

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 EvidenceUpdates alerts.

EBM PEARL: POWER: Statistical power measures a study's probability to detect an effect of a chosen size if it exists. By convention, researchers have chosen a power of 80% (or 90% in some cases) to be sufficient. The sample size required to detect a clinically meaningful effect depends on a number of variables, including the power level, the effect size, and the expected variance. Dr Alan Schwartz at the University of Illinois at Chicago and Editor-in-Chief of the journal *Medical Decision Making* recently gave an interesting example at our monthly pediatric-resident EBM Ambulatory Journal Club explaining the relationships among power, effect size, variance, and sample size. Imagine searching for the proverbial needle in a haystack. The likelihood of finding (getting poked by) the needle (power), depends on how many times one sticks one's hand into the haystack (sample size), how large the needle is (effect size), and how large the haystack is (variance). The smaller the effect size (needle size) with a given power level, the more times one needs to stick one's hand in the haystack (sample size). Power is especially important when one does not find a significant effect between groups. If sufficient power was achieved, let's say 80%, and no effect was detected, one may conclude that there was likely no effect to find.

CRITICAL STATISTICAL DISTINCTION PEARL: WHICH STUDY DESIGNS GO WITH WHICH STUDY TYPES?: Study designs differ based on the study type and outcome desired. A randomized controlled trial (RCT) is an appropriate study design for a therapy study comparing 2 treatments. It is not the appropriate design to determine the diagnostic test characteristics of a new diagnostic test compared with the gold standard. A cohort of patients (cohort design) who may have the target diagnosis is the desired study design. Identifying an association between a potentially harmful substance and a patient outcome is typically not studied with an RCT design, as in most cases it would be immoral to randomize patients to a potentially harmful substance. A cohort design or case control design would be more appropriate, even if less scientifically rigorous. The [Table](#) below lists typical study designs for different types of studies, with the most scientifically rigorous design listed at the top. The specific distinctions are listed in the [Table](#).

Table. Typical study designs for different types of studies

Study Type	Typical study design	Typical number of groups	Typical intervention	Outcome
Therapy	RCT	2 or more	New therapy vs control	Absolute risk reduction and number needed to treat
Diagnosis	Prospective cohort	1	New test vs gold standard	Sensitivity/specificity or likelihood ratios
Etiology or harm	Retrospective cohort			
	Prospective cohort	2 or more	Exposure vs no exposure	Relative risk or odds ratio
	Retrospective cohort			
Prognosis	Case control			
	Prospective cohort	2 or more	Suspected risk factor vs no suspected risk factor	Relative risk or odds ratio
	Retrospective cohort			

Use of acid suppressive medications and antibiotics in young infants is associated with development of allergic disease

Mitre E, Susi A, Kropp LE, Schwartz DJ, Gorman GH, Nylund CM. Association Between Use of Acid-Suppressive Medications and Antibiotics During Infancy and Allergic Diseases in Early Childhood. *JAMA Pediatr* 2018;172:e180315.

Question Among infants, what is the association of acid suppression medications or antibiotics given prior to 6 months

of age with the development of allergic disease later in life?

Design Retrospective cohort study employing the US Department of Defense TRICARE Management Activity Military Health System database.

Setting The overseas US military healthcare system.

Participants Children (792,130) of overseas military personnel.

Intervention Prescribed H₂ receptor antagonists (H₂RAs), proton pump inhibitors (PPIs) or antibiotics prior to 6 months of age versus none.

Outcomes Development of allergic disease.

Main Results Recurrent-wheezing adjusted hazard ratios (aHRs) in children prescribed H2RAs and PPIs, respectively, were 1.25 (95% CI, 1.21-1.29) and 1.41 (95% CI, 1.31-1.52) for asthma and 1.50 (95% CI, 1.46-1.54) and 1.44 (95% CI, 1.36-1.52) for allergic rhinitis. The aHR for antibiotics was 2.09 (95% CI, 2.05-2.13) for asthma and 1.75 (95% CI, 1.72-1.78) for allergic rhinitis.

Conclusions H2RAs, PPIs, and antibiotics during the first 6 months of life were associated with an increase in allergic disease.

Commentary Although this study is a retrospective cohort study with a lower evidence level compared with a prospective cohort study, Mitre et al impart an important message regarding the potential risks of using acid-suppressive medications and antibiotics. It is well known that the microbiome plays an important role in a healthy immune system. The intestinal microbiome, altered by exposure to acid-suppressive medications and antibiotics can compromise the immune system, leading to the development of allergic disease. Our team in Japan, in a prospective birth cohort study,¹ also found that the use of antibiotics within the first 2 years of life was associated with asthma and rhinitis. Although acid-suppressive medications and antibiotics are commonly given to infants, we should prescribe them only in appropriate situations during infancy and pay more attention to the risk of adverse effects from these medications.

