly increased.

Conclusions: Increased delirium severity is associated with greater risk for poor outcomes in persons with and without ADRD. Severe delirium increased risk of nursing home placement. In persons with ADRD, delirium was more severe and demonstrated more serious clinical impact, including death. These findings underscore the importance of preventing severe delirium, particularly in persons with ADRD.

An Inflammatory Signature of Postoperative Delirium: Importance of Neuroinflammation and Systemic Inflammation

Sarinnapha Vasunilashorn [1,2], Long Ngo [1,2], Simon Dillon [1,2], Hasan Otu [3], Bridget Tripp [3], Sharon Inouye [1,2,4], Towia Libermann [1,2], Edward Marcantonio [1,2,4]
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Objective: Objective: Using the entire Successful Aging after Elective Surgery (SAGES) study cohort, we examined the independent associations of inflammatory proteins previously associated with delirium in a nested matched case-control study.

Methods: Methods: We used the SAGES cohort of adults age ≥70 without dementia undergoing major non-cardiac surgery. Plasma was collected preoperatively (PREOP) and on postoperative day 2 (POD2). Neuroinflammatory marker chitinase-3-like protein [CHI3l1 or YKL-40]; PREOP and POD2) and systemic inflammatory markers interleukin [IL]-6 (POD2 only) and C-reactive protein (CRP; PREOP and POD2) were measured using enzyme-linked immunosorbent assays. Generalized linear models were used to determine the independent (multivariable) associations between the inflammatory markers, measured in sample-based quartiles (Q), and postoperative delirium incidence (measured using the Confusion Assessment Method [CAM]) and severity (measured using the CAM-Severity [CAM-S]). All models adjusted for age, sex, baseline cognition, surgery type, Charlson comorbidity index, and medical complications.

Results: Results: Among the 555 patients (mean age 77 years, standard deviation, SD 5.2), 58% were female and 86% underwent orthopedic surgeries, with median levels of: YKL-40 (PREOP and POD2: 71.7 and 582.8 ng/ml), IL-6 (167.7 pg/ml), and CRP (PREOP and POD2: 2.5 and 176.8 mg/l). Postoperative delirium occurred in 24%, and the mean of the peak CAM-S was 4.0 (SD 3.2). High YKL-40 PREOP and IL-6 at POD2 (Q4 vs. Q1) were significantly associated with an increased risk of delirium: relative risk (RR) [95% confidence interval (CI)] 2.2[1.1-4.4] and 2.7[1.3-5.7], respectively. Similarly, high YKL-40 PREOP and IL-6 POD2 were associated with greater delirium severity (YKL-40 [Q2 vs. Q1]: 0.9 points higher CAM-S score, p=0.01; IL-6 [Q4 vs. Q1]: 1.2 points higher CAM-S score, p=0.01). CRP (PREOP and POD2) was not significantly associated with delirium (p=0.37 and p=0.73, respectively).

Conclusions: Conclusions: This work underscores the importance of both neuroinflammation (YKL-40) and systemic inflammation (IL-6) in the pathophysiology of postoperative delirium.

2:45-3:45pm NIDUS Session-2
Moderators: A. Auerbach and J. Busby-Whitehead

Association between Cumulative Haloperidol Dose and 28- and 90-day Mortality in Critically ill Adults: Post-hoc Analysis of the REDUCE study

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Objective: The routine use of haloperidol in the ICU is not supported by recent RCTs, however the relationship between cumulative haloperidol dose and mortality remains unclear. We evaluated the association between haloperidol use and both 28-and 90-day mortality in critically ill adults.

Methods: This is an IRB-approved, post-hoc analysis of the REDUCE trial where delirium-free ICU adults were randomized to low-dose haloperidol (up to 2mg IV q8h) or placebo and followed to 28 days until delirium, death, or ICU discharge. If delirium occurred, the clinician, at their own discretion, could initiate open-label haloperidol using a pre-established protocol (2mg IV 3/day up to 5mg IV 3/day). Mortality at both 28 and 90 days was analyzed, accounting for both prophylactic and/or treatment haloperidol use. Cox-regression analysis was performed for both 28- and 90-day mortality and adjusted

for covariates i.e. delirium and coma (both occurrence and duration), age, APACHE-II, sepsis, intubation, and cumulative haloperidol dose (prophylaxis and treatment) administered.

Results: Of 1495 patients enrolled, 542(36%) developed delirium within 28 days (days with delirium 0[0-2], coma 1[0-3], or both 2[0-5]); 295(19.7%) received both prophylactic and treatment haloperidol, 606(40.5%) received only prophylactic haloperidol, 194(13.0%) received only treatment haloperidol, and 400(26.8%) received no haloperidol. Mortality was not different at 28 (p=0.99) or 90 days (p=0.81) between these 4 groups. Of 477/542(88%) receiving treatment haloperidol, the cumulative median dose was 16[5-37] mg. The Cox-regression model revealed total cumulative haloperidol exposure (per mg) to be associated with lower mortality at both 28 (HR=0.99, 95%CI=0.98-0.99) and 90 (HR=0.99, 95% CI=0.98-0.99) days. When only delirium treatment haloperidol was considered, its cumulative administration was also associated with lower mortality at both 28 (HR= 0.98, 95%CI=0.97-0.99) and 90 (HR=0.98, 95%CI=0.98-0.99) days.

Conclusions: The cumulative haloperidol dose administered to critically ill adults is associated with lower mortality at both 28 and 90 days.

Delirium Transitions Clinic: An Innovative Model of Care to Mitigate a Cascade of Problems after Delirium.

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Objective: In the current fractured health care system, the diagnosis of delirium is lost in the transition process without a structured approach towards follow up. A novel delirium transitions clinic was implemented and its preliminary data is provided.

Methods: This is a retrospective chart review quality improvement study of patients referred to our "Delirium Clinic. Intervention: outpatient geriatrics consultation with a focus on memory, medications, function, goals of care and caregiver burnout.

Results: Twenty-six patients were eligible and 9 were seen in the clinic during the 8 month time-frame. Overall mean age was 79 years, 39% were female, 46% were discharged home and 10 (37%) patients were admitted for an acute mental status change. Dementia was noted in 6 (21%), mental health diagnoses in 7 (25%) and Charlson co-morbidity score was >=2 for 18 (64%) patients. All of those who received home health services had formal memory testing, while none were tested at the primary care clinic. Six-month mortality was: overall 4%; not seen in the clinic 6%; and seen in the clinic 0%. The 30-day readmission rate was: overall 23%; not seen in clinic 18% and seen in clinic 33%. In the clinic, 2 (29%) were positive for persistent delirium and family also noted that they were not at their baseline. Four (44%) had multiple episodes of delirium. Average time to be seen in the clinic was 159 (range 7 to 415) days. Interventions in the clinic included medication changes, referral to PT/OT/ST, and referral to pharmacy, social work and neuropsychologist.

Conclusions: A critical gap was found in post-hospital cognitive assessment and coordination for care of patients with a diagnosis of delirium. These patients had multiple hospitalizations, behavioral health diagnoses, medication changes and a cascade of medical problems. Results from this delirium consultative clinic will be used to further develop a delirium transitions program.

Delirium Severity and Clinical Outcomes are Both Predicted by Machine Learning Analysis of Routine EEG

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Objective: Despite delirium's importance, its diagnosis and severity assessment remain clinical and subjective. Specific EEG findings can correlate with delirium in carefully selected cohorts, but it is unknown whether routine EEG can be used to derive a delirium severity score in heterogeneous populations. More importantly, it is unknown whether such a score would also predict meaningful clinical outcomes to the same extent as clinical delirium assessment.

