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Closing in on PFAPA syndrome as "bad luck"

— Sarah S. Long, MD

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) has been a fascinating condition since its description in 1987. Otherwise healthy young children have clockwork timing of episodes every 3-5 weeks in which sudden onset of high fever is followed by the other characteristic findings of the PFAPA name. After 3-4 days the episode ends just as abruptly and complete wellness ensues, until the next episode. After 4-6 years, intervals lengthen and in the majority of patients, episodes disappear. There frequently is a family history of a parent having had mysterious fever episodes in childhood that he or she "grew out of." Hypotheses of etiology, such as an infectious trigger or an immunologic aberration have not been wholly satisfying intellectually, or proven. The clockwork cycles are a problem for an infectious cause. The shortening of the wellness interval between febrile episodes following a few doses of a corticosteroid (which rapidly abort a febrile episode) is a problem for the proposal of an immunologic etiology of PFAPA. This writer once suggested that PFAPA seemed like an "immunokinection" —to marry immunologic-cytokine-infectious aspects of PFAPA.

Amarilyo et al from Israel found over-representation of Mediterranean ancestry among their 303 patients with PFAPA studied, as well as over-representation of heterozygosity for one of the 9 most common *MEFV* gene mutations (which if homozygous cause familial Mediterranean fever) in patients with PFAPA of Mediterranean descent compared with others of similar descent. They further noted in patients with PFAPA of Mediterranean descent the onset of episodes earlier in life and the peculiar occurrence of shortened wellness intervals among children treated with corticosteroid.

With information as in this Israeli study and the recent identification by Manthiram of genetic risk variants in children with PFAPA near the gene mutations associated with Behcet disease (*Proc Natl Acad Sci USA* 2020;117:14405-11), it appears that we are closing in on telling families that PFAPA is "bad luck." PFAPA may join the ranks of the monogenic periodic fever syndromes.

Article page 268 ►

Late prematurity, breastfeeding, and the neonatal intensive care unit

— Raye-Ann deRegnier, MD

Neonatal intensive care unit (NICU) admission rates are variable for infants born at 34-36 weeks of gestation in the United States. Some hospitals admit only infants who have acute illnesses whereas other hospitals routinely admit all infants born below specific gestational age thresholds. The risks and benefits of these variable practices have not been fully evaluated but one concern is that routine admission to a NICU involves routine separation of mothers from their infants and this may have a negative impact on breastfeeding. In this volume of *The Journal of Pediatrics*, Hannan et al capitalized on the variability in NICU admission rates to study breastfeeding and other parenting practices using survey data from mothers of 62 494 infants with late preterm birth. The study showed a slight improvement in the initiation of breastfeeding for infants admitted to a NICU, but rates of breastfeeding

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continuation at 10 weeks were similar regardless of NICU admission status. The authors also found that NICU hospitalizations were associated with greater use of safe sleep practices but not decreased rates of maternal postnatal smoking.

The study results suggest that further research could identify why a NICU stay may have positive effects for breastfeeding initiation. A longer hospital stay may allow more breastfeeding education and practice before going home. The benefits of breast milk may become more salient to mothers when their infants require special care after birth. Close monitoring and encouragement during the hospitalization may alleviate early concerns about milk supply. Further understanding of these factors might allow us to provide better ongoing support at home for breastfeeding mothers of infants born with late prematurity, whether they have a NICU stay or not.

Article page 114 ►

What the heck's with NEC?

