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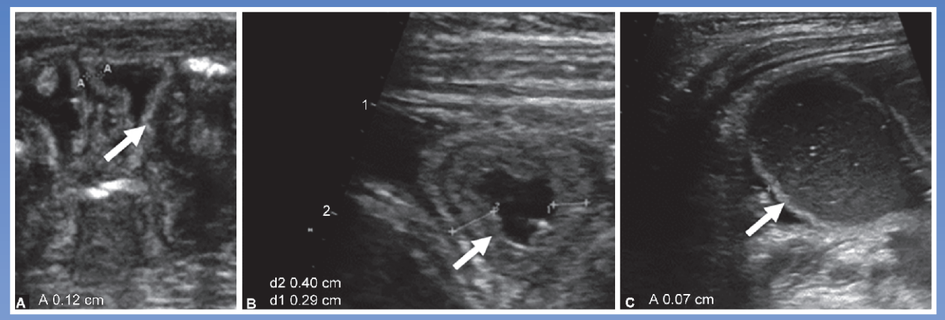
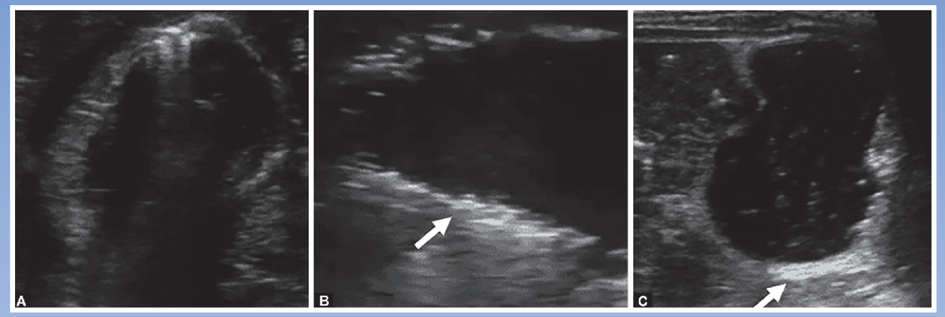


Gut wall thickness: (A) Normal; (B) Increased; and (C) Decreased (arrows)



Pneumatosis intestinalis: (A) None; (B) Discrete dots; (C) More advanced disease with contiguous changes

Point-of-care Ultrasound to Diagnose and Monitor the Course of Necrotizing Enterocolitis

Other highlighted articles:

Neonates with an Extremely Prolonged Length of Stay: An Analysis of Kids Inpatient Database

Epidemiological Study of Congenital Anomalies and Risk Factors in Newborn Infants at a Tertiary Care Hospital in Bangladesh

Respiratory Syncytial Virus Infections in Neonates: A Persisting Problem

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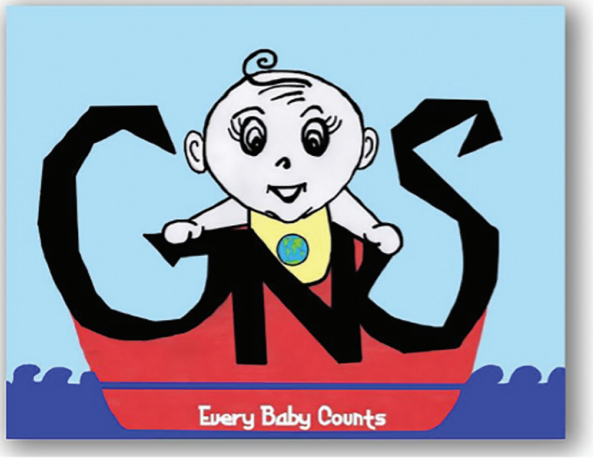

Global Newborn Society

Each time we lose an infant, we lose an entire life and its potential!

Newborn is the official journal of the Global Newborn Society (GNS), a globally-active, non-profit organization that is registered as a 501(c)(3) non-profit formation in the United States and is currently being listed as an analogous charity in many other nations. The aim is to enhance research in newborn medicine, understand epidemiology (risk-factors) of disease, train healthcare workers, and promote social engagement. The GNS was needed because despite all improvements in medical care, infants remain a high-risk patient population with mortality rates similar to 60-year-olds. We need to remind ourselves that *Every Baby Counts*, and that *Each Time We Lose an Infant, We Lose an Entire Life and its Potential*.

Our logo above, a hand-drawn painting, graphically summarizes our thought-process. There is a lovable little young infant exuding innocent, genuine happiness. The curly hair, shape of the eyes, long eye-lashes, and the absence of skin color emphasize that infants need care all over the world, irrespective of ethnicity, race, and gender. On the bib, the yellow background reflects happiness, hope, and spontaneity; the globe symbolizes well-coordinated, world-wide efforts. The age-related vulnerability of an infant, with all the limitations in verbal expression, is seen in being alone in the boat.

The unexpressed loneliness that many infants endure is seen in the rough waters and the surrounding large, featureless sky. However, the shades of blue indicate that the hope of peace and tranquility is not completely lost yet. The acronym letters, GNS, on the starboard are made of casted metal and are pillars of strength. However, the angular rough edges need continued polishing to ascertain adequacy and progress. The red color of the boat symbolizes our affection. The expression "*Every Baby Counts*" seen on the boat's draft below the waterline indicates our commitment to philanthropy, and if needed, to altruism that does not always need to be visible. The shadow behind the picture shows that it has been glued on a solid wall, one built out of our adoption and commitment.

Design of the Journal Cover

The blue color on the journal cover was a careful choice. Blue is the color of flowing water, and symbolizes the abnormalities of blood vascular flow that are seen in many neonatal illnesses. There is a gradual transition in the shades of blue from the top of the cover downwards. The deeper shades of blue on the top emphasize the depth, expertise, and stability, which the renowned authors bring. Light blue is associated with health, healing, tranquility, understanding, and softness, which their studies bring. The small letter "*n*" in the title of the journal, *newborn*, was chosen to emphasize the little size of a newborn baby. The issue editors chose three articles to be specifically highlighted; the two pictures and two titles below reflects an order suggested by them.

Instructions to Authors

The journal welcomes original articles and review articles. We also welcome consensus statements, guidelines, trials methodology, and core outcomes relevant to fetuses/young infants in the first 1000 days. A detailed set of instructions to authors can be seen online at https://www.globalnewbornsociety.org/intructions-for-authors. The manuscripts can be submitted via the online manuscript submission system.

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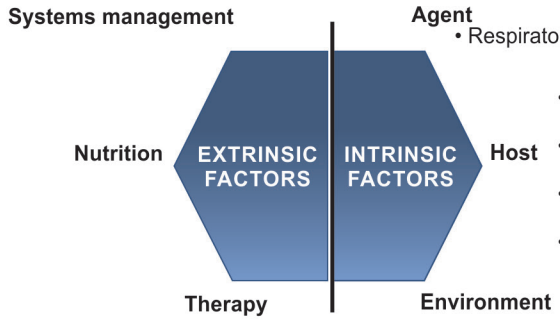
Need for larger cohorts and standardized tools to study diseases in newborn infants

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.

References

1. Transfusion of Prematures Trial. Vol. 2018 (https://ClinicalTrials.gov/show/NCT01702805).
2. Barfield WD, Committee On Fetus and Newborn. Standard terminology for fetal, infant, and perinatal deaths. Pediatrics 2016;137.
3. Assou S, et al. Dynamic changes in gene expression during human early embryo development: from fundamental aspects to clinical applications. Hum Reprod Update 2011;17:272–290.
4. Li Q, et al. Large-scale analysis of de novo mutations identifies risk genes for female infertility characterized by oocyte and early embryo defects. Genome Biol 2023;24:68.
5. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342:1500–1507.
6. Adams Waldorf KM, McAdams RM. Influence of infection during pregnancy on fetal development. Reproduction 2013;146:R151–162.
7. Romero R, et al. The role of inflammation and infection in preterm birth. Semin Reprod Med 2007;25:21–39.
8. Hennekam RC, et al. Elements of morphology: general terms for congenital anomalies. Am J Med Genet A 2013;161A:2726–2733.
9. Reichel TF, et al. Fetal central nervous system biometry on MR imaging. AJR Am J Roentgenol 2003;180:1155–1158.

10. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med 2020;383:2255–2273.
11. Mellembakken JR, et al. Chemokines and leukocyte activation in the fetal circulation during preeclampsia. Hypertension 2001;38:394–398.
12. Pawar R, et al. Neonatal multisystem inflammatory syndrome (MIS-N) associated with prenatal maternal SARS-CoV-2: a case series. Children (Basel) 2021;8.
13. Pietrasanta C, et al. Vascular endothelium in neonatal sepsis: basic mechanisms and translational opportunities. Front Pediatr 2019;7:340.
14. Wynn JL, Wong HR. Pathophysiology and treatment of septic shock in neonates. Clin Perinatol 2010;37:439–479.
15. Celik IH, Hanna M, Canpolat FE, Mohan P. Diagnosis of neonatal sepsis: the past, present and future. Pediatr Res 2022;91:337–350.
16. Peila C, et al. Extrauterine growth restriction: definitions and predictability of outcomes in a cohort of very low birth weight infants or preterm neonates. Nutrients 2020;12.
17. Fenton TR, et al. "Extrauterine growth restriction" and "postnatal growth failure" are misnomers for preterm infants. J Perinatol 2020;40:704–714.
18. Lan S, et al. Extrauterine growth restriction in preterm infants: postnatal growth pattern and physical development outcomes at age 3-6 years. Front Pediatr 2022;10:945422.
19. Sharma D, Shastri S, Sharma P. Intrauterine growth restriction: antenatal and postnatal aspects. Clin Med Insights Pediatr 2016;10:67–83.
20. Zozaya C, Diaz C, Saenz de Pipaon M. How should we define postnatal growth restriction in preterm infants? Neonatology 2018;114:177–180.
21. Panagiotakaki E, et al. Evidence of a non-progressive course of alternating hemiplegia of childhood: study of a large cohort of children and adults. Brain 2010;133:3598–3610.
22. Boateng GO, Neilands TB, Frongillo EA, Melgar-Quinonez HR, Young SL. Best practices for developing and validating scales for health, social, and behavioral research: a primer. Front Public Health 2018;6:149.
23. Denny JC, Collins FS. Precision medicine in 2030-seven ways to transform healthcare. Cell 2021;184:1415–1419.
24. Allgaier J, Mulansky L, Draelos RL, Pryss R. How does the model make predictions? A systematic literature review on the explainability power of machine learning in healthcare. Artif Intell Med 2023;143:102616.
25. Deawjaroen K, Sillabutra J, Poolsup N, Stewart D, Suksomboon N. Clinical usefulness of prediction tools to identify adult hospitalized patients at risk of drug-related problems: a systematic review of clinical prediction models and risk assessment tools. Br J Clin Pharmacol 2022;88:1613–1629.
26. Jung-Poppe L, et al. Systematic review of risk factors assessed in predictive scoring tools for drug-related problems in inpatients. J Clin Med 2022;11.
27. Howe Iii EG, Elenberg F. Ethical challenges posed by big data. Innov Clin Neurosci 2020;17:24–30.
28. Toledano MB, Smith RB, Brook JP, Douglass M, Elliott P. How to establish and follow up a large prospective cohort study in the 21st Century–Lessons from UK COSMOS. PLoS One 2015;10:e0131521.
29. Maheshwari A, Lui K, Motta M. Understanding the impact of maternal health on neonatal disease: a new horizon. Newborn 2023;1:iv–vi.
30. Mutair AA, et al. The effective strategies to avoid medication errors and improving reporting systems. Medicines (Basel) 2021;8.
31. Tayman C, Rayyan M, Allegaert K. Neonatal pharmacology: extensive interindividual variability despite limited size. J Pediatr Pharmacol Ther 2011;16:170–184.
32. Allegaert K, van den Anker JN. Adverse drug reactions in neonates and infants: a population-tailored approach is needed. Br J Clin Pharmacol 2015;80:788–795.
33. Ross EJ, Graham DL, Money KM, Stanwood GD. Developmental consequences of fetal exposure to drugs: what we know and what we still must learn. Neuropsychopharmacology 2015;40:61–87.
34. Allegaert K, van den Anker J. Neonatal drug therapy: the first frontier of therapeutics for children. Clin Pharmacol Ther 2015;98:288–297.
35. Ward ZJ, et al. Estimating the impact of treatment and imaging modalities on 5-year net survival of 11 cancers in 200 countries: a simulation-based analysis. Lancet Oncol 2020;21:1077–1088.
36. Mehta VK, Deb PS, Rao DS. Application of computer techniques in medicine. Med J Armed Forces India 1994;50:215–218.
37. Ahuja AS. The impact of artificial intelligence in medicine on the future role of the physician. PeerJ 2019;7:e7702.
38. Lee D, Yoon SN. Application of artificial intelligence-based technologies in the healthcare industry: opportunities and challenges. Int J Environ Res Public Health 2021;18.
39. Witt WP, Weiss AJ, Elixhauser A. Overview of hospital stays for children in the united states, 2012. in Healthcare Cost and Utilization Project (HCUP) Statistical Briefs (Rockville (MD), 2006).
40. Quality, AfHRa. Healthcare Cost & Utilization Project (HCUP): Kids' Inpatient Database (KID). (Department of Health and Human Services (HHS). Agency for Healthcare Research and Quality (AHRQ), Rockville, MD, 1997).
41. Statistics, NCfH. International classification of diseases, Ninth Revision (ICD-9). Vol. 2023 (U.S. Department of Health & Human Services, Atlanta, Georgia, 2022).
42. King MS, Lipsky MS, Sharp L. Expert agreement in current procedural terminology evaluation and management coding. Arch Intern Med 2002;162:316–320.
43. Services, CfMM. Medicaid services. Vol. 2023 (Centers for Medicare & Medicaid Services, Baltimore, MD, 2023).
44. Commerce, USDo. ZIP Code Tabulation Areas (ZCTAs). Vol. 2023 (USA.gov, 2020).
45. WHO I. The Global Health Observatory. Vol. 2023 (WHO, Int., Geneva, Switzerland, 2023).
46. Society NG. United States Regions. Vol. 2023 (National Geographic Society, Washington, DC, 2023).
47. Alam MZ, et al. Epidemiological study of congenital anomalies and risk factors in newborn infants at a tertiary care hospital in Bangladesh. Newborn 2023;2(3):185–190.
48. Garg PMG, et al. Clinical correlates of cholestasis in preterm infants with surgical necrotizing enterocolitis. Newborn 2023;2(3):191–197.
49. WHO I. Child growth standards/Standards/Weight-for-length/height. Vol. 2023 (WHO, Int., Geneva, Switzerland, 2023).
50. Chauhan K, Bisht B, Kathuria K, Bisht R, Hatwal V. Z score analysis: a novel approach to interpretation of an erythrogram. Indian J Pathol Microbiol 2023;66:85–90.
51. Nitasha Bagga N, et al. Extrauterine growth restriction: need for an accurate definition. Newborn 2023;2(3):198–202.

52. Ong KK, et al. Which infancy growth parameters are associated with later adiposity? The cambridge baby growth study. Ann Hum Biol 2020;47:142–149.
53. Santos S, et al. Associations of infant subcutaneous fat mass with total and abdominal fat mass at school-age: the generation R study. Paediatr Perinat Epidemiol 2016;30:511–520.
54. Chetan C, Garegrat R, Hazarika J, Maheshwari A, Suryawanshi P. Point-of-care ultrasound to diagnose and monitor the course of necrotizing enterocolitis. Newborn 2023;2(3):203–213.
55. Mishra V, et al. Imaging for diagnosis and assessment of necrotizing enterocolitis. Newborn (Clarksville) 2022;1:182–189.
56. Chen Q, et al. Application of abdominal ultrasonography in surgical necrotizing enterocolitis: a retrospective study. Front Microbiol 2023;14:1211846.
57. Janssen Lok M, et al. Value of abdominal ultrasound in management of necrotizing enterocolitis: a systematic review and meta-analysis. Pediatr Surg Int 2018;34:589–612.
58. Epelman M, et al. Necrotizing enterocolitis: review of state-of-the-art imaging findings with pathologic correlation. Radiographics 2007;27:285–305.
59. Hiranandani M, Kaur I, Grover S. Umbilical cord blood gases: sampling, evaluation, and application for clinicians. Newborn 2023;2(3):214–221.
60. Singh S, Maheshwari A, Namazova I, Benjamin JT, Wang Y. Respiratory syncytial virus infections in neonates: a persisting problem. Newborn 2023;2(3):222–234.
61. Caserta MT, O'Leary ST, Munoz FM, Ralston SL, Committee On Infectious D. Palivizumab prophylaxis in infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics 2023;152.
62. Wennergren G, Kristjansson S. Relationship between respiratory syncytial virus bronchiolitis and future obstructive airway diseases. Eur Respir J 2001;18:1044–1058.
63. Roff M, Slifirski O, Grooby E, Marzbanrad F, Malhotra A. Digital stethoscope use in neonates: a systematic review. Newborn 2023;2(3):235–243.

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ORIGINAL RESEARCH

Neonates with an Extremely Prolonged Length of Stay: An Analysis of Kids Inpatient Database

Balagangadhar R Totapally[1], Naveed Hussain[2], Venkata Nakta Raju[3]

Received on: 05 July 2023; *Accepted on*: 10 August 2023; *Published on*: 25 September 2023

Abstract

Background: With scientific and technological advances in intensive care, there is an increasing survival rate among neonates with complex medical problems who experience an extremely prolonged length of stay (EPLOS) of ≥180 days in the hospital. Little is known about the antecedents and characteristics of this particular group of neonates.

Aim: To characterize the risk factors associated with EPLOS in neonates.

Patients and methods: Retrospective study of neonates from the National Hospital Discharge Database for Children, Kids Inpatient Database 2012 (KIDS-2012), maintained by the Healthcare Cost and Utilization Project (HCUP), using data from 4,170 hospitals in 44 states in the US. All neonates with complicated births who were discharged from the hospital other than from the normal newborn nursey during the year 2012 were included. Newborns with uncomplicated hospital stays who were discharged from the normal newborn nursery were excluded. Diagnoses and procedures were retrieved using ICD-9 codes. Descriptive analyses were done to identify incidence and prevalence. Comparisons were made of neonates with EPLOS (LOS ≥180 days) and non-EPLOS (LOS ≤179 days) using univariate and multivariate analyses.