Methods: We prospectively studied non-intubated, adult in patients undergoing routine EEG for altered mental status. Each patient was assessed for delirium within one hour of EEG using the 3-minute Diagnostic Interview for Confusion Assessment Method (3D-CAM) and 3D-CAM severity score (3D-CAM-S). EEGs were automatically filtered and >60,000 features were automatically extracted. We used machine learning regression (cross-validated ridge regression) to predict clinical delirium severity using EEG features. Correlations (R) or odds ratios (OR) were calculated between EEG-predicted delirium severity, clinical delirium severity, and clinical outcomes such as hospitalization length of stay, Glasgow Outcome Score, and mortality.

Results: 185 patients were evaluated (mean age 58.8 years, SD 18.3; 41.6% female). 62.1% of patients were delirious according to 3D-CAM criteria. The median delirium severity (3D-CAM-S) was 4 (interquartile range 2-6). EEG-predicted delirium severity was significantly correlated with clinical severity: R=0.61 (95% CI 0.52-0.70). Results were consistent using other machine learning algorithms and other delirium severity measures. Additionally, EEG-predicted delirium severity correlated with multiple clinical outcomes to the same extent as clinical delirium severity (Length of stay: EEG R=0.34, clinical R=0.32; Glasgow Outcome: EEG R=-0.48, clinical R=-0.53; Mortality: EEG OR=2.55, clinical OR=1.83).

Conclusions: Routine clinical EEG, independent of additional clinical information, can be used to derive an automated delirium severity score that is as good at predicting poor clinical outcomes as clinical measures of delirium severity. EEG may therefore be a useful tool to track delirium severity objectively.

SOMAscan as a Discovery Platform to Identify Plasma Protein Biomarkers for Postoperative Delirium

Simon Dillon [1,2], Hasan Otu [3], Sarinnapha Vasunilashorn [1,2,4], Wenxiao Zhou [1,2], Long Ngo [1,2], Sharon Inouye [2,4], Edward Marcantonio [1,2,4], Towia Libermann [1,2]
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Objective: Circulating proteins that are secreted, shed, or leaked from neuronal and immune cells may reflect postoperative delirium pathophysiology and serve as potential delirium biomarkers. Currently, there are no accepted blood-based biomarkers to predict incidence of postoperative delirium. We evaluated the utility of SOMAscan, an aptamer-based proteomics platform, for identifying plasma proteins associated with delirium pathogenesis.

Methods: SOMAscan protein profiles were generated from samples obtained preoperatively (PREOP) and on postoperative day 2 (POD2) from 18 delirium cases and matched controls from SAGES, a prospective cohort of older adults undergoing major elective surgery. Associations between the 1,305 proteins detected with SOMAscan and delirium were assessed using multiple statistical tests. To identify predictors, prediction accuracy of every combination of the top 12 proteins (4,095 combinations of 1-12 proteins) with $p<0.05$ was determined using Support Vector Machine (SVM). Enzyme-linked immunosorbent assay (ELISA) confirmed delirium-specificity of one SOMAscan-derived predictor protein, CHI3L1/YKL-40, across the full sample.

Results: 91 proteins at PREOP and 143 proteins at POD2, respectively, were significantly associated with delirium ($p<0.05$) with 42 of them being dysregulated at both timepoints. Systems biology analysis of these signatures delineated inflammatory response, immune cell trafficking, NK cell activation, and immune system function as key pathways of delirium pathogenesis impacted at PREOP and POD2. PREOP and POD2 SVM-based predictor models distinguish between delirium and no delirium with high accuracy. Independent ELISA validation of the entire SAGES cohort (PREOP: N=559; POD2: N=562) confirmed that the neuroinflammatory marker CHI3L1/YKL-40, common to PREOP and POD2 models, is elevated at both timepoints in delirium cases. These results indicate that CHI3L1/YKL-40 is a risk marker for delirium at PREOP and a disease marker at POD2.

Conclusions: This study demonstrates the feasibility of SOMAscan proteomics to identify delirium plasma biomarkers and advances our understanding of the importance of neuroinflammation in delirium pathophysiology.

4:15-5:15pm Intensive Care Unit - #1
Moderators: T. Girard and Y. Skrobik

Non-EEG sleep staging for delirium in the ICU: a deep learning approach

Haoqi Sun [1], Wolfgang Ganglberger [1], Syed Quadri [1], Ezhil Panneerselvam [1], Michael Leone [1], Robert Thomas [2], Matt Bianchi [1], M. Westover [1]
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Objective: Staging sleep (N1, N2, N3 and REM sleep) is important to understand sleep quality and to help diagnose and manage sleep-associated disorders such as delirium, sleep apnea, parasomnias and dyssomnias. The electroencephalogram (EEG) is the traditional signal for staging sleep in polysomnography (PSG). Because respiration, heartbeat, and brain activity all influence each other, information about sleep stages is also present in respiration and heartbeat. The latter signals have the advantage of being easily collected over prolonged durations, allowing estimation and tracking of sleep state in the ICU environment.

Methods: Using a large dataset containing 8,682 PSGs from one research hospital's sleep laboratory, we developed a set of deep learning models to stage sleep using heartbeat and respiration. The model's inputs were chosen as one or more of the raw ECG and respiratory effort signals from the chest and abdomen; the output was a probability distribution of the sleep stages for every 30 seconds.

Results: The models were tested on 1000 subjects and performance was dependent on the combination of input signals. Cohen's kappa ranged between 0.49-0.6, when staging all four sleep stages and wake, and between 0.65-0.76 when staging NREM, REM and wake. Combined ECG and abdominal effort yielded

best results overall. The performance was typically better for younger subjects (<60 years old) and for the non-severe sleep apnea group (apnea-hypopnea index<30 events/hour).

Conclusions: Using the largest annotated sleep dataset compiled to date, we demonstrated that estimating sleep stage is feasible with a deep neural network, solely from heartbeat and respiration. It has special advantages in the ICU environment, especially in the assessment of delirium, where continuous, prolonged monitoring is crucial, and EEG may not be feasible for this requirement.

ICU Delirium Education Materials for Family Caregivers of Critically Ill Patients

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Objective: Family caregivers of critically ill patients are invaluable partners in the prevention and management of delirium. However, not all family caregivers have knowledge about delirium and its fluctuating course. The objective of this study was to develop a Caregiver ICU Delirium Knowledge Questionnaire (CIDKQ) to evaluate caregiver knowledge about ICU delirium and create, validate and refine an ICU delirium education module to educate caregivers about delirium.

Methods: The CIDKQ was developed by modifying the Caregiver Delirium Knowledge Questionnaire using relevant literature on ICU delirium. The education module was created using the PRECEDE (Predisposing, Reinforcing and Enabling Constructs in Educational Diagnosis and Evaluation) model: 1) predisposing (delirium and its risk factors), 2) reinforcing (detecting delirium using case vignettes of hypothetical ICU patients and previously validated family-administered delirium detection questionnaires) and 3) enabling (preventing and managing delirium). The CIDKQ and case vignettes were validated during a prospective study of family caregivers recruited from ICU waiting rooms. Each participant completed the CIDKQ and the reinforcing part of the education module using the Family Confusion Assessment Method (FAM-CAM) and Sour Seven. Descriptive statistics were calculated for all study variables. Past-ICU patients and family caregivers and a multidisciplinary team were involved as research partners throughout this study.

Results: The CIDKQ showed adequate internal consistency (Cronbach Î± = 0.78) among 80 recruited family caregivers (mean age 47 years; 43% female). Family caregivers correctly identified delirium presence or absence in the case vignettes using the FAM-CAM (specificity=75%, sensitivity=75%) and Sour Seven (specificity=90%, sensitivity=65%).

