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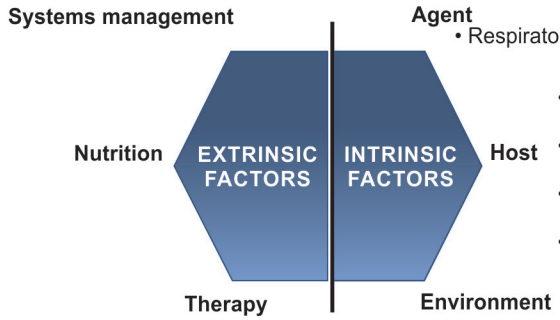
Need for larger cohorts and standardized tools to study diseases in newborn infants

Fetuses, newborns, and young infants are at high risk of morbidity and mortality.[1,2] Genetic variations can alter the development of primordial structures during embryonic and early fetal periods.[3–5] In the more mature fetus, the perinatal period, and during early infancy, infections and consequent systemic inflammatory response syndrome can cause organ damage.[5–7] Later, various infectious and non-infectious, ischemic, and mechanical injuries can disrupt many of these growing structures.[8,9] Many can trigger inflammation and cause tissue damage due to vasomotor dysregulation with associated edema and temperature instability, cytokine storm, and activation of leukocytes.[10–13] Our ability to restore damaged organ structures is still limited, and therefore, the emphasis remains on early detection by imaging and supportive measures to limit tissue damage.[14,15] Many young infants can also show growth failure, a condition named as extrauterine growth restriction or labeled as extrauterine growth retardation and postnatal growth restriction.[16–20]

We need larger cohorts of patients and standardized, accurate tools to study altered development in newborn infants and their eventual outcomes.[21–23] Cautious analysis of these data using both conventional and newer prediction tools can be helpful.[24–26] Similarly, the development of newer, easily portable equipment has raised new possibilities for the collection of standardized data.[27] We need to study large patient cohorts over time or in larger geographical territories to draw clinically relevant conclusions.[28] These studies can/should encompass all the 6 nodes that we seek to pursue to develop pathophysiological/clinical care models.[29] There is a need for information on host factors, infectious agents, environmental causes, therapy, nutrition, and systems management. Most of us are familiar with the agent-host-environmental trinodal pathogenesis models. However, increasing information suggest that many drugs still need evaluation in fetuses and young infants.[30] In addition, some that are currently in use have limited efficacy, whereas others have had unacceptable short- and long-term adverse effects.[31–33] To appropriately tailor these treatments and minimize risk, appropriate nutrition, and also systems management to develop treatment strategies with fewer medication errors and high therapeutic efficacy can be helpful.[32,34] Understanding the temporal evolution of these changes can also be advantageous.[32,34] All treatment modalities are not uniformly available or affordable in different parts of the world, and hence there is a need for computational systems to assess, monitor, and treat these highly susceptible patients.[35–37] If we know the possibilities, we can educate and motivate our care providers to acquire and learn these tools.[38]

Our journal, the *Newborn* aims to cover fetal/neonatal problems that begin during pregnancy or occur after birth during the first 1000 days after birth. In this 3rd issue of the second volume, we present 8 important articles (**Figure 1**). Totapally and colleagues examined the determinants of extremely prolonged length of hospital stay of ≥180 days in the records of 1,314,066 neonates. They performed a retrospective study in the 2012 Health Care Utilization Project (HCUP)'s Kid's Inpatient Database (KID-2012).[39] KID-2012 is a large publicly available pediatric database derived from 4,179 participating hospitals from 44 states in the United States.[40] All neonates who were discharged from the hospital following complicated births during the year 2012 are included. Diagnoses and procedures were retrieved using the international classification of diseases, 9th revision (ICD-9) and the current procedural terminology (CPT) codes.[41,42] Extremely prolonged length of hospital stay was noted in 6.2/10,000 infants (n = 812); it was associated with African American race, medicaid insurance,[43] zone improvement plan (ZIP) codes[44] associated with lower median incomes,[45] and birth in South and Midwest regions of the US.[46] Most were neonates who had a surgical procedure done, especially tracheostomy and gastrostomy. Overall, the occurrence of extremely prolonged length of hospital stay was relatively uncommon among hospitalized neonates. However, these infants had distinct clinical and demographic characteristics, which can be anticipated using prediction models. Such prediction may be important for public policy issues and allocation of healthcare resources.



- Respiratory syncytial virus infections in neonates: A persisting problem
- Neonates with an extremely prolonged length of stay: An analysis of kids inpatient database
- Clinical correlates of cholestasis in preterm infants with surgical necrotizing enterocolitis
- Epidemiological study of congenital anomalies and risk factors in newborn infants in a tertiary care hospital of Bangladesh
- Extrauterine growth restriction: Need for an accurate definition

- Umbilical cord blood gases: Sampling, evaluation, and application for clinicians
- Digital stethoscope use in neonates: A systemic review
- Point-of-care ultrasound to diagnose and monitor the course of necrotizing enterocolitis

Fig. 1: **Areas of focus in the *Newborn*, Volume 2, Issue 3.** In the *Newborn,* we have expanded the traditional agent-host-environment trinodal disease model to a hexagonal system. The three additional foci represent extrinsic factors that can affect health; those originating in therapy, nutrition, and systems management. This issue covers 4 of these foci, namely infectious diseases, host factors and treatment/monitoring systems.