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Vitamin D reduces risk of recurrent wheezing in premature black infants

Hibbs AM, Ross K, Kerns LA, Wagner C, Fuloria M, Groh-Wargo S, et al. Effect of Vitamin D Supplementation on Recurrent Wheezing in Black Infants Who Were Born Preterm: The D-Wheeze Randomized Clinical Trial. *JAMA* 2018;319:2086-94.

Question Among premature infants, what is the therapeutic efficacy of vitamin D supplementation, compared with placebo, in development of recurrent wheezing?

Design Randomized controlled trial.

Setting Ohio, South Carolina, and New York.

Participants 300 premature black infants, 28-37 weeks' gestation.

Intervention 400 IU vitamin D daily or placebo until 6 months adjusted age.

Outcomes Recurrent wheeze.

Main Results The absolute risk reduction for wheezing among vitamin D supplemented and placebo infants at 12 months adjusted age was -10.7% (95% CI, -27.4% to -2.9%) in favor of the supplemented group, accounting for within-family covariance (twins and triplets).

Conclusions Vitamin D supplementation reduced the risk of recurrent wheezing.

Commentary Primary prevention of wheezing illnesses and asthma remains elusive. Vitamin D supplementation is hypothesized to prevent wheezing illnesses and asthma via multiple mechanisms, including improved lung growth and decreased airway reactivity, anti-inflammatory effects, and antimicrobial mechanisms.¹ Prenatal vitamin D supplementation studies in diverse populations have shown promise in decreasing early-life wheezing illnesses.² However, these prenatal-supplementation trials did not supplement the infants postnatally, and recent findings suggest that postnatal deficiency can increase the risk for asthma in later childhood.³ The study by Hibbs et al extends previous findings of prenatal supplementation and shows that postnatal vitamin D supplementation for the first 6 months of life can decrease the incidence of recurrent wheezing in infancy. The study population was at high risk for both wheezing (due to prematurity and as evidenced by the high rates of wheezing in both arms) and vitamin D deficiency. Whether prenatal supplementation would have further decreased the rates of wheezing found in the study remains unanswered. Although the authors were careful to estimate total vitamin D intake, some of the infants may have exceeded the upper limit of the current recommendations. Despite that, and despite some children having 25-hydroxy vitamin D levels as high as 76 ng/ml at the 3-month follow-up, no adverse events were attributed to the intervention. Future trials should now target both prenatal and sustained postnatal supplementation beyond the first 6 months in a more diverse group of infants, thus, bringing us closer to primary prevention of infant wheezing, and possibly asthma.

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3. Hollams EM, Teo SM, Kusel M, Holt BJ, Holt KE, Inouye M, et al. Vitamin D over the first decade and susceptibility to childhood

allergy and asthma. *J Allergy Clin Immunol* 2017;139:472-81, e9.

Inhaled long-acting beta agonist combined with a corticosteroid does not increase risk of death compared with corticosteroid alone

Busse WW, Bateman ED, Caplan AL, Kelly HW, O'Byrne PM, Rabe KF, et al. Combined Analysis of Asthma Safety Trials of Long-Acting β_2 -Agonists. *N Engl J Med* 2018;378:2497-505.

Question Among adolescents with asthma, what is the serious-event risk of inhaled corticosteroid plus a long-acting beta agonist (ICS-LABA) compared with an ICS alone?

Design Systematic review and meta-analysis of the FDA-mandated randomized controlled trials from each of the 4 US LABA-manufacturing companies.

Setting US and international.

Participants Asthmatic adolescents (12 to 17 years of age) and adults.

Intervention ICS with or without LABA.

Outcomes Composite of asthma-related intubation or death.

Main Results A total of 4 patients (out of 36,000) experienced 3 asthma-related intubations (2 in the ICS group and 1 in the ICS-LABA group) and 2 asthma-related deaths (both in the ICS-LABA group). Serious asthma-related events (a composite of hospitalization, intubation, or death) did not differ between the 2 groups, relative risk, 1.09 (95% CI, 0.83 to 1.43). Patients in the ICS-LABA group had fewer exacerbations, relative risk, 0.83 (95% CI, 0.78 to 0.89).

Conclusions ICS-LABA did not result in an increased risk of death or intubation compared with ICS alone but was associated with fewer exacerbations.

Commentary Safety concerns about LABA were prompted in the 1990s by reports that LABA users were at potentially increased risk of fatal asthma. These findings were based on small numbers of events and were inconsistent with a steady (and ongoing) national decline in asthma deaths—despite concurrent increases in the use of ICS-LABA therapy. Although most experts concluded that the risk was largely, if not entirely, due to excessive use of LABA alone, as opposed to combination therapy (ICS-LABA), the uncertainty led the FDA, in 2006, to assign a “black box” warning to LABA-containing products. A 2009 editorial in the *New England Journal of Medicine* urged the FDA to mandate a large safety study on LABAs “to prove that they are safe.”¹ In 2010, the FDA issued another advisory and mandated that the 4 companies marketing LABAs for asthma perform safety trials. These trials were harmonized to permit data pooling, which were reported by Busse et al. This enormous meta-analysis (involving 36 010 patients) found only 5 asthma-related intubations or deaths (among 4 patients). The investigators confirmed that ICS-LABA, as compared to ICS alone, lowered the risk of asthma exacerbations and did not increase the risk of serious asthma-related events. The find-

ings support national and international asthma guidelines, which recommend ICS-LABA therapy for asthma management. Recently, the FDA removed the black-box warning for ICS-LABA products.