Results: A total of 1,314,066 neonates with complicated births discharged from US hospitals in 2012 were included in the analysis. The incidence of EPLOS was 6.2/10,000 (n = 812). On univariate analyses, neonates with EPLOS were more likely to have the following risk factors: Black race, Medicaid insurance, ZIP codes associated with lower median incomes, and born in the South and Midwest regions of the US. Most were neonates who had a surgical procedure done, especially tracheostomy and gastrostomy, being the most common procedures.

Conclusion: The occurrence of EPLOS is relatively uncommon among hospitalized neonates. The clinical and demographic characteristics of this subset of complicated neonates are distinct and can be anticipated using prediction models. Prediction models for EPLOS may be important for public policy issues and the proper allocation of healthcare resources.

Keywords: Hospital Length of Stay, Neonatal Intensive Care Unit, Pediatric Intensive Care Unit.

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Introduction

With advances in scientific knowledge and technology in intensive care units, there has been an increased survival of extremely sick neonates with conditions that would previously be considered lethal. Consequently, the need for ongoing advanced technological support in these infants has probably resulted in extremely prolonged hospital stays. Another reason for the prolonged hospitalization of neonates may be the increased societal and parental expectations for technology-assisted care for what may be considered futile care by nurses, physicians, and members of the healthcare team.[1] The length-of-stay for preterm birth is also increasing at a pace of 0.59% each year, probably related to the survival of extremely immature infants.[2] The use of advanced technologies in the hospital has also influenced the increased use of technology post-discharge, especially with the capability to provide respiratory and renal support at home for small children. It is reported that infants with prolonged initial hospitalization may also be at risk for increased morbidity and mortality post-discharge.[3] Given the changing landscape in this field of study, it is important to identify the risk factors for neonates who are likely to have extremely prolonged hospital lengths of stay. However, a current review of the literature shows a paucity of research and information on this subject. Therefore, we designed this study with the aim to evaluate the risk factors and clinical correlates of neonates with an EPLOS – defined as a hospital stay of ≥180 days.

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Patients and Methods

Definition of EPLOS: The use of an operational definition of extremely prolonged length of stay is derived from an extension of the concept of prolonged length of hospital stay. Prolonged

length of hospital stay for neonates has been defined previously based on evidence, which suggests that the majority of extremely premature infants are discharged by 42 weeks post-menstrual age (PMA = gestational age at birth in weeks + weeks after birth); which for a 25-week GA infant would be about 120 days of hospital stay.[4,5] We extrapolated this to surmise that about 180 days of hospital stay, which constitutes almost half a year, would be an appropriate cut-off point for distinguishing an extremely prolonged length of hospital stay. For a 25-week GA infant, this would be about 50–51 weeks post-menstrual age (PMA).

This is a retrospective study using data available from the 2012 Health Care Utilization Project's (HCUP) Kids' Inpatient Database (KID-2012).[6] Kids' Inpatient Database is the largest publicly available pediatric database derived from 4,179 participating hospitals from 44 states in the United States, taking care of patients <20 years of age. This database is one in a family of databases and software tools developed as part of the HCUP. The project is coordinated through the Center for Organization and Delivery Studies, which is within the Agency for Healthcare Research and Quality (AHRQ). The database is derived from discharge abstracts and typically includes clinical and resource utilization information with >100 clinical and non-clinical variables for each hospital stay. There may be up to a maximum of 25 diagnoses and 15 procedures per hospitalization. The information in the database represents approximately 80% of complicated hospital births and 10% of uncomplicated hospital births per participating state. Hospital regions are classified as Northeast, Midwest, South, and West. The KID database was specifically designed to permit researchers to study a broad range of conditions and procedures related to child health issues. Researchers and policymakers can use the KID to identify, track, and analyze national trends in healthcare utilization, access, charges, quality, and outcomes. The KID contains clinical and resource use information included in a typical discharge abstract, with safeguards to protect the privacy of individual patients, physicians, and hospitals (as required by data sources). The KID excludes data elements that could directly or indirectly identify individuals. Healthcare Cost and Utilization Project publishes a new KID every 3 years.

We performed a retrospective review of the KID-2012 for neonatal (within 28 days of birth) admissions with complicated births (UNCBRTH = 0). Normal neonates were excluded from the analysis. All neonatal admissions with complicated births were included in the data analysis. We evaluated the prevalence, and clinical correlates of neonates with an EPLOS as defined by length of stay ≥180 days. We have compared the EPLOS group with the group having a length of stay ≤179 days (non-EPLOS) among infants who were considered complicated births. International Classification of Diseases, ninth revision (ICD-9) diagnosis and procedure codes were used to retrieve various diagnoses and procedures, respectively.

Statistical Analysis

The prevalence of EPLOS is reported per 10,000 discharges of neonates with complicated births. The mortality rate is reported per 100 neonates. All categorical variables [gender, race, patient location, median household income (MHI)] were analyzed with Chi-square tests. Healthcare Cost and Utilization Project defines MHI by the zip code in which the child resides. The zip codes are stratified by quartiles with quartile 1 representing the lowest and quartile 4 representing the highest income. Binomial data are presented as odds ratios with 95% confidence intervals and *p* values. *P*-values < 0.05 are considered statistically significant. All continuous variables (total charges, length of stay, number of procedures, and the number of diagnoses) were analyzed by the Mann-Whitney *U* test. Their analyses are presented as a median and interquartile range (IQR). All data were weighted according to HCUP recommendations prior to analysis to calculate national estimates. Demographic variables were compared between EPLOS and non-EPLOS groups. Univariate analyses were done to evaluate the variable associated with an extremely prolonged length of hospital stay. Binary logistic regression analysis was done to evaluate predictive variables for EPLOS. All variables with a frequency of at least 0.1% and a *p*-value < 0.05 on univariate analysis were included in the binary regression model. Then adjusted odds ratios were calculated after controlling for characteristics that were significant on univariate analysis including, birth weight, race, region of the country, socioeconomic ZIP code quartile, disease diagnoses, and procedures. Missing values were coded as a separate category for the variables of interest.

These data were analyzed with SPSS version 28 (IBM Corporation, Armonk, NY) or StatCalc of Epi Info™ (Centers for Disease Control and Prevention, Atlanta). This study was exempt from IRB review.

Results

Prevalence of EPLOS

From a total of 3,118,814 hospital discharges recorded in the KID-2012 database, there were a total of 1,314,066 neonates with complicated births. Out of these complicated births, 812 neonates (6.2/10,000) had an EPLOS. Although EPLOS neonates represented only 0.06% of all complicated birth admissions, these infants, because of their prolonged hospitalization, accounted for 2% of all occupied beds.

Demographic Variables

Demographic variables were compared within EPLOS and non-EPLOS neonates and the results are shown in Table 1. There were no significant differences in the sex distribution of neonates between the two groups. Significantly lower proportions of neonates were born in the hospital they were cared for in the EPLOS group [47.7% vs 84.9%, $p < 0.0001$; OR: 0.16 (95% CI: 0.14–0.19)]. Neonates from the South and Midwest were more highly represented in the EPLOS group compared to neonates from the Northeast and the West [76.1% vs 59.7%, $p < 0.0001$; OR: 2.2 (95% CI: 1.8–2.5)]. The proportion of neonates with Medicaid insurance was higher and private insurance was lower in the EPLOS group [72.3% vs 53.6%, $p < 0.0001$; OR: 2.3 (95% CI: 1.9–2.7)]. Similarly, the proportion of Blacks was higher [33.5% vs 16.5%, $p < 0.0001$; OR: 2.6 (95% CI: 2.2–3.0)] and Whites was lower (37.0% vs 51.3%; $p < 0.0001$) in EPLOS group. A significantly higher proportion of neonates were residents from ZIP codes that were classified in the lower half of median income in the EPLOS group [66.3% vs 54.2%, $p < 0.0001$; OR: 1.7 (95% CI: 1.4–1.9)].

Complications and Interventions

A comparison of clinical correlates of neonates in the two groups is presented in Table 2. Overall, medical complications and the need for procedural interventions were higher in the EPLOS group. A major operating procedure was performed in 87.4% of neonates in the EPLOS group compared to 26% in the non-EPLOS group [$p < 0.0001$; OR: 19.8; (95% CI: 16.1-21.4)]. Tracheostomy and gastrostomy procedures were the most common procedures performed in neonates with EPLOS. The median hospital day on which tracheostomy was performed was 135 days (IQR: 90–161).

