Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Translating Best Evidence into Best Care

EDITOR'S NOTE: Studies for this column are identified using the Clinical Queries feature of PubMed, "hand" searching *JAMA*, *JAMA Pediatrics*, *Pediatrics*, *The Journal of Pediatrics*, *The New England Journal of Medicine*, AAP daily briefing, and from customized EvidenceAlerts.

EBM PEARL: CONFOUNDING BY INDICATION (CBI): Acetaminophen is a common symptomatic treatment for respiratory viral infections with fever. Early-life respiratory viral infections are associated with (not currently proven to cause) asthma development later in life. Concluding that early-life acetaminophen use causes later-life asthma exemplifies potential CBI. Acetaminophen may be indicated to treat fever, but it cannot, therefore, be concluded that it causes later-life asthma. CBI occurs when an exposure (acetaminophen) appears to be associated with an outcome (later-life asthma) but may be due to an indication (respiratory viral infection with fever) that led to the exposure (acetaminophen). CBI is a peril of observational studies. In many cases, randomized trials could mitigate CBI. However, as randomized trials are often impractical or unethical, one needs to be mindful of CBI when evaluating association studies. See the commentary to the Qiu et al study, below, for another example.

SENSITIVITY ANALYSIS: INTRODUCTION AND THE E-VALUE: Sensitivity analysis assesses clinical-study results' causal-association robustness: exposure-X causes outcome-Y. Sensitivity analysis asks the following question: will reasonable/minor outcome definition adjustment, statistical methodology changes, missing data assumptions, sub-group inspection, or unmeasured effects render the previously statistically significant exposure-outcome association not statistically significant, thereby confounding causation? Although this question can be asked of strong methodology studies, such as randomized controlled trials, it is even more important to ask of observation studies. The E-value assesses observation-study robustness. It estimates an unmeasured confounder's minimum risk ratio, which would fully explain away a study's exposure-outcome (causal association) conclusion. The larger the E-value, the less likely an unmeasured confounder will affect the study's results. The commentary by Khashan to the Qiu et al study, below, demonstrates E-value utilization.

— **Jordan Hupert, MD**

Labor epidural anesthesia associated with autism

Qiu C, Lin JC, Shi JM, Chow T, Desai VN, Nguyen VT, et al. Association Between Epidural Analgesia During Labor and Risk of Autism Spectrum Disorders in Offspring. *JAMA Pediatr* 2020;174:1168-75.

Question Among women in labor, what is the association of labor epidural anesthesia (LEA) to autism spectrum disease (ASD), compared with not receiving LEA?

Design Retrospective longitudinal cohort study data were extracted from the Kaiser Permanente Southern California (KPSC) electronic medical record and birth certificate records.

Setting KPSC hospitals.

Participants 147 895 singleton children born by vaginal delivery, 28 to 44 weeks gestation.

Intervention LEA exposure or not.

Outcomes ASD as determined by the *International Classification of Diseases*, Ninth Revision.

Main Results 109 719 (74.2%) were born to mothers receiving LEA. The ASD adjusted hazard ratios were 1.33 (95% CI, 1.17-1.53), 1.35 (95% CI, 1.20-1.53), and 1.46 (95% CI, 1.27-1.69) for LEA exposure <4 hours, 4 - 8 hours, >8 hours, respectively, compared with no LEA. The linear trend of ASD adjusted risk was statistically significant with increasing LEA exposure.

Conclusions LEA is associated with increased ASD risk.

Commentary Qiu et al conducted a large cohort study suggesting that LEA was associated with a 37% increased risk of ASD and estimated the E-value to be 1.76. An E-value is an unmeasured confounder's minimum risk ratio with both the exposure and outcome to fully explain away the observed association, which, in relation to this study, would be 1.76. Although the authors adjusted for a number of potential confounders, they did not account for confounding by indication (treatment indications tend to be strongly associated with intended outcomes), such as maternal depression and other familial confounding. For example, maternal depression/anxiety has been reported to be associated with LAE use in multiparous women with an odds ratio of 1.65.[1] Maternal treated and untreated depression has been reported to be associated with increased risk of ASD with risk

ratios of 1.7 and 1.5, respectively.[2] Therefore, maternal depression, based on its association with LAE and ASD, and both risk ratios close to the E-value of 1.76, could explain most of the reported association between LAE and ASD. It would be important to further examine this research question using large cohorts that account for familial confounding and confounding by indication.

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Higher-calorie vs lower-calorie refeeding in patients with anorexia improves time to medical stability without compromising safety

Garber AK, Cheng J, Accurso EC, Adams SH, Buckelew SM, Kapphahn CJ, et al. Short-term Outcomes of the Study of Refeeding to Optimize Inpatient Gains for Patients With Anorexia Nervosa: A Multicenter Randomized Clinical Trial. *JAMA Pediatr* 2020:e203359.

Question Among patients with anorexia nervosa, what is the therapeutic efficacy of higher-calorie refeeding compared with lower-calorie refeeding, in enhancing safety and time to medical stability?

Design Multicenter randomized controlled trial (RCT).

