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*, and *The New England Journal of Medicine*, and from customized EvidenceAlerts.

EBM PEARL: SECONDARY DATA ANALYSIS (SDA): Primary data analysis requires data set generation from a sufficient number of study participants—often a time-consuming and expensive endeavor. SDA is a time-sparing and inexpensive method to answer clinical research questions, as it analyzes previously-developed data sets (primary data set [PDS]). SDA, when done well, requires attention to a number of steps: developing a research question, identifying one or more appropriate PDSs, and evaluating PDS suitability. PDS suitability includes the PDS-generation purpose, the specific information collected, when and how (eg, survey instruments) was it collected, consistency with other similar PDSs (if available), and access to the raw data. SDA limitations include all the issues related to using a data set developed by other investigators for their own purposes. These include 1) data may not be a perfect fit for the clinical question, the data collection years, the geographic area, or the population of interest, and 2) the data accuracy—how was the data collected, the response rate, and subject response accuracy (level of survey question understanding). SDA strengths are listed above and the reason for SDA being a popular clinical research method. Several studies below employed SDA. (*Qualitative and Quantitative Methods in Libraries*. 2014;3:619-26. http://www.qqml-journal.net/index.php/qqml/article/view/169)

CRITICAL STATISTICAL DISTINCTION PEARL: SENSITIVITY/SPECIFICITY (SENS, SPEC) AND POSITIVE/NEGATIVE PREDICTIVE VALUE (PPV, NPV): Sens is the true positive rate among all patients with disease; Spec is the true negative rate among all patients who are well (**Figure 1**). PPV is the true positive rate among all patients who test positive; NPV is the true negative rate among all patients who test negative. The critical distinction is that Sens/Spec describe the diagnostic test characteristics. PPV/NPV describe the diagnostic test results—probability of disease or non-disease—within the context of a specific disease prevalence. Sens/Spec are disease-prevalence independent. PPV/NPV are prevalence dependent. Prevalence (pre-test probability), when mathematically combined with Sens/Spec will result in the probability of disease. PPV and NPV derived from a clinical article may be applicable to your clinical setting if a number of validity and application conditions are satisfied and especially if the disease prevalence described in the clinical study is similar to that of your clinical setting.

	Reference standard 'stroke'	Reference standard 'no stroke'	
Self-report 'stroke'	True positive (TP)	False positive (FP)	$PPV = \frac{TP}{(TP+FP)}$
Self-report 'no stroke'	False negative (FN)	True negative (TN)	$NPV = \frac{TN}{(FN+TN)}$
	$Sensitivity = \frac{TP}{(TP+FN)}$	$Specificity = \frac{TN}{(FP+TN)}$	

Figure 1. Calculation of PPV, sensitivity, specificity, NPV and stroke prevalence. Republished from Woodfield R, UK Biobank Stroke Outcomes Group, UK Biobank Follow-up and Outcomes Working Group, Sudlow CLM. Accuracy of Patient Self-Report of Stroke: A Systematic Review from the UK Biobank Stroke Outcomes Group. *PLOS ONE* 2015;10:e0137538. https://doi.org/10.1371/journal.pone.0137538

Apgar score in premature infants associated with neonatal death prediction

Cnattingius S, Johansson S, Razaz N. Apgar Score and Risk of Neonatal Death among Preterm Infants. *N Engl J Med* 2020;383:49-57.

Question Among premature infants, what is the correlation of the Apgar resuscitation score with risk of death?

Design Secondary analysis of the Swedish Medical Birth Register.

Setting Sweden.

Participants 113 300 infants born prematurely (22 weeks-36 weeks 6 days of gestation).

Intervention Apgar score.

Outcomes Risk of death.

Main Results Among 1986 deaths, lower Apgar scores were associated with a higher risk of death. For example, at 28 to 31 weeks' gestation, compared with the reference score (Apgar 9 or 10), the 5 minute Apgar score death-risk rate differences were Apgar 0 or 1: 51.7 (95% CI, 38.1 - 65.4), 2 or 3: 25.5 (95% CI, 18.3 - 32.8), 4 - 6, 7.1 (95% CI, 5.1 - 9.1), 7 or 8: 1.2 (95% CI, 0.5 - 1.9). Improved Apgar scores at 10 minutes were associated with lower neonatal mortality.

Conclusions Apgar scores in premature infants are associated with neonatal death risk.