Conclusions: The findings support the validity of the CIDKQ to evaluate caregiver ICU delirium knowledge and the ability of family caregivers to recognize delirium in the provided case vignettes. Results from this study support a pilot study to assess the feasibility and acceptability of employing the complete education module to family caregivers of critically ill patients.

Prophylactic Haloperidol Effects on Long-term Quality of Life in Critically Ill Patients at High Risk for Delirium: Results of the REDUCE study

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Objective: To evaluate the effects of prophylactic haloperidol use on long-term quality of life in critically ill patients at high risk for delirium, and to explore which factors are associated with change in quality of life.

Methods: A pre-planned secondary analysis of long-term outcomes of the REDUCE study was conducted. In this multicenter randomized clinical trial, non-delirious Intensive Care Unit (ICU) patients were assigned to the prophylactic haloperidol or placebo group. Long-term outcomes were assessed using the Short Form-12 questionnaire at ICU admission (baseline), and after 1 and 6 months. Quality of life was summarized in the physical component summary (PCS) score and mental component summary (MCS) score. Differences between the haloperidol and placebo group, and factors associated with changes in quality of life were analyzed.

Results: Of 1789 study patients, 1245 ICU patients were approached of which 887 (71.2%) responded. Long-term quality of life did not differ between the haloperidol and placebo group (mean±SD PCS score of 39.3Â±11.0 and 38.9Â±10.6, respectively; P=0.35, and mean±SD MCS score of 50.3±10.1 and 51.1Â±10.0, respectively; P=0.68). Factors associated with physical decline after 6 months were age (odds ratio (OR) 1.02; 95%CI 1.01-1.04), medical admission (OR 2.08; 95%CI 1.39-3.10), trauma admission (OR 5.34; 95%CI 1.65-17.27), baseline PCS score (OR: 1.06; 95%CI 1.04-1.08) and number of sedation-induced-coma days (OR 1.15; 95%CI 1.05-1.25). Factors associated with mental decline after 6 months were age (OR 1.03; 95%CI 1.01-1.04), medical admission (OR 2.09; 95%CI 1.43-3.03), baseline MCS score (OR 1.03; 95%CI 1.01-1.05) and the number of sedation-induced-coma days (OR 1.09; 95%CI 1.01-1.17).

Conclusions: Prophylactic haloperidol use does not affect long-term quality of life in critically ill patients at high-risk for delirium. Several factors, including the modifiable factor number of sedation-induced-coma days, are associated with decline in long-term outcomes.

Sustained Attention Testing in Delirious and Non-delirious Critically Ill Adults

Carol Chan, Carrie Goodson, Margaret Sundel, Aisa Moreno-Megui, Atsushi Kamiya, Dale Needham, Karin Neufeld
Johns Hopkins University School of Medicine, Baltimore, MD, USA

Objective: Our objective was to evaluate the Edinburgh Delirium Test Box for the ICU (EDTB-ICU) against standardized assessment of delirium status and severity in medical ICU patients.

Methods: Data for this analysis were derived from a pilot study evaluating the impact of usual care physical therapy interventions on patient attention in the ICU. Patients included in this study were English-speaking adult medical ICU patients, without neurological pathology, dementia, or coma, who were receiving physical therapy. All patients were assessed for delirium using the Confusion Assessment Method (CAM) and Delirium Rating Scale (DRS-R98), and thereafter completed a standardized test of attention using the EDTB-ICU. The EDTB-ICU is a non-invasive, computerized neuropsychological testing device that quantitatively measures attention via a method that is suitable for non-verbal ICU patients. The EDTB-ICU includes 3 levels of increasing difficulty, consisting of 3 trials each, with a total score range of 0-9. A higher score indicates greater accuracy of responses.

Results: 35 patients (median age 60 years, 17 (49%) Male, median SOFA score 6, 14 (40%) CAM positive) were included in the analysis. There was a significant difference in mean (SD) EDTB-ICU test results between delirious vs non-delirious patients (2.9 (2.6) vs. 7.7 (1.5), $p<0.001$). EDTB-ICU results correlated with delirium severity ($r=-0.575$, $p<0.001$). An EDTB-ICU score of 6.5 had 86% sensitivity

and 86% specificity for delirium as determined by CAM (Area Under Receiver Operating Characteristics Curve 0.93, 95% CI: 0.85-1.00).

Conclusions: In a small sample of medical ICU patients, the EDTB-ICU has good sensitivity and specificity for delirium detection and correlated with delirium severity.

Tuesday June 18, 2019

10:30-11:30am Mechanisms/Pathophysiology
Moderators: N. Terrando and S. Vasunilashorn

A Human and Mouse Model Study of Inflammatory Chemokines at the Blood Cerebrospinal Fluid Barrier and Their Role in Delirium

Lucas Tortorelli [1], Arshed Nazmi [1], Leiv Otto Watne [2], Colm Cunningham [1]
[1] Trinity College Dublin, Dublin, Ireland, [2] Oslo University Hospital, Oslo, Norway

Objective: Systemic inflammation can trigger delirium but mechanisms by which inflammation actually causes dysfunction are poorly understood. It is widely assumed that circulating inflammatory mediators cross the blood brain barrier and have actions in the brain. In the current study we investigate the extent to which chemokines are synthesised directly at the blood CSF barrier (BCSFB) in mice and interrogate which, among those chemokines, are associated with delirium in a hip fracture cohort.

Methods: We have exposed mice to systemic inflammation (bacterial LPS) to interrogate which inflammatory chemokines are synthesised at the BCSFB using quantitative PCR, immunohistochemisty and FACS analysis. We have used Mesoscale V-plex assays to assess chemokine expression in human CSF to examine associations with delirium in a hip fracture cohort.

Results: Chemokine mRNAs were enriched in the isolated choroid plexus. Immunohistochemistry and FACS showed that MCP1 and IL-1Î² were expressed by choroid plexus stromal macrophages and MIP1, MIP1 and CXCL1 were expressed in choroidal epithelial cells after systemic LPS (100 μg/kg). All of these chemokines were detected in the CSF of human hip fracture patients. Using these mouse data to propose directional hypotheses about associations between chemokines and delirium, we detected significant associations between delirium and elevated IL-8 and MIP1 in univariate analyses. In bivariate analyses, stratified by dementia status, CCL2 was significantly higher in delirium/dementia while MIP1 was significantly higher in delirium/no dementia. Addressing the impact of blood brain barrier leakiness, the CSF concentrations of IL-8 and MCP1 were found to be unaffected by BBB leakiness (Qalb > 10.2), while MIP1 was associated with leaky BBB.

Conclusions: These data demonstrate that systemic inflammation drives chemokine synthesis at brain ventricular surfaces. This local synthesis of chemokines may provide a more proximate inflammatory trigger for acute brain dysfunction and roles of individual chemokines in acute brain dysfunction now require detailed analysis.

Energy Metabolism is a Driver of Cognitive Dysfunction in an Animal Model of Delirium during Dementia

Carol Murray, John Kealy, Colm Cunningham
Trinity College Dublin, Dublin, Ireland

Objective: It is established that systemic inflammation is a trigger for delirium, particularly in those with existing dementia, but the mechanisms by which inflammation actually causes dysfunction are not well understood. We have sought to clarify the mechanistic basis of this relationship using animal models of chronic neurodegenerative disease and superimposed inflammation. Circulating, rather than brain, interleukin 1 beta (IL-1) is causative of dysfunction in prior animal model studies. Here we address the hypothesis that this occurs through impaired energy metabolism.

