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Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer Research and recommendations In Child Health-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialties of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology, vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

Upendra Kinjawadekar
National President 2023
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What happens to the survivors of necrotising enterocolitis? The verdict is out!

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BASED ON ARTICLE

Vaidya R, Yi JX, O'Shea TM, Jensen ET, Joseph RM, Shenberger J, Gogcu S, Wagner K, Msall ME, Thompson AL, Frazier JA, Fry R, Singh R; ELGAN-ECHO. Study Investigators. Long-Term Outcome of Necrotizing Enterocolitis and Spontaneous Intestinal Perforation. *Pediatrics*. 2022;150(5):e2022056445. doi: 10.1542/peds.2022-056445.

SUMMARY

ELGAN-ECHO (Extremely low gestational age newborns- Environmental influences on Child Health Outcomes) study group prospectively assessed the outcome of necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP) survivors over a span of 10-15 years for growth and neurodevelopmental (ND) outcomes. They compared children with medical NEC vs. surgical NEC vs. surgical SIP vs. neither NEC, nor SIP (controls). SIP was defined as an isolated gastrointestinal perforation on radiograph and managed by exploratory laparotomy or an abdominal drain (without surgery) in the absence of other corroborative features of NEC. The authors assessed anthropometrics, neurocognition, attention-deficit/hyperactivity disorder, epilepsy, and gross motor function. For ND assessment various assessment systems were used such as Gross Motor Function Classification System (GMFCS), School-Age Differential Ability Scales-II (DAS-II) Verbal and Nonverbal Reasoning subscales, Latent Profile Analysis (LPA), Wechsler Abbreviated Scale of Intelligence-II and Child Symptom Inventory, Fourth Edition (CSI-4). At 10 years of age (baseline), 889 ELGAN children (medical NEC = 138, surgical NEC = 33, SIP = 29, no NEC/SIP = 689) were enrolled. 694 control children could be followed up to 15 year's age. Children with medical NEC had similar weight, body mass index (BMI), height, and head circumference when compared with controls at 10 and 15 years. At 15 years, children with surgical NEC had lower weight z-score (adjusted β : -0.75, 95% confidence interval [CI]: -1.25 to -0.25), lower BMI z-score (adjusted β : -0.55, 95% CI: -1.09 to -0.01), and lower height z-score (adjusted β : -0.65, 95% CI: -1.16 to -0.14). Children with SIP had lower weight and height z-scores at baseline when adjusted for sample attrition, but these differences were not significant when adjusted for confounders. They did not observe any differences in long-term ND outcomes between the groups. Authors concluded that surgical NEC- and SIP-associated growth impairment may persist through late childhood. ND outcomes among school-aged children born extremely preterm with NEC/SIP are no different from children without NEC/SIP [1].

NEC and SIP are gastrointestinal complications in preterm infants associated with high morbidity and mortality, more so in extremely low birth weight (ELBW) infants. NEC is

characterized by ischemic necrosis of the intestinal mucosa, severe inflammation, invasion by enteric gas-forming organisms, and dissection of gas into the bowel wall and portal venous system. Pathophysiology of SIP is distinct from NEC and typically presents as a focal intestinal perforation at the terminal ileum. Among ELBW infants, the incidence of NEC is ~7% and SIP is 3-8% [2]. Short-term outcome studies for 18-24 months show ND impairment in 25% and 59% of medical and surgical NEC patients, respectively [3,4]. Studies in older children are few and conflicting regarding the growth failure and ND impairment. Does NEC really impact growth and development beyond infancy? Do they catch up? This has been a point of debate among neonatologists, pediatricians, gastroenterologists and neurologists. There is definitely “an elephant in the room”! But so far, based on the referral pattern, each “blinded” speciality was appreciating the elephant differently and reporting conflicting outcomes. In this light, Vaidya et al answered the question to near perfection. It almost appears like a verdict that was long and overdue in a court. The study was performed under the umbrella of ECHO which is supported by the National Institute of Health, USA.

Surgically intervened patients (NEC and SIP) have poor growth due to short gut syndrome. The residual gut is not mature enough for recovery and adaptation at such a premature age. Extremely low birth weight would mean extremely low circulating levels of trophic factors. Many growth factors stimulate intestinal growth such as glucagon like peptide-2, epidermal growth factor, growth hormone, and insulin like growth factor-1. For a “train” carrying nutritive factors, the terminal ileum is the most crucial “station” to stop and unload the goods. Resection of the terminal ileum in NEC/SIP will dent the nutritive supply to the rest of the body. This is contrast to medical NEC where antibiotics heal the condition and complete mucosal recovery prevails over time. In the study cohort, the growth outcomes for surgical NEC were not different at age 10 years but were significantly lower at age 15 years, even after adjustments. This suggests that if the patients have weight catch-up at early childhood up to age 10 years, they are still at risk for poor growth at phases of accelerated growth especially adolescence.

Hence the growth pattern was expected, but what is interesting is the ND outcome that the authors have shown. In an everlasting debate, one would argue that there will always be too many confounders to correctly assess ND impairment in ELGAN such as ventilation, cerebral ischemia and dyselectrolytemia. In this statistical analysis, the authors painstakingly attempted to cover as many confounders as possible. Authors’ findings were contrast with those of Roze et al, who found that infants with NEC/SIP had lower IQ and worse motor function when compared with controls. While Roze at all recruited preterms 27-34 weeks and accounted for severe cerebral pathology, Vaidya et al recruited preterms 23–27 weeks and accounted for multiple risk factors [1, 5]. The exact cause of NDI in children with surgical NEC and SIP is largely unknown but is probably multifactorial. Some key factors are systemic circulation of proinflammatory proteins, illness severity, exposure to perioperative anesthetic and pain medications, poor nutrition (especially with short gut), and ongoing need for parenteral nutrition (risk for sepsis). Any surgical intervention potentially results in a proinflammatory cytokine surge, as well as exposure to anesthesia, both of which are known to be associated with ND impairment.

The strengths in this study were the prospective and multicentre approach. Authors also performed an inverse probability weighting to iron out any confounding effects of socioeconomic factors. Large numbers were recruited in medical NEC and controls but not in the surgical groups. Critiques may point out about the inadequate “surgical” power of study but doesn’t this also reflect the standard of preterm care which India is yet to achieve? Neonatal practices and thresholds evolve rapidly. Over two decades and 15 years of observations, the policies of the past may not match present day outcomes. Nevertheless, this study provides renewed encouragement for parents and physicians to strive for ELGAN and salvage during episodes of NEC.

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