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High adverse-event rates among hospitalized pediatric patients

Stockwell DC, Landrigan CP, Toomey SL, Loren SS, Jang J, Quinn JA, et al. Adverse Events in Hospitalized Pediatric Patients. *Pediatrics* 2018;142:pii: e20173360.

Question Given recent efforts to prevent hospital adverse events (AEs), what are the AE occurrence trends over time among hospitalized children?

Design Retrospective surveillance cohort study, 2007-2012.

Setting Sixteen “Pediatric Research in Inpatient Settings Network” hospitals across the US.

Participants Randomly selected patients (patient records).

Intervention Global Assessment of Pediatric Patient Safety (GAPPS) Trigger Tool, which identifies clues found in patient records that suggest medically induced harm.

Outcomes AE trends over time.

Main Results Teaching hospitals had higher AE rates than nonteaching hospitals (AEs per 1000 patient days), 26.2 (95% CI 23.7-29.0) vs 5.1 (95% CI 3.7-7.1), $P < .001$. Analysis did not detect AE rate variation over time.

Conclusions Pediatric patients experienced high AE rates, especially in teaching hospitals, and rates did not improve over time.

Commentary Stockwell et al add to the literature by applying a novel pediatric trigger tool to a sample of 16 teaching and nonteaching hospitals to examine temporal trends in AE rates and compare teaching and nonteaching hospital AE rates over a 5-year period between 2007-2012. They found that, despite widespread efforts over the past 2 decades to improve safety, pediatric AE rates across hospitals did not meaningfully change. Teaching hospitals had 5 times the AE rates of nonteaching hospitals, and children with chronic conditions had 2 times the AE rates as their counterparts. The authors rightly point out that effectively achieving system-wide reductions in AE rates will require more comprehensive safety measurement tools. The GAPPS trigger tool is one important such tool. In addition, future safety surveillance efforts should include patient/family safety reporting, both in hospital incident reporting systems and in systematic safety

surveillance research. Families have been shown to be reliable reporters of AEs that are often otherwise unreported, particularly for children with medical complexity.^{1,2} Moreover, patients/families have the potential to help prevent AEs by helping staff detect them sooner. Families can serve as vigilant partners in safety in both teaching and nonteaching hospitals (for instance, helping provide continuity in teaching hospitals and another set of eyes in nonteaching hospitals), and in children with medical complexity. Families should be included in safety, both when examining AE rates and designing interventions to reduce their incidence.

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Heart-rate-characteristic monitoring decreases NICU length of stay

Swanson JR, King WE, Sinkin RA, Lake DE, Carlo WA, Schelonka RL, et al. Neonatal Intensive Care Unit Length of Stay Reduction by Heart Rate Characteristics Monitoring. *J Pediatr* 2018;198:162-7.

Question Among neonatal intensive care unit (NICU) infants, what is the benefit of heart rate characteristic (HRC) monitoring, compared with control, in reducing length of stay?

Design Retrospective analysis of a randomized control trial.

Setting NICUs across the US.

Participants 3003 infants <1500 g.

Intervention HRC monitoring (which displays a sepsis high-risk score) or not.

Outcomes Discharge before day 120.

Main Results HRC-monitored infants were more likely to be discharged alive and before day 120 (83.6% vs 80.1%, $P = .014$).

Conclusions HRC monitoring decreased NICU length of stay.

Commentary Fortunately for very low birth weight infants in the NICU, rates of sepsis have declined substantially over the past decade, but given the high associated mortality and morbidities, strategies for early detection are still warranted. The HeRO (heart rate characteristics) monitor displays a score that indicates high risk for sepsis and thus identifies infants needing heightened vigilance, and the RCT conducted from 2004-2010 reported lower mortality for infants whose scores were displayed to clinicians (8.1% vs 10.2% with conventional monitoring). Since death and NICU length of stay are competing outcomes, Swanson et al present follow-up analyses focusing on survivors, and show that length of stay was shorter for those in the HRC display group, which is an important finding. The tradeoff is a slightly higher number of sepsis evaluations and days on antibiotics. Another caveat is that the HRC index is frequently elevated in infants without sepsis,¹ particularly those with respiratory and neurologic compromise.^{2,3} Additional research is warranted to refine sepsis early warning systems to further assist clinicians in the difficult task of "right-timing" antibiotics in this vulnerable population.

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