Commentary The Apgar score is a simple and robust way of assessing the status of the newborn infant shortly after birth. Throughout the years, the validity of the Apgar score, especially in infants born prematurely, has been questioned. The well-performed study by Cnattingius et al is based on a large national population cohort of infants born preterm and contributes significantly to the discussion. The study shows that 5-minute and 10-minute Apgar scores have a good predictive capacity for neonatal mortality in infants born prematurely, even in those born close to the border of viability (22-27 gestational weeks). The results seem to contradict the recent recommendation by the American Academy of Pediatrics not to use the Apgar score for prediction of neonatal mortality.[1] The Swedish registry data did not allow for individual-component Apgar-score performance analysis, and there were no data available on the postnatal development of the infants. The question is thus still open whether or not the Apgar score or its components possess predictive capacity with regard to the long-term neurological morbidity in infants born prematurely. Furthermore, in infants born extremely preterm, active perinatal management is a prerequisite for their survival. It would be important to further evaluate models combining the Apgar score and postnatal interventions.[1,2]

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Underweight is the highest PICU mortality risk factor among all other weight categories

Ayalon I, Woo JG, Basu RK, Kaddourah A, Goldstein SL, Kaplan JM; AWARE Investigators. Weight as a Risk Factor for Mortality in Critically Ill Patients. *Pediatrics* 2020; 146:e20192829.

Question Among critically ill children and young adults, what is the risk of short-term mortality among underweight patients compared with patients in other weight groups?

Design Secondary analysis of the Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology study.

Setting International.

Participants Ages 3 months to 25 years with a PICU stay of at least 48 hours.

Intervention Weight categories (underweight, normal weight, overweight, obese) based on body mass index (BMI).

Outcomes Primary: 28-day mortality.

Main Results In the overall cohort and for the sepsis subgroup, mortality was 5.8%, 3.1%, 2.2%, and 1.8%, and 15.4%, 6.6%, 3.6%, and 4.7% for underweight, normal weight, overweight, and obese, respectively. In a fully adjusted, full cohort and sepsis subcohort models, mortality was 1.8-fold and 2.9-fold higher in the underweight group compared with the normal group, respectively.

Conclusions Underweight patients have a higher short-term mortality rate compared with all other weight groups.

Commentary Pediatric intensivists have been attempting to prove or disprove the obesity paradox: overweight is associated with lower mortality. Ayalon et al remind us we should focus on the other end of the growth curve. Increased mortality for underweight critically ill children has been demonstrated in several studies.[1,2] Increased mortality remains even when controlling for a number of comorbidities or syndromes as well as for initial severity of illness. Underweight children have increased mechanical ventilation, length of stay, and fluid overload. We need to investigate whether this results from malnutrition or failure to thrive that is associated with specific syndromes. Although it did not appear to be a confounder for Ayalon et al, we may find that underweight as a mortality risk factor varies greatly by geography. Calculations of BMI are insufficient to determine causality.

More interest and resources need to be applied to study the underweight-mortality association. Pediatric intensivists would do as much for any other disease process that increases mortality 2 to 3 times. Why have we not done so for the underweight children?

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Pets associated with enhanced early-childhood social-emotional development

Christian H, Mitrou F, Cunneen R, Zubrick SR. Pets Are Associated with Fewer Peer Problems and Emotional Symptoms, and Better Prosocial Behavior: Findings from the Longitudinal Study of Australian Children. *J Pediatr* 2020; 220:200-6.e2.

Question Among children who have pets in the home, what is the association of pet ownership with social-emotional development?

Design Secondary analysis, focusing on children at 2 sequential time points (age 5 and then 7) of the Growing Up in Australia: The Longitudinal Study of Australian Children, which included the Strengths and Difficulties Questionnaire.

Setting Australia.

Participants Children ages 5 (n = 4242) and 7 (n = 4431) years.

Intervention Pet ownership.

Outcomes Social and emotional development.

Main Results 75% of children had pets by age 7. Pet ownership was associated with decreased abnormal scores for emotional symptoms, peer problems, and for enhanced social behavior, OR 0.81 (95% CI, 0.67-0.99), OR 0.71 (95% CI, 0.60-0.84), OR 0.70; (95% CI, 0.38-0.70), respectively, compared with non-ownership.

Conclusions Among early school age children, pet ownership was associated with fewer emotional problems and with enhanced social behavior.