Table 1: The differences in demographic variables in neonates with extremely prolonged length of stay and non-extremely prolonged length of stay

Variable	*EPLOS group*	*Non-EPLOS group*	*p-value; (OR; 95% CI)*
Male (%)	56.0	54.6	$p = 0.42$; (1.06; 0.92–1.22)
Gestational age <27 weeks (%)	37.2	1.6	$p = 0.000$; (37.2; 32.3–43.0)
Birth weight <1000 gm (%)	51.1	2.08	$p = 0.000$; (49.3; 42.9–56.6)
Race and ethnicity			
White (%)	37.0	51.3	$p = 0.000$; (2.6; 2.2–3.0); Black vs all others
Black (%)	33.5	16.5	
Hispanic (%)	17.5	19.1	
Asian (%)	3.2	5.1	
Insurance			
Medicaid (%)	72.3	53.6	$p = 0.000$; (2.3; 1.9–2.7); Medicaid vs private insurance
Private (%)	27.7	46.4	
In-born (%)	47.7	84.9	$p = 0.000$; (0.16; 0.14–0.19)
Children's hospital (%)	36.5	4.8	$p = 0.000$; (11.5; 10.0–13.2)
U.S. region			
South and Midwest (%)	76.1	59.7	$p = 0.000$; (2.2; 1.8–2.5)
Northeast and West (%)	23.9	40.3	
ZIP codes with median income quartiles			
Quartile 1 (%)	38.5	29.8	$p = 0.000$
Quartile 2 (%)	27.8	24.4	
Quartile 3 (%)	21.8	23.9	
Quartile 4 (%)	11.9	21.9	

Table 2: Comorbid conditions and complications in neonates with extremely prolonged length of stay and non-extremely prolonged length of stay

Variable	*EPLOS group*	*Non-EPLOS group*	*p-value; (OR; 95% CI)*
Birth weight <1000 gm (%)	51.1	2.1	$p < 0.0001$; (49.3; 42.9–56.6)
RDS (%)	53.6	7.1	$p < 0.0001$; (15.0; 13.1–17.2)
Pulmonary air leaks (%)	17.4	1.5	$p < 0.0001$; (13.5; 11.2–16.2)
Pulmonary hemorrhage (%)	5.6	0.2	$p < 0.0001$; (34.4; 25.4–46.6)
Atelectasis (%)	18.0	0.7	$p < 0.0001$; (31.0; 25.9–37.1)
BPD (%)	46.1	0.8	$p < 0.0001$; (109.9; 95.6–126.3)
Mechanical ventilation (%)	68.9	10.9	$p < 0.0001$; (18.1; 15.6–21.0)
Tracheostomy (%)	28.1	0.05	$p < 0.0001$; (733; (618–869)
PDA (%)	55.4	4.4	$p < 0.0001$; (26.7; 23.3–30.7)
Cardiopulmonary arrest (%)	6.3	0.12	$p < 0.0001$; (55.9; 41.9–74.5)
NEC – any stage (%)	22.3	0.4	$p < 0.0001$; (65.3; 55.3–77.2)
Gastrostomy (%)	30.4	0.28	$p < 0.0001$; (157; 134–183)
Ileostomy (%)	12.0	0.1	$p < 0.0001$; (125; 100–155)
Colostomy (%)	7.9	0.1	$p < 0.0001$; (84.0; 64.7–109)
Retinopathy of prematurity (%)	24.0	1.4	$p < 0.0001$; (22.0; 18.7–25.9)
Intraventricular hemorrhage – any grade (%)	30.2	1.2	$p < 0.0001$; (34.9; 30.1–40.6)
Ventricular shunt (%)	7.5	0.1	$p < 0.0001$; (73.6; 56.4–96.1)
Major operating room procedure (%)	87.4	26.0	$p < 0.0001$; (19.8; 16.1–24.4)
Phototherapy (%)	20.2	14.1	$p < 0.0001$; (1.6; 1.3–1.8)
ECMO (%)	5.7	0.1	$p < 0.0001$; (67.7; 50.0–91.7)

ECMO, extracorporeal membrane oxygenation; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome

Outcome

Overall, approximately 80% of all neonatal deaths occur within 10 days of admission for a complicated birth. The mortality rate was significantly higher in the EPLOS group (10.9% vs 1.1%; $p = 0.000$; OR: 11.0 (95% CI: 8.8–13.7). Only 0.6% of all deaths in neonates occurred with EPLOS. The median [IQR] length of hospital stay was longer [214 (193–247) days vs 2 (2–3) days; $p = 0.000$] and the hospital charges were higher [$1,859,847 (1,334,863–2,537,870) vs $3,211 (2,115–5,623)] in EPLOS group compared to the non-EPLOS group. In the EPLOS group, the disposition at discharge from the hospital was

Table 3: Summary of binary regression analysis for variables predicting extremely prolonged length of stay in neonates

				95% CI for Odds ratio	
Independent variable	*β*	*Significance*	*Odds ratio*	*Lower*	*Upper*
Birth weight <1000 gm	1.643	0.000	5.171	4.043	6.614
African American race	0.421	0.000	1.523	1.269	1.828
Hospital: South or Midwest	0.397	0.000	1.487	1.238	1.786
Born in the same hospital	–0.373	0.001	0.688	0.555	0.854
Children's hospital	0.958	0.000	2.606	2.084	3.260
Insurance: Medicaid	0.475	0.000	1.609	1.351	1.916
Major operating procedure	1.927	0.000	6.867	5.461	8.633
Extracorporeal membrane oxygenation	2.354	0.000	10.532	7.206	15.392
Dialysis	0.825	0.044	2.281	1.022	5.091
Patent ductus arteriosus	0.630	0.000	1.878	1.557	2.265
Transient tachypnea of newborn	–1.178	0.000	0.308	0.164	0.579
Respiratory distress syndrome	0.407	0.000	1.503	1.217	1.855
Pulmonary air leaks	0.366	0.001	1.442	1.151	1.807
Atelectasis	0.345	0.003	1.413	1.125	1.774
Bronchopulmonary dysplasia	1.191	0.000	3.292	2.666	4.064
Tracheostomy	3.606	0.000	36.810	29.046	46.650
Necrotizing enterocolitis	0.976	0.000	2.654	2.108	3.340
Gastrostomy	1.765	0.000	5.840	4.756	7.172
Ileostomy	0.703	0.000	2.019	1.493	2.731
Colostomy	1.459	0.000	4.302	3.058	6.054
Intraventricular hemorrhage	0.379	0.000	1.461	1.194	1.788
Constant	–10.268	0.000			

Income levels, mechanical ventilation, pulmonary hemorrhage, and cardiopulmonary resuscitation were included in the regression model but were not reached statistical significance

to a home destination in only 47.8% of neonates compared to 88.9% in the non-EPLOS group ($p < 0.0001$). A significantly high proportion of EPLOS (31.0%) were discharged to skilled nursing homes or with provisions for home health care compared to a small minority (4.7%) needing such arrangements in the non-EPLOS group ($p < 0.0001$).

Binary Logistic Regression

Binary logistic regression was performed to assess the effects of the independent variable listed in Table 3 on the likelihood that neonates have EPLOS. The logistic regression analysis was statistically significant at χ^2 (25) = 6541, $p < 0.0001$. A regression model based on this analysis explained 48.2% (Nagelkerke R^2) of the variance in extremely prolonged length of stay and correctly classified 99.9% of neonates with EPLOS. Neonates requiring tracheostomy procedures are 36.8 times more likely to have EPLOS. The effect of clinical variables (diagnoses or procedures) on EPLOS is presented in Table 3. The tests of the assumption of independence of independent variables showed no collinearity. Pearson bivariate correlation showed a correlation of <0.4 among all independent variables. The Variance in Inflation Factor was <3 for all independent variables in the collinearity diagnostics of linear regression analysis.

Predicted_Logit = –10.268 + (1.643*BW_LessThan1000) + (0.475*Medicaid insurance) + (0.421*Race_Black) + (0.958*Childrens hospital) + (0.397*Region_South or Midwest) + (1.926*Major operating procedure) + (.630*PDA) + (0.407*RDS) + (0.366*Air leaks) + (0.345*Atelectasis) + (.379*IVH_Any) + (1.191*BPD) + (2.354*ECMO) + (3.606*Tracheostomy) + (0.976*NEC_Any) + (1.765*Gastrostomy) + (0.703*Ileostomy) + (1.459*Colostomy) + (0.825*Dialysis) – (0.373*Born in same hospital) – (1.178*Transient tachypnea of newborn)

Predicted_Probability = (2.718281828^Predicted_Logit)/(1 + 2.718281828^Predicted_Logit) [^ is exponent sign]

Discussion

This study describes the prevalence of EPLOS (6.2 per 10,000 discharges) in non-uncomplicated neonatal births in the US for the year 2012 based on data from HCUP's KID database. In this study, we were also able to describe for the first time, the clinical correlates and risk factors in neonates with a hospital stay ≥180 days versus neonates who had a shorter length of stay. Based on the data available for analysis, we derived a predictive model that would predict EPLOS.

The length of hospital stay for neonates is primarily dependent on the maturity of the infant at birth, with more immature infants needing longer hospital stays.[7] The average duration of the length of stay of extremely premature babies (23–28 weeks of gestation) during 1977 to 1986 was 95 days and was inversely proportional to gestational age.[8] A recent large multicenter study of infants, born ≤28 weeks gestation and admitted to one of 12 tertiary US centers between January 1998 and October 2001 showed that 18% of infants had a prolonged length of stay defined as discharge at >42 weeks post-menstrual age.[4] An audit of hospital admissions to children's hospital groups in Ireland showed that of all infants that needed a hospital stay of >1 month, there were 4.4% (19/436) that needed a hospital stay of >6 months with an average stay of 331 days.[9] They also showed a temporal trend towards longer hospital stays but no details of demographics or clinical correlates were

provided.[9] The only study published to date relating to extremely long hospitalization of neonates identified 680 infants from the KID-2003 data, that needed hospitalization of about 6 months (≥180 days) or longer.[1] In this study, no denominator was provided to estimate prevalence. Our results in this study based on KID-2012 data using the same definition (≥180 days) identified 812 neonates. The difference in patient number may not be due to a real change in prevalence but may be due to several factors such as changes in nature, number, or characteristics of hospitals contributing to the KID data. However, the prevalence rate of 6.2 per 10,000 neonates with non-uncomplicated births has not been reported heretofore and needs to be corroborated with data from other large databases such as the Vermont-Oxford Network.