Methods: An animal model of chronic neurodegeneration (ME7) was used to provide a predisposed state and systemic bacterial lipopolysaccharide was used to trigger acute dysfunction in assays of locomotor activity and cognitive dysfunction. We measured glucose levels in blood and cerebrospinal fluid, used insulin treatment to mimic hypoglycemia and used 2-deoxyglucose to block glycolysis.

Results: Both LPS (250 g/kg) and IL-1 (250g/kg) induced systemic hypoglycemia in C57BL6/J mice and this was also apparent in the brain, as measured in cerebrospinal fluid (CSF). Lower systemic glucose concentration correlated with suppression of locomotor activity and, consistent with this, LPS-induced sickness behavior was reversed in C57BL6/J mice by pre-treating mice with glucose (2g/kg). The glycolysis inhibitor 2-deoxyglucose (2-DG; 2g/kg) blocked glycolysis and produced locomotor suppression despite preventing LPS-induced IL-1Î² production, proving that uncoupling of IL-1 from acute sickness is possible. When superimposed upon existing neurodegeneration, LPS produced acute working memory dysfunction that was absent in LPS-treated normal animals. This could be mimicked with acute treatment with insulin (400 µg/kg), to cause hypoglycemia. Crucially, glucose treatment (2g/kg) could significantly reduce LPS-induced working memory deficits.

Conclusions: These data demonstrate that glucose metabolism is a major determinant of LPS-induced cognitive impairment during systemic inflammation and focus attention on brain energy metabolism as a key area for study in delirium.

Serum Neurofilament Light Chain Is Persistently Elevated Following Delirium in Older Adults Undergoing Elective Surgery

Tamara Fong [1,2,3], Annie Racine [1,3], Sarinnapha Vasunilashorn [1,2], Long Ngo [1,2], Towia Libermann [1,2], Edward Marcantonio [1,2], Sharon Inouye [1,2,3]
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Objective: To examine the association of plasma neurofilament light (NfL), an indicator of neuroaxonal injury, and delirium.

Methods: Using the Successful Aging after Elective Surgery (SAGES) Study of adults age ≥70 undergoing major noncardiac surgery, we conducted a nested, longitudinal, matched delirium case-no delirium sub-study (n=52 matched pairs). Delirium cases and no delirium controls were selected from the overall SAGES cohort (N = 566; 24% delirium). Plasma NfL was measured using Simoa technology (Quanterix, Lexington, MA) at three timepoints: preoperative (PREOP), postoperative day 2 (POD2) and 30 days post-operation (PO1MO). Sample-based quartiles (Q) of NfL were used in some analyses. Delirium occurrence was determined using the Confusion Assessment Method (CAM). Nonparametric signed rank tests and conditional logistic regression models were used to estimate the association effects between NfL and postoperative delirium.

Results: Median PREOP plasma NfL levels were similar in patients with delirium (33.0pg/ml [interquartile range, IQR=12.5-50.0]) and without delirium (26.5pg/ml [IQR=19.6-39.8]), p=0.08, but

significantly increased on POD2 among patients with delirium (45.0pg/ml [IQR=35.6-65.2]) compared to patients without delirium (33.5pg/ml [IQR=24.6-48.],p=0.002). Higher levels of NfL among delirious cases persisted at PO1MO, 49.0pg/ml (IQR=37.1-88.4) relative to no-delirium controls (40.5pg/ml [IQR=29.5-51.3],p=0.004). Patients with PREOP NfL values in the highest quartile (Q4) had an odds ratio (OR) for delirium of 3.9 (p=0.03); POD2 NfL values in Q3 and Q4 had an OR of 3.9 (p=0.03) and 6.3 (p=0.01), respectively.

Conclusions: Patients with the highest baseline levels of NfL (i.e., Q4) were more likely to develop delirium, suggesting that patients with pre-existing neuronal injury may be more vulnerable to developing delirium. Higher plasma NfL at POD2 and PO1MO in patients with delirium suggest that delirium may contribute to neuroaxonal injury, which persists for at least 1 month following the delirium episode. If confirmed with additional studies, this finding would provide evidence for long-term neuronal injury following an episode of delirium.

Cholinergic Trajectories in Patients with Postoperative Delirium

Anika Mueller [1], Maria Olbert [1], Rudolf Moergeli [1], Carolin Herrmann [2], Pimrapat Gebert [2], Claudia Spies [1]
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Objective: The hypothesis of regulatory mechanisms of peripheral cholinesterases has been described in surgical patients. Aim of the study [Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BioCog)] was to develop biomarkers on postoperative delirium (POD). This subproject analyzes the perioperative trajectory of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) activities in relation to the occurrence of postoperative delirium.

Methods: The multicenter, prospective FP-7 BioCog study took place from October 2014 until November 2017 (ethical approval: EA2/092/14, registration NCT02265263). Patients ≥ 65 years of age scheduled for stationary elective surgery were included, and AChE/BuChE activities were measured via point of care testing preoperatively, on the first postoperative day, and three months after surgery. Delirium was diagnosed by a bundle of validated scores. Long-term medication was screened for anticholinergic side-effects. Generalized Estimating Equation (GEE) was performed for exploring the association between the time course of cholinesterase activity and postoperative delirium.

Results: Of 628 analyzed patients, 129 patients (20.5%) developed delirium within the first seven postoperative days. Although AChE activity did not differ in patients with or without delirium (preop P=0.109, 1stpost-op P=0.093, 2ndpost-op P=0.907), BuChE activity was lower in patients with delirium at every measured time point (preop P<0.001, 1stpost-op P<0.001, 2ndpost-op P=0.002). Anticholinergic long-term medication had no influence on the development of POD (p=0.725).

Conclusions: In contrast to AChE activity, BuChE activity is significantly lower in elderly surgical patients that go on to develop postoperative delirium. Further studies are still required to assess the clinical relevance of these findings.

11:30-12:30am Postoperative Delirium #1
Moderators: L. Evered and S. Vasunilashorn

Delirium Detection Methodologies: Implications for Outcome Measurement in Clinical Trials in Postoperative Delirium

Karin Neufeld, Esther Oh, Frederick Sieber, Charles Brown, Nae-Yuh Wang
Johns Hopkins University, Baltimore, MD, USA

Objective: Delirium prevention studies require valid and reliable delirium outcome measures. In this secondary analysis we compare the Confusion Assessment Method (CAM) and Delirium Rating Scale Revised-98 (DRS-R-98) to DSM-IV/consensus outcome measures in a published RCT of depth of sedation during regional anesthesia for hip fracture surgery.

Methods: English-speaking adults, ≥ 65 years old, with Mini-Mental State Exam scores ≥15 without delirium preoperatively, and undergoing hip fracture repair with spinal anesthesia and propofol sedation were included. Research staff performed standardized examinations and rated CAM and DRS-R-98. Final diagnoses were made by a consensus panel rating delirium DSM-IV criteria.

Results: Of 200 individuals, 73 (37%) developed postoperative delirium by DSM-IV/consensus. By CAM (positive/negative) 60 (30%), and DRS-R-98 (cut off severity scale > 15) 27 (14%) met delirium diagnoses. Compared to DSM-IV/consensus diagnosis, CAM sensitivity (95%CI) and specificity (95%CI) was 0.80 (0.68, 0.90) and 0.98 (0.96, 1.00) respectively; DRS-R-98 was 0.32 (0.20, 0.45) and 1.00 (1.00, 1.00) respectively. Depth of sedation was not associated with postoperative delirium using any binary diagnostic method. In heavier vs. lighter sedation groups, the DSM-IV/consensus identified 39 (39%) vs 34 (34%) (P=0.46) respectively as delirious; CAM identified 30 (30%) vs 27 (27%) (P=0.64) respectively; DRS-R-98 identified 15 (15%) vs 12 (12%) (P=0.53) respectively. However, mean DRS-R-98 severity scores on postoperative day 1 (POD1) were statistically significantly different between groups, with lighter sedation associated with lower severity scores (Wilcoxon z=2.61, p=0.009); this difference remained significant after adjusting for baseline DRS-R-98 using a mixed effects model (mean difference: 1.27, t=2.36, p=0.019).