Commentary Studies focused on the outcomes of child-pet interactions are less common than those focused on relationships between pets and adult owners.[1] As the authors of this study point out, more than 75% of children in their sample lived with a pet by the age of 7. The current study adds to a body of evidence[1,2] that suggests pet ownership may be associated with at least some measures of social and emotional wellbeing in children, including more prosocial behavior, a factor that may be especially relevant for children without siblings,[2] and reduced likelihood of abnormal scores on a social-emotional development scale. One important aspect of this study was an analysis that took pet type into consideration. Although pet ownership in general was associated with better socio-emotional outcomes overall, cat ownership alone corresponded with significantly decreased odds of having an abnormal emotional system score, while both dog and cat ownership corresponded with better peer and prosocial outcomes. However, children with pets (and especially children with cats) were more likely to have high scores on the hyperactivity scale, a reminder that pet ownership may be associated with a range of behaviors, not all of which are considered beneficial. Critically, the results of this study were correlational, not causal. It is possible, for example, that the social or emotional characteristics of children contribute to the likelihood that a family obtains a pet or a particular kind of pet. Overall, this study provides a meaningful look at relationships between pet ownership and aspects of child development, presenting several important questions and associations that are ripe for future exploration, time markers of when might be optimal windows of opportunity to catch families pre- and post-pet acquisition, and also an important reminder that pet type should be considered. It is especially noteworthy that cat-ownership was uniquely associated with high or low scores on multiple emotional and behavioral scales, highlighting the need for more research on child-cat interactions, as most studies to date have focused on the influence of dogs or pets more broadly.

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Down Syndrome associated with early hyperbilirubinemia

Bahr TM, Henry E, Hulse W, Baer VL, Prchal JT, Bhutani VK, et al. Early Hyperbilirubinemia in Neonates with Down Syndrome. *J Pediatr* 2020;219:140-5.

Question Among neonates with Down syndrome, what is the risk of an initial elevated (>95%ile) total serum bilirubin (TSB), compared with control neonates?

Design 15-year, retrospective cohort study.

Setting Intermountain Healthcare system (primarily in Utah).

Participants All neonates, ≥35 weeks born between January 1, 2004, and December 31, 2018.

Intervention Initial bilirubin levels of 357 patients with Down syndrome versus controls (377 368).

Outcomes Primary: bilirubin >95%ile risk.

Main Results Compared with controls, neonates with Down syndrome demonstrated higher initial risk of TSB levels >95%ile, 4.7 (95% CI, 3.9-5.7), phototherapy usage, 8.9 (95% CI, 8.1-9.8), and jaundice readmission 3.6 (95% CI, 1.6-8.2).

Conclusions Down syndrome is associated with elevated early hyperbilirubinemia risk.

Commentary Systematic assessment of clinical factors that predispose to subsequent severe hyperbilirubinemia are key to identify newborns at jaundice risk during the birth hospitalization and following discharge. Such factors include among others: lower gestational age, exclusive breastfeeding, hemolytic disease, and an elevated pre-discharge total serum or transcutaneous bilirubin level.[1] That Down syndrome poses a similar increased hyperbilirubinemia risk has been recognized for decades but given limited emphasis. Bahr et al highlight and quantify the magnitude of this hyperbilirubinemia risk in a large cohort of neonates with Down syndrome. They report a significant, several-fold increased risk for an initial total serum bilirubin exceeding the 95th percentile, and for hospital readmission for jaundice compared with control newborns. Notably, two-thirds of the studied newborns with Down syndrome received phototherapy. The increased hyperbilirubinemia risk in newborns with Down syndrome is likely multifactorial including a higher red cell count, hemoglobin, and hematocrit, an enhanced enterohepatic bilirubin circulation secondary to feeding problems, and, as suggested by the authors, a hemolytic component secondary to neocytolysis. Regardless of its genesis, clinicians should be mindful of the increased risk for hyperbilirubinemia when caring for newborns with Down syndrome and ensure adequate bilirubin surveillance. To enhance provider awareness, the American of Academy of Pediatrics and others should amend their hyperbilirubinemia clinical practice guidelines to include Down syndrome as an important risk factor for severe hyperbilirubinemia.

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Delayed-intervention management of ingested Hijab pins

Yogev D, Mahameed F, Gileles-Hillel A, Millman P, Davidovics Z, Hashavya S, et al. Hijab Pin Ingestions. *Pediatrics* 2020;145:e20193472.

Question Among children who ingest Hijab pins, how does a delayed intervention protocol impact the endoscopy rate?