Investigation of hospital length of stay to mortality has shown that the majority of neonatal mortality is within the first 1–2 weeks of birth.[8,10] A study by Catlin et al. using the KID 2003 data of 680 neonates who stayed ≥180 days reported a mortality rate of 16%.[1] In the present study, 812 neonates stayed for ≥180 days with a mortality rate of 10.9%. Although the mortality rate is high in babies with EPOLS, the total number of children dying after EPLOS is relatively small compared to all neonatal deaths. However, this small proportion of patients with EPLOS does occupy a significant proportion of ICU or hospital beds.[9,11]

In our study, the following factors were associated with at least a 2.5-fold or more increase in the unadjusted odds ratio for EPLOS – birth-weight <1000 gm (extremely low birth weight – ELBW); diagnosis of BPD, NEC or cardiopulmonary arrest; the need for a major surgical procedure, especially procedures for placement of colostomy, gastrostomy or tracheostomy. The highest unadjusted odds ratio was for tracheostomy (>36-fold increase). Other factors with lower than 2-fold increase in unadjusted odds ratios were black race, births in South or Midwest regions of the US, Medicaid insurance, diagnosis of PDA, diagnosis of respiratory problems such as RDS, pulmonary air-leaks or atelectasis, or the need for ileostomy surgical procedure.

Many morbidities have been shown to be higher in black neonates, but the issue of prolonged hospital length of stay has not been adequately studied in this population.[12] Higher hospital stays for conditions such as surgery for congenital heart disease have been noted in the black race compared to other racial groups in the US.[13] Therefore, the finding of increased EPLOS in blacks in this study was not unexpected. However, this finding needs to be interpreted with caution as the black race is highly correlated with other risk factors such as lower socioeconomic status and Medicaid insurance status.[13] Therefore in an analysis adjusted for these two variables, we found that black neonates have 1.5 times the odds of EPLOS than other neonates.

In our study, EPLOS was associated with multiple procedures and other neonatal comorbidities. In a study evaluating clinical correlates of prolonged length of stay (>42 week post-menstrual age), development of chronic lung disease, necrotizing enterocolitis requiring surgery, and two or more episodes of sepsis were found to be the major risk factors.[4]

Extreme prematurity or very low birth weight (VLBW, <1000 gm birth weight) are known to be associated with prolonged length of stay.[4] In most of these infants, the length of stay is a factor of the time needed for full maturity of physiological functions. For example, a 23-week gestational age infant needs 119 days (17 weeks) just to reach full maturity of 40 weeks. However, even within this group, some infants have other major morbidities that may prolong hospital stay by another 2 months or more. Among the respiratory morbidities that contribute to EPLOS, we found that BPD has the most impact (OR-3.4) with relatively minor effects of the need for mechanical ventilation (OR-1.3), RDS (OR-1.6), and pulmonary air leaks (OR-1.4) or atelectasis (OR-1.5). The effect of respiratory morbidities on prolonging hospital stay (>42 PMA) has been previously reported but their impact on EPLOS has not been previously described.[4] It is well recognized that the need for tracheostomy represents the highest level of intervention for the continuing care of neonates with respiratory compromise.[14,15] Therefore, it is not surprising that tracheostomy, in our study, had the highest unadjusted OR (36.8) for EPLOS. The median age of tracheostomy in our study cohort was 135 days, which is similar to the previous reports.[14,15]

Another contributor to prolonged length of stay that has been previously reported is complications resulting from NEC, especially the need for surgical procedures.[4,16] Even though the diagnosis of NEC increased the adjusted odds for EPLOS by 2.7-fold, the need for major surgical intervention of any kind (OR-6.8) or specific procedures such as ileostomy (OR-2.0), colostomy (OR-4.3) or gastrostomy (OR-5.8) made EPLOS even more likely. Other studies focused on outcomes of neonates with NEC have shown that the need for surgery and the type of surgery affect hospital length of stay; but there are no published reports on the impact of NEC on EPLOS.[17]

Although the proportion of neonates receiving cardiopulmonary resuscitation in the EPLOS group was significantly higher in univariate analysis, the adjusted odds ratio in regression analysis was not significantly different between both groups.

There are several limitations of our study and analyses. The use of a large administrative database, while providing a large sample size, also limits the availability of detailed clinical information. The accuracy and completeness of coding may vary, but the errors can be mitigated by the extensive sampling of data. Birthweight category was used as a proxy for the degree of immaturity of the neonate. Additionally, the temporal sequence of the clinical factors studied is lacking; therefore, we can only comment on the association but cannot infer whether the given factor was the cause or the result of EPLOS. Despite these limitations, the available data and the conducted analyses provide information that has significant implications for policy, planning, and practice of healthcare in the United States.

Conclusion

In conclusion, we have shown that neonates with EPLOS, though relatively few, have important implications for provisions of healthcare within NICUs and PICUs. Our study is one of the first attempts at characterizing the clinical correlates of this population of patients. More studies using other data sources need to be done to further define this group of neonates and develop strategies for their optimal management.

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References

1. Catlin A. Extremely long hospitalizations of newborns in the United States: Data, descriptions, dilemmas. J Perinatol 2006; 26(12):742–748. DOI: 10.1038/sj.jp.7211617.

2. Ounpraseuth S, Bronstein J, Gauss CH, et al. Time trends and payer differences in lengths of initial hospitalization for preterm infants, Arkansas, 2004 to 2010. Am J Perinatol 2015;32(1):33–42. DOI: 10.1055/s-0034-1373843.
3. Yu VY, Kinlay S, Orgill AA, et al. Outcome of very low birthweight infants who required prolonged hospitalization. Aust Paediatr J 1984;20(4):293–296. DOI: 10.1111/j.1440-1754.1984.tb00097.x.
4. Cotten CM, Oh W, McDonald S, et al. Prolonged hospital stay for extremely premature infants: Risk factors, center differences, and the impact of mortality on selecting a best-performing center. J Perinatol 2005;25(10):650–655. DOI: 10.1038/sj.jp.7211369.
5. Tyson JE, Younes N, Verter J, et al. Viability, morbidity, and resource use among newborns of 501- to 800-g birth weight. National Institute of Child Health and Human Development Neonatal Research Network. JAMA 1996;276(20):1645–1651. PMID: 8922450.
6. HCUP Kids' Inpatient Database (KID). https://hcup-us.ahrq.gov/kidoverview.jsp. Accessed on: 28 July 2023.
7. Manuck TA, Rice MM, Bailit JL, et al. Preterm neonatal morbidity and mortality by gestational age: A contemporary cohort. Am J Obstet Gynecol 2016;215(1):103.e1–103.e14. DOI: 10.1016/j.ajog.2016.01.004.
8. Yu VY, Shah V, Gomez JM, et al. Duration of hospitalization in extremely preterm infants. J Paediatr Child Health 1991;27(3):167–170. DOI: 10.1111/j.1440-1754.1991.tb00379.x.
9. McGlacken-Byrne SM, Geraghty L, Murphy JF. The Prolonged neonatal admission: Implications for our National Children's Hospital. Irish Medical Journal 2016;109(6):428. PMID: 27814445.
10. Meadow W, Lee G, Lin K, et al. Changes in mortality for extremely low birth weight infants in the 1990s: Implications for treatment decisions and resource use. Pediatrics 2004;113(5):1223–1229. DOI: 10.1542/peds.113.5.1223.
11. Marcin JP, Slonim AD, Pollack MM, et al. Long-stay patients in the pediatric intensive care unit. Crit Care Med 2001;29(3):652–657. DOI: 10.1097/00003246-200103000-00035.
12. DiBardino DJ, Pasquali SK, Hirsch JC, et al. Effect of sex and race on outcome in patients undergoing congenital heart surgery: An analysis of the society of thoracic surgeons congenital heart surgery database. Ann Thorac Surg 2012;94(6):2054–2059; discussion 2059–2060. DOI: 10.1016/j.athoracsur.2012.05.124.
13. Peterson JK, Chen Y, Nguyen DV, et al. Current trends in racial, ethnic, and healthcare disparities associated with pediatric cardiac surgery outcomes. Congenit Heart Dis 2017;12(4):520–532. DOI: 10.1111/chd.12475.
14. Wai KC, Keller RL, Lusk LA, et al. Trial of late surfactant study G: Characteristics of extremely low gestational age newborns undergoing tracheotomy: A secondary analysis of the trial of late surfactant randomized clinical trial. JAMA otolaryngology–head & neck surgery 2017;143(1):13–19. DOI: 10.1001/jamaoto.2016.2428.
15. Sisk EA, Kim TB, Schumacher R, et al. Tracheotomy in very low birth weight neonates: Indications and outcomes. Laryngoscope 2006, 116(6):928–933. DOI: 10.1097/01.MLG.0000214897.08822.14.
16. Berry MA, Shah PS, Brouillette RT, et al. Predictors of mortality and length of stay for neonates admitted to children's hospital neonatal intensive care units. J Perinatol 2008;28(4):297–302. DOI: 10.1038/sj.jp.7211904.
17. Zhang Y, Ortega G, Camp M, et al. Necrotizing enterocolitis requiring surgery: Outcomes by intestinal location of disease in 4371 infants. J Pediatr Surg 2011;46(8):1475–1481. DOI: 10.1016/j.jpedsurg.2011.03.005.