Conclusions: While sedation depth was not associated with delirium diagnosis, it was associated with mean DRS-R-98 delirium severity score on POD1. Use of continuous severity scales as an outcome measure may be important to include in future trials.

Association between Delirium and Patient Reported-Outcomes 30-Days Following Major Surgery

Angela Mickle, Jordan Oberhaus, Thaddeus Budelier, Daniel Park, Arbi Ben Abdallah, Michael Avidan
Washington University School of Medicine, St. Louis, MO, USA

Objective: To evaluate the association between postoperative delirium and patient reported outcomes.

Methods: Patients 60 years and older undergoing major surgery were recruited and consented to the ENGAGES study (NCT02241655) [1] or to the PODCAST study (NCT01690988) [2]. Patients were assessed for delirium using the Confusion Assessment Method (CAM) or CAM for the intestine care unit (CAM-ICU) in the afternoon postoperative day (POD) 1-5 for the ENGAGES study and morning and afternoon POD 1-3 for the PODCAST study. In lieu of morning assessments for the ENGAGES study a retrospective chart review for evidence of delirium was completed [3]. Patients who had delirium

outcomes (either positive or negative) were included in this sub-study. Approximately 30 days following surgery, patients were contacted to complete the Veterans Rand-12 Health Survey (VR-12), the eight-question Patient Health Questionnaire (PHQ-8) and the 10-word Positive Affect Schedule. Difference in median outcome scores were calculated with Mann-Whitney U tests. No imputation was done for missing answers on the questionnaires.

Results: A total of 1866 patients had at least one delirium assessment and were included in this analysis. The overall delirium rate was 22.8%. A total of 1808 patients were eligible to complete a 30-day follow up (33 died and 25 withdrew) with 1440 patients completing at least one questionnaire. Patients with delirium had significantly less physical and mental VR-12 scores as well as mild depression scored by the PHQ-8. Patients positive affect scores were also found to be statistically different.

Conclusions: Intermediate self-reported patient outcomes including quality of life (VR-12), depression (PHQ-8) and positive affect approximately 30 days post major surgery were found to be significantly different between patients with postoperative delirium compared to patients without postoperative delirium. Therefore, additional focus and support on patient's quality of life and mental health may improve longer term outcomes in patients who experience postoperative delirium.

Baseline Depression in Relation to Postoperative Delirium in Hip Fracture Patients

Carol Chan [1], Karin Neufeld [1], Paul Rosenberg [1], Jeannie Leoutsakos [1], Nae-Yuh Wang [2], Constantine Lyketsos [1], Frederick Sieber [3], Esther Oh [1]
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Objective: There is increasing evidence of an association between preoperative depressive symptoms and postoperative delirium. However, the relationship between preoperative depression and postoperative delirium in the hip fracture population remains unclear. Furthermore, the study of this association has been complicated by confounding factors, such as cognitive impairment. The goal of these analyses was to examine the effect of depressive symptoms before surgery on the risk of postoperative delirium in hip fracture patients.

Methods: Data for this secondary analysis were derived from individuals enrolled in the randomized clinical trial: A Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients (STRIDE) study who had a 15-item Geriatric Depression Scale (GDS-15) completed preoperatively. English speaking adults ≥65 years old with Mini-mental State Exam (MMSE) score ≥15 who did not have preoperative delirium, and were undergoing hip fracture repair with spinal anesthesia and propofol sedation were included. Postoperative delirium was diagnosed by a consensus diagnosis panel from postoperative day 1 to 5 or hospital discharge. Logistic regression models were used to examine the relationship between baseline GDS-15 and incident postoperative delirium.

Results: 199 individuals (mean age 81.82, 146 (73%) female, 194 (97%) Caucasian, MMSE 24.29, GDS-15 3.83) were included in the analysis. 72 patients (36%) developed delirium postoperatively. Individuals with postoperative delirium had higher GDS-15 score (no delirium M= 3.14, SD=3.11; delirium M=5.01, SD=3.78; $p<0.001$) and lower MMSE score (no delirium M=25.05, SD=3.34; delirium M=22.99, SD=3.89; $p<0.001$) before surgery. Higher GDS-15 score before surgery was associated with greater risk of postoperative delirium after adjusting for baseline MMSE, age, sex, race and education (OR=1.15, 95% CI = [1.05, 1.26], p=0.003).

Conclusions: Depressive symptoms before surgery are associated with postoperative delirium in individuals undergoing hip fracture repair, even after adjusting for baseline cognition, and may be useful in identifying persons at risk for postoperative delirium.

The Effect of Preoperative Depressive Symptoms on Postoperative Cognitive Dysfunction (POCD)

Friedrich Borchers, Lukas Roediger, Henning Krampe, Claudia Spies
Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

Objective: Post-operative cognitive dysfunction (POCD) is defined as cognitive decline after surgery. Studies have shown that depressive symptoms can be a risk factor for POCD. The aim of this analysis is to further investigate whether a preoperative positive screening for clinically significant depressive symptoms is associated with higher incidence of POCD.

Methods: Patients aged 65 years or older scheduled for elective surgery were prospectively recruited within the multicenter FP-7 BioCog study (ethical approval: EA2/092/14, registration NCT02265263). A preoperative sum score of 5 or higher on the Geriatric Depression Scale Short Form (GDS-S) indicated clinically significant depressive symptoms. Neurocognitive testing was performed before surgery, seven days after surgery (or discharge), and 3 months after surgery. POCD was defined using the Reliable Change Index model as proposed by Rasmussen et al. in the International Study of Postoperative Cognitive Dysfunction (ISPOCD).

Results: 552 patients with preoperative GDS-S screening completed the follow-up cognitive testing at 3 months, and 30 (5.4%) patients developed POCD. Of these 30 patients with POCD, 7 (23.3%) screened positive for clinically significant preoperative depressive symptoms (unadjusted OR 3.88, 95% CI [1.56-9.61], p=0.007). A multiple logistic regression model revealed that the significant association between preoperative depressive symptoms and POCD persisted (OR 3.04, 95% CI [1.13-8.17], p=0.03) when simultaneously including the covariates age, gender, Mini Mental State Exam (MMSE) and level of education (ISCED).

Conclusions: In this preliminary analysis, scoring 5 or more points on GDS-S at baseline was found to increase the risk of developing POCD 3 months after surgery by a factor of three.
Future studies should address the role of screening geriatric patients for depressive symptoms, as positive results may indicate a risk factor to incur cognitive decline following surgery.

2:00- 3:00pm Postoperative Delirium #2/Assessment

Moderators: P. Pandharipande and R. Arora

Preoperative Frailty Increases the Risk for Postoperative Delirium in Major Non-Cardiac Surgical Patients

Elizabeth Mahanna-Gabrielli [1], Kenneth Boockvar [2], Frederick Sieber [3], Stacie Deiner [2]
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Objective: Postoperative delirium's most consistent risk factors are non-modifiable: age and pre-existing cognitive impairment. Current research on reversible risk factors such as anesthetic type and depth have

brought inconsistent results [1,2]. Frailty, increased vulnerability to stress, holds promise as a modifiable risk factor. Frailty predicts the onset of future cognitive impairment and is associated with a risk of delirium [3]. We aimed to prospectively determine the association of frailty and delirium after major non-cardiac surgery.