Zahirul Alam and his coworkers[47] examined a large cohort of 54,800 infants in outpatient visits at a center in Bangladesh and recorded the first 100 with congenital anomalies. Sixty-nine infants were male and 31 were female (gender ratio 2.2:1). Abnormalities of the central nervous system were seen in 30 infants, the musculoskeletal system in 24, gastrointestinal in 24, cardiovascular in 13, and the genitourinary system in 9 infants. Thirty-eight infants had a history of antenatal exposure to radiation and 35 to pesticides. Twenty-two infants were born to mothers with diabetes, and 18 to mothers with hypertension. Studies have shown considerable regional variation in such background exposures. We need more studies so that regionally appropriate interventions can be designed.

Postnatal exposures to developing preterm infants may also be important. In an original study, Garg *et al*.[48] studied retrospectively collected data from a cohort of 62 infants with surgical necrotizing enterocolitis to investigate the clinical determinants and outcomes of cholestasis. Cholestasis was seen more frequently in infants who had developed systemic inflammatory response syndrome and sepsis with positive blood cultures. They had received parenteral nutrition for longer durations. They had longer lengths of hospital stay, more surgical complications, and developed intestinal failure more frequently. Interestingly, the weight-for-length Z-scores were higher at a postmenstrual age of 36 weeks.[49,50] In other analytical paradigms, the duration of postoperative ileus and need for parenteral nutrition were independently associated with severe cholestasis at 2 months of age.

There are 5 reviews. Bagga and colleagues[51] reviewed our definitions of extrauterine growth restriction in neonates and then collaborated with experts from various parts of the world to refine the information. We know that newborn infants can show considerable variation in growth parameters.[52] In addition to conventional measurements such as weight, length, and head circumference, many growth-restricted infants also show limited subcutaneous and total body fat.[53] *In utero,* these biometric data may be influenced by parental genetic, nutritional, and anthropometric factors. After birth, infant growth may be affected by feeding and caloric intake, metabolic activity, genetics, and the overall health status. The team has raised important questions about appropriate and timely recognition of suboptimal growth during early infancy. They have also summarized currently available information on the risk of neurodevelopmental abnormalities.

Chetan *et al*.[54] reviewed the value of gut ultrasound in infants in the first 28 days after birth for diagnosing necrotizing enterocolitis. They noted that altered bowel perfusion, decreased peristalsis, and bowel wall thickening showed better precision than abdominal radiographs. These findings are similar to those seen in many systematic and narrative reviews.[55–58] The high specificity and positive predictive value could make this tool a guide for early identification and prompt surgical intervention in the dreaded diagnosis of necrotizing enterocolitis.

Hiranandani and coworkers[59] reviewed ways to evaluate and interpret umbilical cord blood gases as a marker of neonatal vitality at the time of birth. Although there have been many advancements in fetal monitoring, a time lag can still be seen in many infants in the onset of fetal heart rate abnormalities and delivery. Measurement of cord blood pH and gas values can be one way to determine the degree of compromise. These data can help in assessing whether the precipitating event was acute, prolonged, or had occurred much before the onset of labor. Timely recognition of fetal circulatory compromise can help in appropriate institution of preventive measures and help prevent birth asphyxia.

Singh *et al*.[60] reviewed respiratory syncytial virus (RSV) as a cause of lower respiratory tract infections in young infants. Globally, RSV accounts for 2.3% of deaths among neonates 0–27 days of age. It is an enveloped, single-stranded, non-segmented, negative-strand RNA virus, a member of the family *Pneumoviridae*. These infections are seen most frequently in children aged below 24 months; most patients present with cough, fever, and wheezing. Reverse transcriptase-polymerase chain reaction, culture, and rapid antigen tests can be useful. Therapy is mainly supportive; standard precautions, hand hygiene, breastfeeding, and contact isolation should be followed. Recent AAP guidelines do not recommend routine pavilizumab prophylaxis for preterm infants born at 29–35 weeks unless they have chronic lung disease, hemodynamically significant congenital heart disease, and other coexisting conditions.[61] RSV can lead to long-term sequelae such as wheezing and asthma, which can increase healthcare costs and impair the quality of life.[62]

Roff *et al*.[63] assessed the evidence for the efficacy of digital stethoscopes in neonates. They performed a systematic review of studies published between January 1, 1990, and May 29, 2023; a total of 41 papers were identified as appropriate for narrative synthesis based on pre-decided criteria. There were 13 non-full-text articles, including journal letters or conference abstracts, and 28 were full-text articles appropriate for full qualitative analysis. These data showed that digital stethoscopes have been studied in the context of artificial intelligence for sound quality assessment and chest sound separation ($n = 5$), cardiovascular sounds ($n = 11$), respiratory sounds ($n = 4$), bowel sounds ($n = 4$), swallowing sounds ($n = 2$), and telemedicine ($n = 2$). This article discusses the potential utility of digital stethoscope technology for the interpretation of neonatal sounds for both humans and artificial intelligence. Digital stethoscopes can enable enhanced interpretation of neonatal cardiac sounds, although there is a need for refinement of the quality of sounds.

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