ORIGINAL RESEARCH

Epidemiological Study of Congenital Anomalies and Risk Factors in Newborn Infants at a Tertiary Care Hospital in Bangladesh

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Abstract

Background: Congenital anomalies are structural/functional defects in various organs (systems) that are apparent at birth. These anomalies originate prior to birth due to altered embryonic/fetal development. These are significant contributors to stillbirths/infant mortality over the world; the global variation in incidence is possibly related to regional differences in exposure to various etiological factors.

Objectives: To investigate the epidemiological profile of various congenital abnormalities in newborn infants in Bangladesh.

Materials and methods: This cross-sectional observational study was conducted in Central Medical College Hospital, Cumilla, Bangladesh. We recorded 100 consecutive congenital anomalies in 54,800 infant visits in our outpatient clinics. Data were collected from families after informed written consent.

Results: Out of the 100 infants with congenital anomalies, 69 infants were male and 31 were female (gender ratio 2.2:1). Congenital abnormalities were seen in the central nervous system (CNS) in 30, in 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 of them to pesticides. Twenty-two were born to mothers with diabetes, and 18 to mothers with hypertension.

Conclusion: We identified antenatal exposure to radiation, pesticides, maternal diabetes, and maternal hypertension as important predisposing factors for congenital anomalies. Congenital anomalies of the CNS and musculoskeletal/gastrointestinal defects were seen most frequently. Identification of risk factors can help in designing appropriate interventions.

Keywords: Ambiguous genitalia, Anencephaly, Atrial septal defect, Bangladesh, Birth-defect registries, Chromosomal abnormalities, Cleft palate, Cleft lip, talipes, Congenital anomalies, Congenital diaphragmatic hernia, Cytomegalovirus, Duodenal atresia, Embryonic development, Environmental contaminants, Epidemiological profile, Epidemiology, External teratogens, Fetal development, Folic acid deficiency, Global Burden of Disease study, Hydrocephalus, Hypospadias, ICD-9, ICD-10, Infant, Inguinal hernia, Iodine deficiency, Imperforate anus, Meningomyelocele, Micronutrients, Multifactorial transmission, Newborn, Patent ductus arteriosus, Pesticides, Polydactyly, Radiation, Rubella, Single-gene disorders, Spina bifida, Syndactyly, Tetralogy of Fallot, Tracheoesophageal fistula, Undescended testis, Ventricular septal defect.

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Highlights

- Congenital anomalies are structural/functional defects in various organs (systems) that are apparent at birth.
- In this study, we investigated the epidemiological profile of various congenital abnormalities in newborn infants in Bangladesh.
- We recorded 100 consecutive congenital anomalies in 54,800 infant visits in our outpatient clinics.
- Congenital anomalies of the central nervous system (CNS) and musculoskeletal/gastrointestinal defects were seen most frequently.
- Antenatal exposure to radiation, pesticides, maternal diabetes, and maternal hypertension as important predisposing factors for congenital anomalies. Identification of risk factors can help in designing appropriate interventions.

Introduction

Congenital birth defects include structural/functional abnormalities present since birth. An estimated 7.9 million infants are born all

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over the world with these conditions and are at risk of physical impairment after birth and perinatal mortality.[1,2] More than 90% of these defects are seen in low-resource regions that have very few birth-defect registries with detailed information.[3] Due to low awareness, inadequate diagnostic capabilities, under-presentation to medical institutions, and consequent under-reporting, the prevalence of congenital anomalies is considerably underestimated in these areas.[4]

We know that congenital malformations are caused by a variety of factors, including single-gene disorders, chromosomal abnormalities, multifactorial transmission, external teratogens, and micronutrient shortages.[5] Maternal infections such as rubella and cytomegalovirus; diabetes mellitus; iodine and folic acid deficiencies; exposure to medicinal and recreational drugs such as alcohol and tobacco; certain environmental contaminants; and radiation are important than other important predisposing factors.[6] In the 2015 Global Burden of Disease study, congenital abnormalities accounted for 11% of infant deaths. These were the sixth most common cause of mortality in under-5-years-old children.[7] These issues can also cause long-term impairment, affecting society, families, healthcare systems, and individuals.[8] Overall, 1 in 40 (2.5%) infants are born with one or more detectable deformities; nearly half of these cases were born with 1 deformity, whereas the other half had more than one.[9]

Regular prenatal assessment and directed care can reduce perinatal mortality.[10] Malformations are broadly classified into the following three types: (A) Single deformity; (B) multiple deformities with a recognizable pattern (syndrome); and (C) multiple malformations without an identifiable pattern. Minor malformations are structural defects that may not alter clinical function but may have esthetic implications, such as preauricular tags. Major malformations, such as cleft lip and palate, or ventricular septal defects, have a substantial impact on function or social acceptability.[11]

Congenital birth defects can often present as syndromes, where several pathophysiologically connected abnormalities originate in a shared cause.[11] Organ development is crucial throughout the first trimester, especially between the 3–8-week period of pregnancy. During this time, any type of injury might induce multiple congenital abnormalities.[12] In many regions, perinatal infections, or macro- and micronutrient malnutrition might increase the risk of birth malformations; up to 94% of all birth defects may be seen in such settings[5,13] In some regions, dietary supplementation with folic acid has reduced the prevalence of neural tube abnormalities. Genetic factors may also be at play; the incidence of congenital deformities may be higher in low-birth-weight (LBW) infants and in those born from consanguineous marriages.[14] The risk of congenital malformations increases with advanced maternal age, exposure to certain drugs, teratogens, radiation, maternal illnesses, smoking, and alcohol consumption.[15] The incidence and type of congenital abnormalities in various geographic regions may also change with ethnicity, socioeconomic level, diet, environmental variables, maternal age, and lifestyle.[16]

There is a need for further work to identify the cause and possible interventions to prevent congenital anomalies. An improved understanding of the epidemiology of birth abnormalities can help design directed efforts to prevent these defects. In this study, we took the first steps to screen for the prevalence of different congenital anomalies in infants in our community.

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Materials and Methods

Study Design and Setting

This cross-sectional observational study was performed at the outpatient clinics in the Central Medical College Hospital in Cumilla, Bangladesh during the period from June 2019 to June 2022. The approval of the ethics review committee was obtained prior to the initiation of the study. Parents' consent was obtained prior to enrollment for data collection, and strict confidentiality was maintained while processing the data and creating the reports by eliminating all personal identifiers. Data were collected from the first 100 patients with congenital anomalies who presented to the outpatient clinics during the period from June 2019 to June 2022. The total number of patients seen during the study period was 54,800. Various anomalies were recorded based on physical examinations of the infants. Information such as maternal parity, gestational age, education, social standing, family history of congenital malformations, illness in a sibling, cousin marriages, relationships with cousins, concomitant medical conditions, industrial exposure, and viral infections in the first trimester were also noted. The frequency and pattern of anomalies, male-to-female ratio, and the severity of congenital malformations were noted as outcome variables.

Statistical Analysis

Microsoft Excel and statistical package for the social sciences (SPSS) software, version 25.0, were used for data entry and analysis. Sociodemographic information, risk variables, and congenital malformations were all summarized using descriptive statistics. Qualitative data are reported as frequency and percentage, whereas quantitative data are given as mean and standard deviation. Comparisons were made using tabulation and graphic displays such as tables and bar diagrams.

Results and Observation

Out of the 54,800 patients seen during the study period, 100 patients were identified with congenital anomalies. The recorded anomalies encompassed a range of conditions, including cardiovascular, musculoskeletal, and neurological anomalies, among others. The calculated percentage of patients with congenital anomalies was approximately 0.1825%.

Table 1 shows demographic characteristics. Gender distribution of the neonates revealed that out of 100 cases, 69.0% of patients were male and 31.0% were female. Male–female ratio was 2.2:1. A total of 57% of the respondents came from urban areas. Notably, 67% of them had a history of hospital delivery.

Evaluation of maternal risk factors showed that 38.0% of the patient had been exposed to antenatal radiation, 35% had exposure

to pesticides, 22% were diagnosed to have had diabetes, and 18% had hypertensive disorders (Table 2).

Table 3 shows the prevalence of different types of congenital malformations. Cleft lip/palate was detected in 13 patients; talipes in 12, polydactyly in 9, hypospadias in 8, and meningomyelocele in five patients. Other common malformations were atrial septal defect, inguinal hernia, ventricular septal defect, imperforate anus, duodenal atresia, tracheoesophageal fistula, anencephaly, syndactyly, etc.

The pattern of congenital abnormalities present in neonates is summarized in Figure 1. Anomalies were noted most frequently in the CNS (30%), followed by the musculoskeletal system (24%), gastrointestinal system (24%), cardiovascular system (CVS) (13%), and the genitourinary system (9%).