Methods: The study is a secondary analysis of a prospective observational, cohort study: Optimizing Postoperative Cognitive Dysfunction in the Elderly-PRESERVE. We included patients >65 years-old having major noncardiac surgery with general anesthesia. Exclusion criteria were dementia, inability to consent, and cardiac, intracranial or emergency surgery. Frailty was determined by the FRAIL scale consisting of five domains: Fatigue, Resistance (inability to climb 1 flight of stairs), Ambulation (inability to walk 1 block), Illnesses (>5 co-morbidities), Loss of weight (>5%) [4]. A score of 1 is assigned to each positive domain. A score of 0 equates to being robust, a score of 1-2 to being prefrail and >3 to being frail. Delirium was assessed with the CAM-ICU daily, starting in the recovery room until hospital discharge.

Results: 120 patients completed the study. The mean age was 71.4 years. 55% were female. Surgery type was 42.5% spine, 35% general, 12% thoracic, 18.3% urologic. 23 patients (19.2%) were frail. No difference existed between age, education, gender, mini-mental state exam, ASA status or surgery type between cohorts. Frail subjects had increased delirium compared to those without frailty (43.5% versus 21.7% respectively), p=0.032.

Conclusions: Frailty increased risk for postoperative delirium in major non-cardiac surgical patients. Future studies aimed to preoperatively intervene on frailty to decrease postoperative delirium are warranted.

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Depth of Sedation as an Interventional Target to Reduce Postoperative Delirium: Mortality and Functional Outcomes of the STRIDE Randomized Clinical Trial

Frederick Sieber, Karin Neufeld, Esther Oh, Nae-Yuh Wang
Johns Hopkins Medical Institutions, Baltimore, MD, USA

Objective: Introduction: The Strategy to Reduce the Incidence of Post-operative Delirium in the Elderly (STRIDE) trial tested the hypothesis that limiting sedation during spinal anesthesia decreases in-hospital postoperative delirium (POD) following hip fracture repair. This manuscript reports the STRIDE trial secondary outcomes including mortality and function.

Methods: Methods: 200 patients (≥65 years) undergoing hip fracture repair with spinal anesthesia were randomized to heavier (modified Observer's Assessment of Alertness/Sedation score (OAA/S) 0-2) or lighter (OAA/S 3-5) sedation and assessed for POD. Secondary outcomes included mortality and return to pre-fracture ambulation level (return.amb) at 1-year. Kaplan-Meier analysis, multivariable Cox proportional hazard model and logistic regression were used to evaluate intervention effects on mortality and odds of return.amb.

Results: Results: One-year mortality was 14% in both groups (log rank p=0.96). Independent 1-year mortality risk factors included: Charlson co-morbidity index (HR=1.23 [1.02-1.49]; p=0.03), instrumental activities of daily living (HR=0.74 [0.60-0.91]; p=0.005), body mass index (HR=0.91 [0.84-0.998];

p=0.04), and POD severity (HR=1.20 [1.03-1.41]; p=0.02). Ambulation returned to pre-fracture levels, worsened, or was not obtained in 64%, 30%, and 6% of 1-year survivors, respectively. Lighter sedation did not improve odds of return.amb at 1 year (OR=0.76 [0.24-2.4]; p=0.63). Independent risk factors for return.amb included Charlson co-morbidity index (OR=0.71 [0.53-0.97]; p=0.03) and POD (OR=0.32 [0.10-0.97]; p= 0.04).

Conclusions: Conclusion: The STRIDE results provide reassurance that there is no difference in mortality or return to ambulation 1 year after hip fracture surgery in elderly patients receiving heavier and lighter intraoperative sedation.

Marginal Benefit of Cognitive Screening to Identify Patients at Risk for Postoperative Delirium

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Objective: The primary aim/objective of this study is to assess the marginal benefit of adding a brief cognitive screen to the standard preoperative evaluation to identify patients at risk for developing postoperative delirium.

Methods: We enrolled 250 patients 65 years of age and older scheduled for elective total knee or hip replacement surgery presenting for preoperative evaluation at the Brigham and Women's Hospital between February 1, 2016 and March 30, 2017. After obtaining informed consent, study investigators a) asked each patient if they had spoken to a medical professional about or been evaluated for a change in memory or thinking, b) administered two cognitive screening tools (Mini-Cog and Animal Verbal Fluency), and c) systematically conducted medical record review to identify evidence of cognitive impairment preoperatively. The primary outcome was the development of postoperative delirium as detected by the Confusion Assessment Method (CAM) and/or comprehensive chart review. Data were analyzed using a Likelihood ratio test vs. base model with a $p < 0.05$ considered statistically significant.

Results: Two hundred and twenty-seven patients completed the study, 26 of whom developed postoperative delirium (11.5%). The variables that best fit the model for predicting the development of postoperative delirium when compared to the baseline model that included age and routine preoperative evaluation included lower scores on the Mini-Cog ($p = 0.008$) or Animal Verbal Fluency ($p = 0.001$).

Conclusions: The use of cognitive screening tools such as the Mini-Cog or Verbal Fluency have marginal benefit in identifying older surgical patients that are at risk for developing postoperative delirium following elective lower extremity joint replacement surgery.

Diagnostic Accuracy of the DelApp Smartphone Test for Assessing Inattention in Delirium in Geriatric and Intensive Care Settings

Zoë Tieges [1], David Stott [2], Jonathan Evans [2], Christopher Weir [1], Elizabeth Wilson [1], Tim Walsh [1], Tara Quasim [2], Alasdair MacLullich [1]
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Objective: To determine the diagnostic performance of the smartphone Delirium Application (DelApp) combined arousal and attention test for delirium in hospital inpatients.

Methods: Consecutively-approached, unselected patients were recruited from geriatrics and acute orthopaedic wards (Study 1; aged ≥65) and from Intensive Care Units (ICU; Study 2; aged ≥18). Algorithm-based reference standard assessment incorporating neuropsychological testing based on DSM-5 was performed. Separate blinded assessors administered the DelApp (total score 0-10, 10=good performance). Pre-determined cut-points from prior case-control studies were evaluated.

Results: Study 1: 382 older inpatients were recruited, mean age 82.3y (range 65-99), delirium: n=58 (15.2%); dementia/no delirium: n=60 (15.7%). Area under the curve (AUC) was 0.83 (95% Confidence Interval (CI): 0.77-0.89). At a cut-point of 8, sensitivity for delirium was 75.4% (95% CI: 64.9-85.9) and specificity 83.6% (95% CI: 78.7-88.5). Specificity for delirium versus dementia was 84.5% (95% CI: 75.2-93.8; cut-point of 6). Study 2: 165 ICU patients were recruited, mean age 61.0y (range 24-89); delirium: n=39 (23.4%). The AUC was 0.90 (95% CI: 0.85-0.97). Sensitivity for delirium was 81.6% (95% CI: 69.3-93.9) and specificity 85.6% (95% CI: 79.3-91.9; cut-point of 6).

Conclusions: The DelApp provides a brief, objective test with acceptable diagnostic accuracy for detecting delirium in unselected inpatient populations.

3:00-4:00pm Delirium Assessment

Moderators: J. Saczynski and R. Jones

A Single Question on the Acuity of Mental Status Change Improves the Nu-DESC's ability to Discriminate Delirium

Mark Terrelonge Jr., Patrick Yuan, Vanja Douglas, Anita Hargrave, Jim Bourgeois, Jesse Bastiaens, Jackie Leung
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Objective: We sought to determine whether the addition of the Confusion Assessment Method- Long Form (CAM-L) question on whether a patient experienced an acute change in mental status could improve the ability of the Nursing Delirium Screening Scale (Nu-DESC) to correctly identify delirium in a university hospitalized population.