Setting Inpatient programs at University of California San Francisco and Stanford University.

Participants Adolescents and young adults aged 12 to 24 years.

Intervention Higher-calorie refeeding, beginning at 2000 kcal/d, increasing 200 kcal/d vs lower-calorie refeeding, beginning at 1400 kcal/d, increasing 200 kcal every other day.

Outcomes In-hospital outcome: medical stability (heart rate, blood pressure, temperature, normalization of orthostatics, weight increase). Safety outcome: electrolyte abnormalities.

Main Results Higher-calorie refeeding restored medical stability sooner than lower-calorie refeeding, hazard ratio, 1.67 (95% CI, 1.10-2.53) and 3 days earlier (95% CI, -4.9 to -1.2 days). Electrolyte abnormalities did not differ between groups. Higher-calorie refeeding cost less compared with lower-calorie refeeding, $19 056 (95% CI, $9293 - $28 819).

Conclusions Higher-calorie refeeding demonstrated superior time to medical stability without sacrificing safety.

Commentary This well-conducted study by Garber et al provided a timely and important addition to the literature regarding the use of inpatient higher-calorie refeeding for youth with both anorexia nervosa and atypical anorexia nervosa. To date, research examining the efficacy and safety of higher-calorie refeeding has been retrospective with varying effects on refeeding electrolyte abnormalities, weight gain, and length of stay.[1] Evaluating the efficacy and safety of higher-calorie refeeding has been challenging as retrospective studies displayed heterogeneity in the higher-calorie refeeding approaches, management of electrolyte abnormalities, and the determination of medical stabilization.[1,2] Garber et al demonstrated that higher-calorie refeeding was efficacious, with much earlier achievement of medical stability, improved weight gain, as well as decreased length of stay. Importantly, this prospective RCT, with standardized medical-stabilization and electrolyte-abnormality management criteria, showed no increase in safety events with the use of higher-calorie refeeding. These results should increase providers' confidence in the relative efficacy and safety of higher-calorie refeeding protocols. The demonstrated decrease in health care cost is a critical, and often overlooked, outcome. We look forward to the 12-month clinical remission rates of this study to elucidate the role of early weight gain in long term outcomes for patients with both anorexia nervosa and atypical anorexia nervosa.

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Family Integrated Care reduces NICU length of stay and improves medical outcomes across China

Hei M, Gao X, Li Y, Gao X, Li Z, Xia S, et al. Family Integrated Care for Preterm Infants in China: A Cluster Randomized Controlled Trial. *J Pediatr* 2021;228:36-43.

Question Among preterm infants, what is the therapeutic efficacy of Family Integrated Care (FICare), compared with standard care, in reducing length of stay (LOS) and adverse outcomes, and enhancing medical/wellness neonatal outcomes?

Design Multicenter prospective cluster–randomized controlled trial (sites randomized).

Setting 11 NICUs in 8 provinces in China.

Participants Preterm infants, gestational age >28 and <35 weeks, enteral feeds for >24 hours, and vital signs stable for >24 hours.

Intervention FICare versus standard care.

Outcomes Primary: LOS. Other: Nosocomial infections, duration of supplemental oxygen, breastfeeding, weight gain, and medical expenditure.

Main Results 601 infants' adjusted LOS was improved with FICare, 28.26 vs 35.04 days, mean ratio, 0.81 (95% CI, 0.72-0.91) compared with standard care. Medical expenditures, weight gain velocity, supplemental oxygen duration, nosocomial infection rates, antibiotic exposure, breastfeeding rates, and rehospitalization rates also demonstrated statistically significant improvement compared with standard care. FICare neonates demonstrated higher breastfeeding rates and greater weight gain at 18 months follow-up.

Conclusions FICare improved LOS, medical/wellness neonatal outcomes, and reduced medical expenditure.

Commentary FICare is a multidimensional model that supports parents to become active caregivers for their infant in the NICU. This well-executed cluster-randomized controlled trial involving NICUs in 8 provinces of China demonstrated that FICare improved infant outcomes both in hospital and beyond hospital discharge. It is remarkable that despite cultural differences and environmental barriers, the intervention sites were able to implement FICare, re-affirming the adaptability of the model. The study highlights the impact of FICare on LOS, which can be translated into decreased hospital expenditures. This supports the broader adoption of this model of care while recognizing that environmental adjustments may need to be made to accommodate parental presence, such as providing space and comfortable chairs. Although we have incomplete understanding of exactly how FICare works, its implementation provides NICUs with the tools to educate and engage parents in their infant's care, decreasing the negative impact of the hospital stay, and preventing further problems post discharge. This research supports the international movement to view family members as care-providers in NICUs, improving both parent and infant outcomes.[1]

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Isolated neutropenia appears unlikely to require intervention

Nagalapuram V, McCall D, Palabindela P, Howard TH, Bemrich-Stolz C, Lebensburger J, et al. Outcomes of Isolated Neutropenia Referred to Pediatric Hematology-Oncology Clinic. *Pediatrics* 2020;146:e20193637.