Table 4 shows the relationship between congenital abnormalities and maternal and fetal factors. It was evident that male subjects are commonly affected by CNS and gastrointestinal anomalies, females are commonly affected by musculoskeletal system deformities. Maternal parity is an important predictor of congenital anomalies. Infants born to primigravidae women showed more anomalies in the central nervous and genitourinary systems. The CVS malformations were more common in multiparous women. Births in urban areas showed more CVS and genitourinary system anomalies, whereas gastrointestinal system

Table 1: Demographic characteristics of the newborn ($n = 100$)

	Frequency		
Variables	*Male (n, %)*	*Female (n, %)*	*Total*
Gender distribution	69	31	100
Residence			
Rural	29 (42.0%)	14 (45.1%)	43
Urban	40 (57.9%)	17 (54.8%)	57
Place of delivery			
Home	21 (30.4%)	10 (32.2%)	31
Hospital	48 (69.5%)	21 (67.7%)	69
Mode of delivery			
NVD	43 (62.3%)	19 (61.2%)	62
CS	26 (37.6%)	12 (38.7%)	38

CS, cesarean section; NVD, normal vaginal delivery

Table 2: Maternal risk factors ($n = 100$)

Variables	*Number of patients*
Exposed to antenatal radiation	38
Exposure to pesticides	35
Maternal diabetes	22
Maternal hypertensive disorder	18
Prior history of antiseizure medication	7
Poor nutritional status	27

Table 3: Different types of congenital malformations observed in neonates ($n = 100$)

Clinical diagnosis	*Number of patients*
Cleft palate and cleft lip	13
Talipes	12
Ventricular septal defect	5
Patent ductus arteriosus	4
Tetralogy of Fallot	3
Congenital diaphragmatic hernia	2
Anencephaly	3
Tracheoesophageal fistula	4
Polydactyly	9
Meningomyelocele	5
Hydrocephalus	5
Hypospadias	8
Inguinal hernia	5
Imperforate anus	5
Syndactyly	3
Duodenal atresia	4
Undescended testis	2
Atrial septal defect	5
Spina bifida	2
Ambiguous genitalia	1

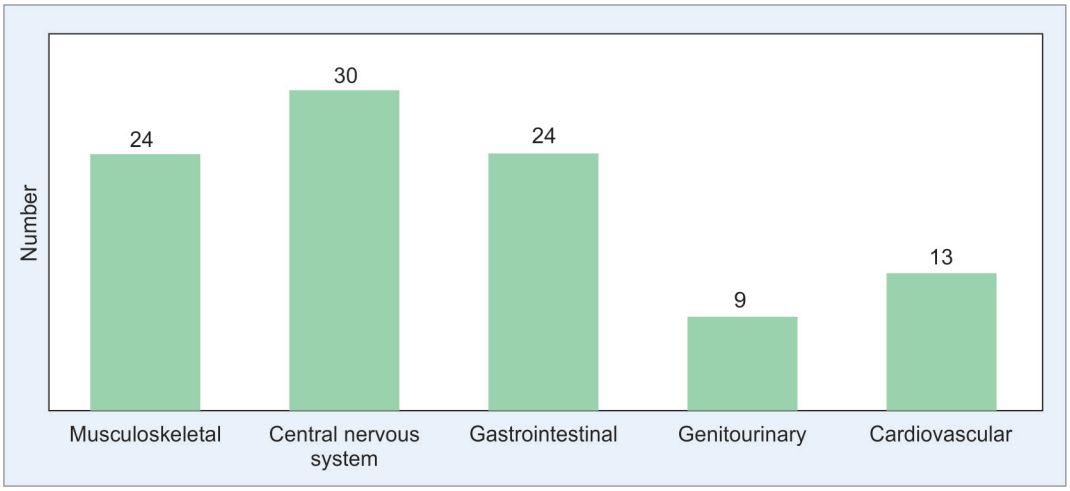

Fig. 1: Distribution of the pattern of congenital anomalies ($n = 100$)

Table 4: Congenital malformations in relation to maternal and fetal factors ($n = 100$)

	CNS	*Musculoskeletal system*	*Gastrointestinal system*	*CVS*	*Genitourinary system*	*Total*
Newborn gender						
Male	21	11	19	9	9	69
Female	9	13	5	4	0	31
Maternal history						
Primigravida	26	13	14	6	6	65
Multigravida	4	11	10	7	3	35
Residence						
Urban	17	14	11	8	7	57
Rural	13	10	13	5	2	43
Exposed to antenatal radiation						
Yes	17	15	5	0	1	38
No	13	9	19	13	8	62
Exposure to pesticides						
Yes	14	11	3	5	2	35
No	16	13	21	8	7	65

anomalies were seen more frequently in rural regions. Maternal exposure to radiation and pesticides were important risk factors for congenital malformations.

Discussion

Out of 100 cases in this study, 69% were male and 31% were female (gender ratio was 2.2:1). A total of 57% of responders were from urban areas; 69% of our patients had a history of hospital delivery. Most (62%) had been delivered vaginally. Our study differed from other cohorts, where the gender ratios were relatively similar. In a screening study of 50 patients, 54% were males with a gender ratio of 1.2:1.[5] In a larger cohort of 3,210 admissions, 226 newborns (7%) had congenital malformations.[11] In this study, 130 (57.5%) were male patients and 96 (42.5%) were female patients. Another study with congenital anomalies in 8.4% showed 52 (54.1%) males and 44 (45.8%) females.[13] These studies show a wide variation in geographic distribution, cultural influences, and socioeconomic conditions.

We recorded a high frequency of cleft lip and palate, talipes, polydactyly, hypospadias, and meningomyelocele. Other common malformations were an atrial septal defect, inguinal hernia, ventricular septal defect, imperforate anus, duodenal atresia, tracheoesophageal fistula, anencephaly, and syndactyly. Overall, the CNS (30%) was the most often afflicted system in this study, followed by the musculoskeletal system (24%), gastrointestinal system (24%), CVS (13%), and genitourinary system (9%) of total abnormalities. However, a review of the literature shows considerable variability between cohorts. One study showed a high frequency of neurological anomalies (2.3%); anencephaly (11.5%), spina bifida (11.5%), and meningocele (12.3%). Clubfoot (7.7%), omphalocele (3.8%), and gastroschisis (3.8%) were the most prevalent musculoskeletal abnormalities (3.1%). The most prevalent gastrointestinal tract abnormalities were esophageal atresia (4.6%), Pierre–Robin syndrome (4.6%), cleft lip (18.5%), and cleft palate (16.2%).[1] In another cohort, the circulatory system was most frequently implicated, followed by the neurological and musculoskeletal systems.[16] Another study showed a relatively large number of neural tube defects but also two with Down's syndrome, one with a facial abnormality, and three with congenital cardiac disease.[17]

Many risk factors were associated with congenital anomalies. In our cohort, parental consanguinity, maternal undernutrition, obesity, a history of abnormalities in the family, LBW, and preterm birth were associated with a higher prevalence of congenital malformation with non-significant differences for maternal age and neonate sex.[5] Evaluation of maternal history and risk factors, 38% of the mothers had been exposed to antenatal radiation and 35% to pesticides. Male infants were more frequently affected by CNS and gastrointestinal anomalies, unlike females who had a higher incidence of musculoskeletal system deformities. Interestingly, maternal parity was also an important predictor of specific congenital anomalies. Primigravidae women more frequently carried fetuses with CNS and genitourinary system anomalies. Multiparous mothers frequently gave birth to fetuses with CVS malformations. On the evaluation of residence, infants born in urban areas frequently showed cardiovascular and genitourinary system anomalies, unlike the higher numbers of gastrointestinal defects seen in rural areas.

One study focused on maternal and infant risk factors for congenital malformations. Although not statistically significant, low or high maternal ages (<20 or >35 years) were associated with a higher risk of congenital deformities.[18] Parental consanguinity was an important risk factor. Maternal malnutrition and obesity were both related to an increase in congenital malformations in their fetuses. Fetal gender was not an important determinant. Prematurity and LBW increased the risk of congenital abnormalities.[5] Birth weight, maternal diseases, inadequate prenatal care, smoking, prior abortion, past congenital abnormalities, and consanguinity have been associated with congenital malformations.[19] Circulatory problems appear to be more prevalent when compared to previous research, which is important to know because many of these infants can be salvaged with timely intervention.[20] Public education about various risk factors, maternal health, and the need for early prenatal identification and therapy can help.[21] Timely intervention in known risk factors such as folic acid or iodine deficiency may

help, although more work is needed to confirm the size of the therapeutic impact.[22,23] There is a need for standardized systems for categorizing birth defects (such as the International Classification of Diseases [ICD]-9 or ICD-10) so that data can be compared across various geographical regions and over time.[24] The Global Burden of Disease Study and WHO reviews show that up to 17–42% of infant mortality may be related to congenital anomalies.[25] There is considerable variability in the incidence of various congenital abnormalities in different regions, so the efforts need to be directed more precisely.

Conclusion

The CNS and musculoskeletal issues are the most common congenital defects. Congenital anomalies were more common when the mother had a history of exposure to radiation, chemicals, paternal consanguinity, and diseases. Long-term disabilities resulting from congenital defects may have a considerable effect on a child's health and development as well as on families, healthcare systems, and on society as a whole. Proper evaluation and appropriate treatment prevent the burden of congenital anomalies.

Authors' Contributions

Md. Zahirul Alam designed the study and supervised the project; Minhazur Rahman Tareq and Dildar Sultana Shapna participated in patients' enrollment. Akhil Maheshwari helped in preparing the draft and confirmed the manuscript's accuracy; Mainul Hasan Sohel and Kawser Hamid performed data analysis; Md. Mahabubul Islam Majumder contributed significantly and took part in the enrolling of patients. The final version of the work has been reviewed and approved by all authors.