Methods: The study was conducted at a university hospital in San Francisco from August 2015 to February 2016. Patients with positive Nu-DESC (score ≥ 2; n=213) were matched with Nu-DESC-negative patients (score < 2; n=192) by age, sex, and nursing unit. A Nu-DESC-blinded research assistant evaluated Nu-DESC positive and negative patients through chart reviews and structured interviews with patients, nurses, and caregivers. Information was used to compile a structured clinical vignette, which was evaluated by a board-certified neurologist and psychiatrist using DSM-5 criteria. Both physicians were blind to each patient's Nu-DESC score. Response from the question on the CAM-L asking if there evidence of an acute change in mental status from the patient's baseline and Nu-DESC score were compared to DSM-V identified delirium cases to determine whether combined information from the two sources would improve the positive predictive value (PPV) and negative predictive value (NPV) in this sample compared to the Nu-DESC alone.

Results: The Nu-Desc had a positive predictive value (PPV) of 75.12% (160/213) and a negative predictive (NPV) of 88.02% (169/192) for identifying delirium. The Nu-Desc screen with the addition of the CAM question had a PPV of 89.20% (157/176) and NPV of 88.65% (203/229).

Conclusions: Addition of a question about an in-hospital change in mental status to the Nu-Desc increased both the positive and negative predictive value for determining delirium. This was primarily

due to the combined tests' improved ability to exclude patients with pre-morbid dementia and psychiatric illness.

Evaluation of Screening Instruments for the Detection of Pediatric Delirium during Critical Illness

Debbie Long [1,2], Rebecca Paterson [3], Belinda Dow [3], Alexandra DeYoung [3,4], Leanne Aitken [5], Justin Kenardy [3]
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Objective: Delirium is common in the PICU and it is important that accurate, reliable and feasible screening instruments are available. Several instruments for screening paediatric delirium have been developed, however they have not undergone external, concurrent validation. Objectives were to explore the psychometric properties and feasibility of the Cornell Assessment for Pediatric Delirium (CAP-D), and the Pediatric- and Preschool- versions of the Confusion Assessment Method for the Intensive Care Unit (pCAM-ICU and psCAM-ICU) for delirium screening in clinical practice.

Methods: A prospective observational study was conducted assessing delirium in critically ill children developmentally aged 6 months to 17 years with a PICU length of stay ≥18 hours. Patients were screened for delirium by their bedside nurse and an expert PICU nurse (CAP-D and pCAM-ICU/psCAM-ICU) once daily, on up to five consecutive days. Delirium status identified using screening instruments was compared to delirium diagnosis using the diagnostic criteria for Delirium (DSM-5).

Results: One hundred and nineteen patients were enrolled in the study and 189 paired assessments were included in data analysis. All three instruments had acceptable discriminant ability. Overall, the CAP-D was a highly sensitive instrument (sensitivity = 89%, specificity = 74%), but its accuracy was impacted by younger patient age ($p < .001$), greater sedation ($p = .031$) and subsyndromal symptoms ($p = .003$). The psCAM-ICU (sensitivity = 67%, specificity = 90%) and pCAM-ICU (sensitivity = 67%, specificity = 93%) were less sensitive than previous validation studies, and their accuracy was impacted by sedation status ($p = .023$) and subsyndromal symptoms ($p = .006$), respectively.

Conclusions: In this sample, the CAP-D performed better than the pCAM-ICU or psCAM-ICU in screening for pediatric delirium. Overall accuracy of the screening tools are affected by patient variables. Further direct comparisons and evaluation of factors which impact screening accuracy should be performed.

Validation of the Quick Stanford Proxy Test for Delirium (qS-PTD), a Highly Effective and Straightforward Screening Tool for Delirium

Jose Maldonado , Mario Benitez-Lopez , Fahad Alosaimi [1]
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Objective: The qS-PTD is a shorter version of the previously developed Stanford Proxy Test for Delirium (S-PTD) that uses highly predictive prompts and age to predict delirium in both the ICU and non-ICU setting.

Methods: The qS-PTD was developed using data from the S-PTD validation study at Stanford, in an effort to increase predictive power, we performed a stepwise regression analysis to identify which of the

twelve prompts from the S-PTD were the most predictive for delirium. We confirmed our model using bootstrapping, resulting in a tool that retains six of the original twelve prompts as well as age. The new tool was then validated using additional data from a second S-PTD validation study performed in King Khalid University Hospital in Saudi Arabia. In both studies, all patients from specified clinical units were independently assessments: the S-PTD, the CAM/CAM-ICU, and a neuropsychiatric assessment using DSM-5 criteria.

Results: Using 194 patients from Stanford University Hospital plus 282 patients in King Khalid University Hospital, we obtained a sensitivity of 84% and a specificity of 90% for the qS-PTD. This is superior to the CAM, which demonstrated a sensitivity of 46% and a specificity of 98% in our study.

Conclusions: The qS-PTD is an innovative screening tool that has proven to be highly effective in detecting delirium in both ICU and non-ICU patients. The S-PTD is considerably more effective than the CAM and CAM-ICU, which would potentially make it the most effective delirium screening tool currently available. Unlike other screening tools, the qS-PTD is simple to use, requires no patient interaction, and can be effectively used by nursing staff. Adaptation of the qS-PTD to current medical practice has the potential to reduce morbidity and mortality of the delirium through early detection and opportune treatment.

Use of the brief Confusion Assessment Method in a Veteran Palliative Care Population: A Pilot Validation Study

Jo Wilson [1,2], Leanne Boehm [1,2], Lauren Samuels [1,2], Christianne Roumie [1,2], Eugene Ely [1,2], Robert Dittus [1,2], Sumi Misra [1,2], Jin Han [1,2]
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Objective: Many patients with advanced serious illness or at the end of life experience delirium, a potentially reversible form of acute brain dysfunction, which may impair ability to participate in medical decision making and to engage with their loved ones. Screening for delirium provides an opportunity to address modifiable causes. Unfortunately, delirium remains under-recognized. The main objective of this pilot was to validate the brief Confusion Assessment Method (bCAM), a 2-minute delirium screening tool, in a veteran palliative care sample

Methods: This was a pilot prospective observational study that included hospitalized patients evaluated by the Palliative Care service at a single Veterans Administration Medical Center. The bCAM was compared against the reference standard, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Both assessments were blinded and conducted within 30 minutes of each other.

Results: We enrolled 36 patients who were a median of 67 years old (IQR: 63, 73). The primary reasons for admission to the hospital were sepsis or severe infection (33%), severe cardiac disease (including heart failure, cardiogenic shock, and myocardial infarction) and (17%) or gastrointestinal / liver disease (17%). The bCAM performed well against the DSM-5 for detecting delirium, with a sensitivity (95% Confidence Interval) of 0.80 (0.4, 0.96) and specificity of 0.87 (0.67, 0.96).

Conclusions: Delirium was present in 27% of patients enrolled and never recognized by the Palliative Care service in routine clinical care. The bCAM provided good sensitivity and specificity in a pilot of palliative care patients, providing a method for non-psychiatrically trained personnel to detect delirium

4:00-5:00pm Intensive Care Unit - #2
Moderators: K. Fiest and B. Kamdar

Intensive Care Unit (ICU) Delirium Severity Associated with Increased Mortality

Patricia Serrano, Sophia Wang, Anthony Perkins, Sujuan Gao, Sikandar Khan, Heidi Lindroth, Malaz Boustani, Babar Khan
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Objective: We hypothesized that higher severity of ICU delirium and a greater number of delirium/coma days would be associated with higher rates of mortality up to 2 years after hospital discharge.