— James F. Padbury, MD

Necrotizing enterocolitis (NEC) is a thankfully infrequent complication among infants with low birthweight. Nonetheless, the 5-13% incidence makes it an important clinical problem. The severity can range from modest intestinal dysfunction to life-threatening abdominal catastrophe with multiorgan system failure. Thus, this vexing problem remains one of the "monsters under the bed." Too-numerous-to-count publications have been written about its clinical presentation, pathogenesis, diagnosis, and treatment. There is unanimity of opinion that prevention is a wise course. To that end, numerous interventions including feeding protocols, exclusive breast milk feeding, and probiotics have been suggested. More recently, the association with prolonged antibiotic use in the newborn intensive care unit (NICU) has gained appreciation. That observation is why the unexpected results from the report by Li et al in this volume of *The Journal* are so surprising. They report the results of the NEOMUNE-NeoNutriNet study's prospective observational study of the risk factors associated with necrotizing enterocolitis. The study was conducted in 13 NICUs on 5 continents. Almost 3000 infants were included in this pre-planned, prospective observational analysis. A wide range of maternal and neonatal clinical data, laboratory, and investigative data were amassed. Most remarkably, the trial demonstrated that early antibiotic therapy (within the first 3 days after birth) was associated with a *lower* incidence of NEC, 3.9% in the early antibody group versus 9% in the no early antibiotic group. Because this was a prospective observational cohort and not a randomized controlled trial, there were differences between the groups. This includes differences in the number of infants exposed and not exposed to antibiotics, unequal cesarean delivery rate, and unequal timing of initiation of feedings. Nonetheless, the sample size was large, the analysis and collection of the data were prospectively planned, and most importantly, the results were consistent across centers (**Figure**). The authors speculate that the early antibiotic treatment may have delayed the rapid colonization after birth in the immature preterm intestine. They further posit that the brief delay may provide time for "intestinal postnatal adaptation of immune defense mechanism such as mucosal barrier function which undergoes significant maturation within the first few days after birth in preterm infants." An alteration in gut microbiome among the groups is also a potential association. Regardless of the explanation, this unanticipated provocative finding is of importance. The authors took a conservative approach and avoided advocating antibiotics in the first 3 days of life when no other indication exists. Nonetheless, further study is warranted. The data are strong enough to warrant a prospective, randomized clinical trial. This will be a difficult study because the incidence is low enough that a large number of participating centers will be needed to accrue enough infants to address this important question. We anticipate a lively discussion within our field of these unexpected and provocative findings.

Article page 128 ►

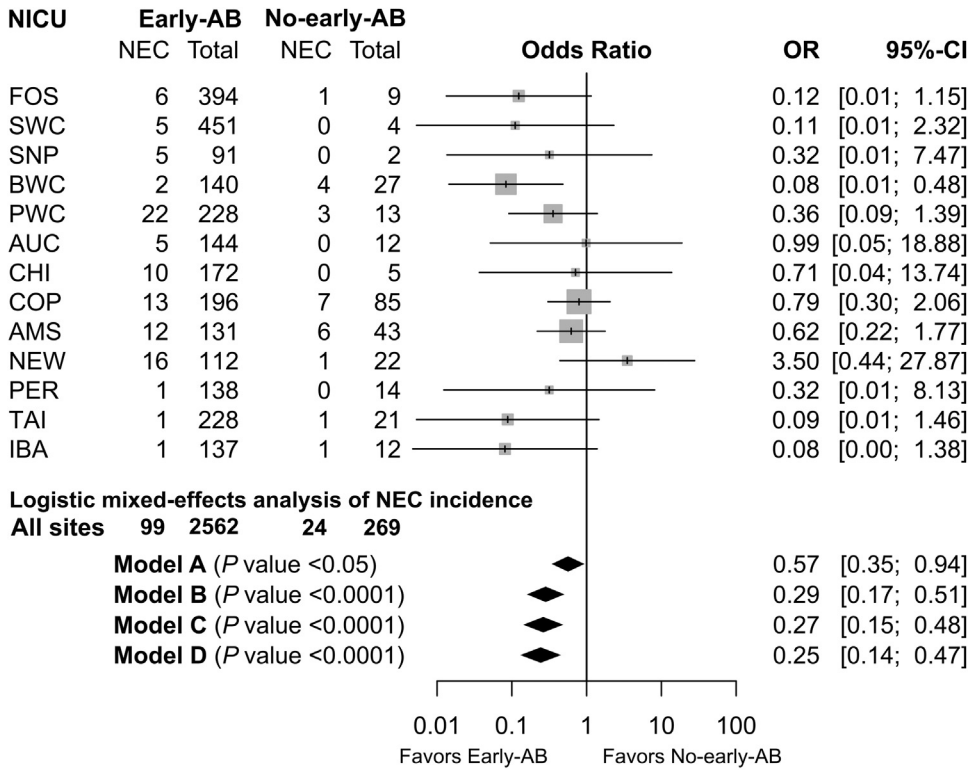

Figure. Forest plot of unadjusted OR of NEC incidence between the early antibiotics and no early antibiotics groups for each NICU. Model A: NICU site as the random effect and no adjustment for other fixed effects; model B: model A with adjustment for gestational age, birth weight, and sex as fixed effects; model C: model B with additional adjustment for delivery mode, use of antenatal steroids, and Apgar score at 5 minutes; model D: model C with additional adjustment for time of initiation of enteral nutrition and type of enteral nutrition in the first week of life.