Design Retrospective case series.

Setting Emergency Department of Hadassah Hebrew University Medical Center, Israel.

Participants 0-25 years old who swallowed Hijab pins.

Intervention Delayed intervention approach with x-ray monitoring.

Outcomes Proportion of patients requiring endoscopy or surgery.

Main Results 208 patients ingested 225 pins. Eighty-eight percent of patients were female. The highest percentage of pins were in the stomach (46.6%). Forty-one (19%) of all ingested pins were impaled and 41 endoscopies were performed. The mean "door to endoscopy" time was 18 (small bowel) to 24 (stomach) hours. Location in the stomach, OR 4.3 (95% CI, 1.9–9.2) and abdominal tenderness, OR 2.7 (95% CI, 1.3–5.6) were independent predictors of impalement. One patient required surgery.

Conclusions Employing a delayed intervention approach, only 19% of patients required endoscopic removal, notably fewer than existing guideline recommendations.

Commentary Foreign body ingestion is common in children, often posing a clinical challenge when to proceed to endoscopic retrieval and when to observe. Though the approach toward the management of sharp objects in the stomach is urgent (adult guidelines) or emergent (pediatric guidelines) removal,[1,2] in practice many recommend a conservative approach of observation in asymptomatic patients. The Hijab is a veil traditionally worn by Muslim women and fastened by pins often held between the lips. Yogev et al characterized the clinical manifestations and outcomes of 225 ingested Hijab pins by 208 patients. Some pins were immediately removed, and some were observed according to the judgment of the attending physician. Overall, the need for endoscopic retrieval from the esophagus, stomach, small bowel, and colon was noted in 33%, 32%, 9.8%, and 6% of cases, respectively. Impaled pins were noted in 19% of cases, 98% were retrieved endoscopically without complications

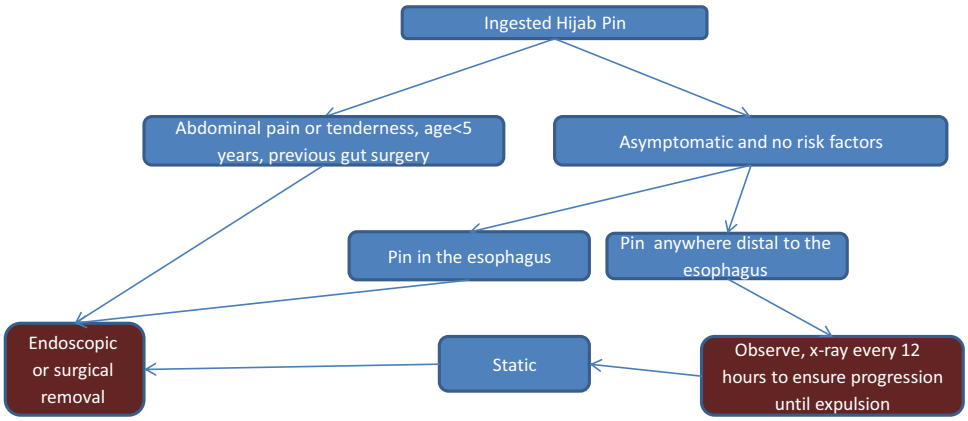

Figure 2. Suggested management algorithm for Hijab pin ingestions.

and only one patient (2%) who presented 2 months after the ingestion required surgery for removal of the pin from the small bowel, without further complications. Abdominal tenderness upon arrival to the hospital was a risk factor for an impaled pin. A previous report by Hubara et al included 203 children and adolescents.[3] The main indication for endoscopic removal of pins beyond the esophagus were presence of symptoms (abdominal pain or tenderness) or lack of pin progression based on plain abdominal x-ray 12 hours later. A total of 153 pins (75%) passed spontaneously and only 25% were removed endoscopically. In these retrospective reports the reason for endoscopic retrieval was not always clear. It is plausible to assume that many more cases of Hijab pin ingestion were successfully managed at home without coming to medical attention, thus the actual success rate was likely higher. Considering the 2 large studies' results, we suggest a management algorithm for Hijab pin ingestions (**Figure 2**). Until validation of this proposed scheme is available, it is advised to be more conservative when in doubt. Moreover, this algorithm cannot be adapted to other sharp objects as the Hijab pins are unique with one side weighted with a plastic ball. Nonetheless, convincing evidence now exists that most ingested Hijab pins may be successfully observed. Current guidelines should be amended to reflect that notion.

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