Question Among otherwise healthy children, what is the association of isolated neutropenia with need for hematologist-oncologist intervention?

Design Case series, retrospective chart review.

Setting University of Alabama at Birmingham pediatric hematology-oncology clinic.

Participants 155 children ages 0-18 years old.

Intervention Referral to hematology-oncology.

Outcomes Medical intervention by a pediatric hematologist-oncologist.

Main Results Among 155 children, 29%/42%/19%/10% had mild/moderate/severe/very severe neutropenia (absolute neutrophil count (ANC) >1000/501-1000/201-500/≤200). No specific diagnosis was identified in 55% (95% CI, 47.2%-62.8). Other neutropenia diagnoses included viral-induced, autoimmune, and drug-induced. By 12 months, neutropenia resolved among 65% (95% CI, 55.5%-72.5%). Four children, 2.6% (95% CI, 0.1% - 5.1%) received granulocyte colony-stimulating factor.

Conclusions Most children in this series with isolated neutropenia did not require hematologist-oncologist medical intervention.

Commentary Isolated neutropenia can be an alarming laboratory finding and determining its etiology can be challenging given the broad differential and lack of sensitive and specific testing for common causes.[1] In this cohort, 54% of patients did not have a specific diagnosis confirmed despite access to subspecialty care. The clinical significance of neutropenia, or lack thereof, may be even more difficult to elucidate. Thus, the reported outcomes of children referred for mild neutropenia are of particular interest. None of these patients progressed to severe neutropenia nor had any major infectious complications. Even patients with very severe neutropenia who received granulocyte-colony-stimulating factor treatment did so within the setting of an acute illness, obviating the need for interventions in otherwise well children. In truth, the influence of typical childhood illnesses, genetics, and normal physiologic variations resulting in mild neutropenia can result in repeated or invasive testing and specialty referral that are unlikely to benefit the child. As the authors conclude, isolated mild-moderate neutropenia is rarely a harbinger of severe disease or infection. Rather, most children do well, and neutropenia resolves with time.

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Severity predictors in pediatric SARS-CoV-2 and MIS-C

Fernandes DM, Oliveira CR, Guerguis S, Eisenberg R, Choi J, Kim M, et al. Tri-State Pediatric COVID-19 Research Consortium. Severe Acute Respiratory Syndrome Coronavirus 2 Clinical Syndromes and Predictors of Disease Severity in Hospitalized Children and Youth. J Pediatr 2021;230: 23-31.e10.

Question Among hospitalized children with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and/or multisystem inflammatory syndrome in children (MIS-C), what are the predictors for severe disease?

Design Multicenter, retrospective, and prospective cohort study.

Setting 8 sites in New York, New Jersey, and Connecticut.

Participants Children and youth <22 years of age, with laboratory-confirmed SARS-CoV-2 infection or MIS-C.

Intervention Multivariable logistic regression models were fit to the cohort data.

Outcomes Severity of disease predictors.

Main Results Of 281 patients, 51%/25%/25% had respiratory disease/MIS-C/other manifestations (including gastrointestinal illness or fever). In multivariate analyses, obesity (OR 3.4, 95% CI 1.3-9.1) and hypoxia at admission (OR 4.01, 95% CI 1.1-14.2) were associated with severe disease; lower absolute lymphocyte count (OR 8.33 per unit decrease in 10^9 cells/L, 95% CI 2.3-33.3) and greater C-reactive protein (OR 1.06 per unit increase in mg/dL, 95% CI 1.0-1.1) were associated with MIS-C. Race was not associated with severe disease.

Conclusions Multivariate analysis identified several variables associated with developing severe disease and MIS-C.

Commentary Pediatric COVID-19 is now well recognized to be less severe compared with adults. However, important gaps exist in identifying both diverse clinical sequelae and risk factors for severe disease. This well-done study is a step in the direction of resolving some of the gaps. Fernandes et al performed meticulous clinical and laboratory characterization of clinical phenotypes and outcomes from a large multicenter cohort. The results corroborate some existing hypotheses—obesity as a risk factor for severity similar to older adults, different underlying risk profiles for severe, acute COVID-19 vs MIS-C (fewer comorbidities in the latter), and the prognostic importance of immune response characterization in hospitalization (lymphopenia and inflammatory markers). The choice of study outcome—ICU admission—could have led to variability between centers in terms of the threshold for more intensive observation (eg, lower for infants). It would be interesting to see predictors of related outcomes, such as oxygen requirement or vasoactive support. Age in the analysis is modeled as a continuous variable. It may help further work to look at age categories (eg, infants vs adolescents) particularly because it may interact with other variables (eg, severity of underlying complex conditions or obesity). Race and ethnicity were not statistically significant in the multivariable analysis. However, the striking preponderance of these hospitalized cases were non-white, and this geographically spread-out sample highlights the absolute difference in burden for minority communities. The study does point to some laboratory and imaging results that, at admission, may indicate a more severe course. Yet challenges remain, especially in predicting the disease trajectory earlier in the disease course, before the onset of significant hypoxia or cardiac injury (in MIS-C).

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