Neuropsychological function with single ventricle physiology–The heart of the matter

— Denise M. Goodman, MD, MS

The care of children with single ventricle heart disease has undergone substantial evolution over the past 2 decades, with improved surgical techniques and hemodynamic outcomes. Concurrently, attention is moving beyond immediate postoperative survival, to a greater emphasis on long term neuropsychological functioning, physiologic integrity, and quality of life. Wolfe et al in this volume of *The Journal* add to our understanding with a report on a large cohort of children seen, on average, about 6 years after Fontan procedure. With a Fontan procedure, there is one ventricle supporting systemic perfusion, while pulmonary blood flow is non pulsatile based upon passive flow from cavae directly to pulmonary arteries. As the authors note, Fontan physiology carries a risk of substantial long-term morbidity, both cardiac and extra-cardiac, including ventricular dysfunction, dysrhythmias, portal hypertension, protein-losing enteropathy, plastic bronchitis, sleep-disordered breathing, and neuropsychological impairments.

The authors found that patients scored 0.5-1 standard deviation below population means for neuropsychological testing, with greater impact on specific domains depending on physiological functioning. Sleep-disordered breathing was associated with poorer visual-motor integration, lower arterial oxygen content with poorer executive function, and regurgitation of the atrial-ventricular valve with lower parent-rated adaptive functioning. Findings held when controlling for stroke, SES, and time since the Fontan procedure.

Taken together, these findings have several implications. Acknowledging these risk factors, mitigating physiologic derangements to the extent possible, or revising targets such as tolerable oxygen saturation, may be associated with improved outcomes. In

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addition, early neurodevelopmental intervention may promote better long-term accommodation so that children with single ventricle physiology have the best opportunity to realize their fullest potential.

Article page 239 ►

South African children living with HIV on ART: Can we do better?

— Sarah S. Long, MD

One would hypothesize that through the modern lens of access to effective antiretroviral therapy (ART) from a young age with successful HIV suppression, outcomes for affected children would look to be very good. Shiau et al inform us that for South African children infected at birth, outcomes are *better* (certainly than before ART), may even be *good* (medically) but fall short of being very good. The current study is a report of findings at the exit visit approximately 4 years after enrollment beginning in 2014 of HIV vertically infected children and controls recruited in the same age bands from uninfected siblings, household members, or children attending the same outpatient health services site. Using well validated standardized tools, they measured children's behavioral health and quality of life in the domains of physical and psychosocial health as well as emotional, social, and school functioning. A total of 463 children living with HIV and 122 controls were recruited. Infected children had started ART at the mean age of 6.6 months and 90% had suppression of HIV below the detectable 40 copies/mL. Despite beginning therapy at a young age and having sustained viral suppression, children living with HIV on ART had a higher rate of behavioral and mental health problems and poorer quality of life.

The study identifies markers of risk versus resilience as well as potential harms, benefits, and ameliorating interventions that should be considered as ART is started at even earlier ages so that *very good* outcomes can be at reach.

Article page 308 ►

Genetic testing for congenital heart disease

— Stephen R. Daniels, MD, PhD

It is well understood that there is an important genetic component to the development of critical congenital heart disease. However, the genetics are complex and there is still much to be learned about genotype-phenotype relationships. In this volume of *The Journal*, Shikany et al report on an analysis of 293 infants with congenital heart disease, 213 of whom had isolated congenital heart diseases and 80 of whom who had multiple congenital anomalies. The yield of genetic testing was 39% in those with multiple congenital anomalies and 20% in those with isolated congenital heart disease. They found right ventricular obstructive defects were highly associated with abnormal genetic test results.

The authors present extensive information about genotype and phenotype in the paper and outline. Perhaps as important as the specific findings is support for the need for a geneticist as part of the multidisciplinary team caring for infants with congenital heart disease.

Article page 231 ►