Methods: A secondary data analysis of the Pharmacologic Management of Delirium (PMD) and de-PMD trials. PMD and de-PMD were randomized, controlled clinical trials testing interventions to reduce ICU delirium duration and severity. Coma, delirium and delirium severity were assessed twice daily using the Richmond Agitation Sedation Scale, Confusion Assessment Method for the ICU (CAM-ICU), and CAM-ICU-7 respectively. Delirium severity was measured using mean CAM-ICU-7 scores from randomization to discharge. We used Cox proportional hazards regression to model the time to death. Analyses were adjusted for age, gender, Charlson comorbidity index, APACHE II, discharge location, diagnosis, and ICU team (medical/surgical).

Results: Of 442 patients (mean age 59.8±16.3 years), those with no delirium (mean CAM-ICU-7: 0±2) or mild to moderate delirium (mean CAM-ICU-7: 2.1±5) were less likely to die than those with severe delirium (mean CAM-ICU-7: 5±7) up to 60 days after discharge (no delirium, HR 0.4, 95% CI 0.18, 0.89; mild to moderate delirium, HR 0.35, 95% CI, 0.16, 0.75), but not after 60 days ($P > 0.05$). Duration of delirium/coma ≥ 5 days was associated with higher mortality (HR 1.52, 95% CI 1.07, 2.16) up to 2 years after hospital discharge.

Conclusions: Greater delirium severity and delirium/coma days are associated with higher mortality rates within two years after discharge. Future studies should test whether interventions that reduce delirium and coma can also lower long-term mortality.

Motoric Subtype of Delirium and Disability after Critical Illness

Kimberly Rengel, Christina Hayhurst, Mayur Patel, James Jackson, Pratik Pandharipande, Christopher Hughes
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Objective: Delirium is heterogenous with hypoactive and hyperactive motoric subtypes. Hypoactive delirium is associated with increased mortality and length of stay. The association of motoric subtypes of delirium with disability is unknown. We hypothesized that hypoactive delirium, but not hyperactive delirium, would be associated with disability after critical illness.

Methods: We performed a secondary analysis of a multicenter prospective cohort study of ICU patients that assessed delirium and level of consciousness twice daily with the CAM-ICU and RASS. We defined a day with hypoactive delirium as a day with positive CAM-ICU and corresponding RASS ≤ 0 and a day with hyperactive delirium as a day with positive CAM-ICU and corresponding RASS > 0. We assessed disability at 3 and 12 months with Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL). We used multivariable regression to assess the associations of days with hypoactive delirium and days with hyperactive delirium with disability outcomes, allowing for interaction between days of hypoactive and hyperactive delirium and adjusting for baseline and in-hospital covariates.

Results: Our cohort included 582 patients with median age of 61 years, APACHE II score of 23, and ICU length of stay of 4.9 days, 88% of whom required mechanical ventilation. Hypoactive delirium was present in 71% (median 3 days) and hyperactive delirium was present in 17% (median 1 day). Increased duration of hypoactive delirium was associated with worse disability in IADLs at 3 months (p=0.02) but not 12 months. This association was not modified by hyperactive delirium. Duration of hypoactive delirium was not associated with ADL outcomes. Duration of hyperactive delirium was not associated with ADLs or IADLs outcomes.

Conclusions: Hypoactive delirium predicts disability in IADLs 3 months after discharge. Assessing motoric subtypes of delirium might aid in prognosis, intervention allocation, and future research design.

Incidence and Impact of Delirium in Critically-ill Patients with Cancer

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Objective: Delirium remains a challenge with increased intensive care unit (ICU) and hospital length of stay (LOS) and mortality. Data on delirium in critically-ill patients with cancer are sparse. The purpose of this retrospective analysis is to analyze the characteristics and outcomes of patients admitted to the ICU at a tertiary care cancer center with and without delirium.

Methods: We collected demographic, clinical and outcome variables on all patients admitted to the ICU from February to April 2018. Patients were divided into 2 groups: those with any positive CAM-ICU results and those with negative CAM-ICU results throughout their ICU stay. Only the first admission was included. Statistical analyses were performed using Student t-test, Fisher's Exact Test, Mann-Whitney test, and Pearson Chi-Square. Results are presented as absolute numbers, percentages, mean +/- standard deviation, and mean with first and third interquartile ranges. A $p<0.05$ was considered statistically significant. The institutional review board granted a waiver of authorization for the study.

Results: Of the 263 unique patients included in the analysis, 160 were CAM-ICU negative and 103 CAM-ICU positive. CAM-ICU positive patients were younger (60 +/- 14 vs. 64 +/- 13, p=0.02) and received more mechanical ventilation (54 vs. 25, p=0.0001), vasopressors (41 vs. 38, p=0.006), nursing/non-pharmacologic interventions (62 vs. 18, p=0.0001), and early mobility (30 vs. 7, p=0.0001). Also, they had higher ICU LOS [7 (4, 11) vs. 3 (2, 5), p=0.0001], hospital LOS [23 (12, 41) vs. 13.5 (7, 23), p=0.0001], ICU mortality (27 vs. 15, p=0.0001), and hospital mortality (49 vs. 31, p=0.0001).

Conclusions: Nearly half of critically-ill patients with cancer who screened positive for delirium by CAM-ICU criteria at any time during their ICU stay did not survive to hospital discharge. Providers of critical care services should adopt early systematic strategies to mitigate delirium in patients with cancer.

POTENTIALLY INAPPROPRIATE MEDICATIONS INCREASE DELIRIUM MORE IN HIV+ THAN UNINFECTED

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Objective: Neurocognitive potentially inappropriate medications (NC-PIMS) have clinically significant and potentially serious drug interactions contributing to delirium risk, especially in the setting of alcohol use disorder (AUD). Persons living and aging with HIV (PLWH) may be at particular risk due to drug interactions with antiretrovirals (ARVs). We determined whether outpatient NC-PIMS were associated with delirium risk and whether the effect was modified by AUD and HIV status.

Methods: We conducted a nested case-control study within Veterans Aging Cohort Study (VACS), a cohort of PLWH and uninfected individuals. Eligible individuals included those with non-ARV medication prescription at the start of follow up between 2007-2013. Cases with an inpatient diagnosis of delirium (n=1656) were matched to 5 controls without delirium (n=8280) on age (+/- 1 year), race/ethnicity, sex, HIV, and observation time (+/- 1 year). The index date for comparing exposure history was delirium diagnosis date for cases and date corresponding to same length of time on study for controls. We identified NC-PIMS exposure in the year before the index date. NC-PIMS included anticonvulsants, sedatives/benzodiazepines, opioids, antidepressants, antipsychotics, and muscle relaxants. We used logistic regression to obtain odds ratios (OR) and 95% confidence intervals (CI) for risk of inpatient delirium associated with NC-PIMS, AUD and their interaction, adjusted for demographic and clinical covariates.

Results: Any NC-PIM was associated with delirium risk, but the effect was substantially stronger in PLWH (PLWH OR=2.57 [1.69-3.91]; uninfected OR=1.44 [1.11-1.87]). AUD in the setting of NC-PIMS augmented risk in both groups [PLWH OR=5.12 [3.41-7.69]); uninfected OR=5.68 [4.23-7.63]). All NC-PIMS except anticonvulsants were each associated with delirium, and risk was higher in those with AUD.

Conclusions: NC-PIMS are associated with higher likelihood of delirium for PLWH, especially in the setting of AUD. Next steps will include sensitivity analyses and adding in quantity frequency AUDIT-C data.