Data Availability Statement

Data will be made available on request.

Acknowledgments

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Ethical Approval

The Central Medical College's ethics review committee granted its approval. Patients were informed of the experiment and given their consent prior to the data collection. The strictest confidentiality was upheld while processing the data and creating the report by eliminating names and other personal identifiers.

References

1. Ameen SK, Alalaf SK, Shabila NP. Pattern of congenital anomalies at birth and their correlations with maternal characteristics in the maternity teaching hospital, Erbil city, Iraq. BMC Pregnancy Childbirth 2018;18(1):1–8. DOI: 10.1186/s12884-018-2141-2.
2. Ndibazza J, Lule S, Nampijja M, et al. A description of congenital anomalies among infants in Entebbe, Uganda. Birth Defects Res A Clin Mol Teratol 2011;91(9):857–861. DOI: 10.1002/bdra.20838.
3. Sitkin NA, Ozgediz D, Donkor P, et al. Congenital anomalies in low- and middle-income countries: The unborn child of global surgery. World J Surg 2015;39(1):36–40. DOI: 10.1007/s00268-014-2714-9
4. Lawal TA, Yusuf OB, Fatiregun AA. Knowledge of birth defects among nursing mothers in a developing country. Afr Health Sci 2015;15(1):180–187. DOI: 10.4314/ahs.v15i1.24.
5. El Koumi MA, al Banna EA, Lebda I. Pattern of congenital anomalies in newborn: A hospital-based study. Pediatr Rep 2013;5(1):20–23. DOI: 10.4081/pr.2013.e5.
6. World Health Organization. Birth defects. Available at: https://www.who.int/news-room/fact-sheets/detail/birth-defects. Accessed on: 13 August 2023.
7. Wang H, Bhutta ZA, Coates MM, et al. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980–2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1725. DOI: 10.1016/S0140-6736(16)31575-6.
8. Kumar J, Saini SS, Sundaram V, et al. Prevalence & spectrum of congenital anomalies at a tertiary care centre in north India over 20 years (1998–2017). Indian J Med Res 2021;154(3):483. DOI: 10.4103/ijmr.IJMR_1414_19.
9. Gillani S, Kazmi NHS, Najeeb S, et al. Frequencies of congenital anomalies among newborns admitted in nursery of Ayub Teaching Hospital Abbottabad, Pakistan. J Ayub Med Coll Abbottabad 2011;23(1):117–121. PMID: 22830164.
10. Ahmed W, Dey D, Farid R. Prevalence and pattern of congenital Anomalies and Its Outcome at Chattagram Maa-O-Shishu General Hospital. Chattagram Maa-O-Shishu Hospital Med College J 2017;16(1):22–25. DOI: 10.3329/cmoshmcj.v16i1.34981.
11. Hussain S, Asghar I, Sabir M-u-D, et al. Prevalence and pattern of congenital malformations among neonates in the neonatal unit of a teaching hospital. J Pak Med Assoc 2014;64(6):629–634. PMID: 25252479.
12. Obu HA, Chinawa JM, Uleanya ND, et al. Congenital malformations among newborns admitted in the neonatal unit of a tertiary hospital in Enugu, South–East Nigeria: A retrospective study. BMC Res Notes 2012;5(1):1–6. DOI: 10.1186/1756-0500-5-177. Corpus ID: 51843039.
13. Bastola R, Gurung R, Bastola BS, et al. Pattern and prevalence of congenital birth defect among neonates admitted to special newborn care unit (SNCU) of Pokhara Academy of Health Science (PAHS), Nepal J Biol Med Res 2017;2(1):1. Corpus ID: 51843039.
14. Tayebi N, Yazdani K, Naghshin N. The prevalence of congenital malformations and its correlation with consanguineous marriages. Oman Med J 2010;25(1):37–40. DOI: 10.5001/omj.2010.9.
15. Akinmoladun JA, Famosaya ID, Ogbole GI. Pattern and distribution of prenatally diagnosed congenital anomalies among high risk pregnant women in Ibadan, South Western Nigeria. Pan Afr Med J 2022;41:66. DOI: 10.11604/pamj.2022.41.66.28874.
16. Jain SR, Naik JD, Dhakne BR, et al. Pattern of congenital malformations in newborn: A hospital-based study. Int J Res Med Sci 2016;4(2):524–528. DOI: 10.18203/2320-6012.ijrms20160308.
17. Feldkamp ML, Carey JC, Byrne JLB, et al. Etiology and clinical presentation of birth defects: Population based study. BMJ 2017;357:j2249. DOI: 10.1136/bmj.j2249.
18. Sarkar S, Patra C, Dasgupta MK, et al. Prevalence of congenital anomalies in neonates and associated risk factors in a tertiary care hospital in Eastern India. J Clin Neonatol 2013;2(3):131–134. DOI: 10.4103/2249-4847.119998.
19. Abebe S, Gebru G, Amenu D, et al. Risk factors associated with congenital anomalies among newborns in southwestern Ethiopia: A case–control study. PLoS One 2021;16(1):e0245915. DOI: 10.1371/journal.pone.0245915.
20. Biswas A, Anderson R, Doraiswamy S, et al. Timely referral saves the lives of mothers and newborns: Midwifery led continuum of care in marginalized teagarden communities – A qualitative case study in Bangladesh 2018;7:365. DOI: 10.12688/f1000research.13605.1.

21. Bashir A. Congenital malformations: Prenatal diagnosis and management. Am J Biomed Sci Res 2019;2(1):24–27. DOI: 10.34297/AJBSR.2019.02.000565.
22. Higurashi M, Iijima K, Sugimoto Y, et al. The birth prevalence of malformation syndromes in Tokyo infants: A survey of 14,430 newborn infants. Am J Med Genet 1980;6(3):189–194. DOI: 10.1002/ajmg.1320060303.
23. Rasmussen SA, Olney RS, Holmes LB, et al. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol 2003;67(3):193–201. DOI: 10.1002/bdra.10012.
24. Rasmussen SA, Moore CA. Effective coding in birth defects surveillance. Teratology 2001;64(Suppl. 1):S3–S7. DOI: 10.1002/tera.1077.
25. Boyle B, Addor MC, Arriola L, et al. Estimating global burden of disease due to congenital anomaly: An analysis of European data. Arch Dis Child Fetal Neonatal Ed 2018;103(1):F22–F28. DOI: 10.1136/archdischild-2016-311845.

ORIGINAL RESEARCH

Clinical Correlates of Cholestasis in Preterm Infants with Surgical Necrotizing Enterocolitis

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Abstract

Background: We sought to investigate the clinical determinants and outcomes of cholestasis in preterm infants with surgical necrotizing enterocolitis (sNEC).

Methods: Retrospective comparison of clinical information in preterm infants who developed cholestasis vs those who did not.

Results: Sixty-two (62/91, 68.1%) infants with NEC developed cholestasis at any time following the onset of illness. Cholestasis was seen more frequently in those who had received ionotropic support at 24 hours following sNEC diagnosis (87.1% vs 58.6%; $p = 0.002$), had higher mean C-reactive protein levels 2 weeks after NEC diagnosis ($p = 0.009$), had blood culture-positive sepsis [25 (40.3%) vs 4 (13.8%); $p = 0.011$], received parenteral nutrition (PN) for longer durations (108.4 ± 56.63 days vs 97.56 ± 56.05 days; $p = 0.007$), had higher weight-for-length z scores at 36 weeks' postmenstrual age [–1.0 (–1.73, –0.12) vs –1.32 (–1.76, –0.76); $p = 0.025$], had a longer length of hospital stay (153.7 ± 77.57 days vs 112.51 ± 85.22 days; $p = 0.024$), had intestinal failure more often (61% vs 25.0%, $p = 0.003$), had more surgical complications (50% vs 27.6%; $p = 0.044$), and had >1 complication (21% vs 3.4%; $p = 0.031$). Using linear regression, the number of days after surgery when feeds could be started [OR 15.4; confidence interval (CI) 3.71, 27.13; $p = 0.009$] and the postoperative ileus duration (OR 11.9, CI 1.1, 22.8; $p = 0.03$) were independently associated with direct bilirubin between 2 and 5 mg/dL (mild–moderate cholestasis) at 2 months of age. The duration of PN was independently associated with direct bilirubin >5 mg/dL (severe cholestasis) at 2 months of age in these patients.

Conclusion: Cholestasis was seen in 68% of infants following surgical NEC. The most likely contributive factors are intestinal failure and subsequent PN dependence for longer periods. Our data suggest that identification and prevention of risk factors such as sepsis and surgical complications and early feeds following NEC surgery may improve outcomes.

Keywords: Anthropometric, Adhesions, Bell's criteria, Cholestasis, Farnesoid X, Fenton growth, Fish oil-containing lipid emulsion, Fistula, Ileocecal valve, Intralipids, Infant, Intestinal failure, Liver X receptors, Logistic regression, Necrotizing enterocolitis, Neonate, Outcome, Parenteral nutrition, Perforations, Pneumoperitoneum, Pneumatosis, Portal venous gas, Preterm, Premature, Soybean oil–medium chain triglycerides–olive oil–fish oil, Surgical site infection, Stricture, Term-equivalent age, Weight-for-length, Wound dehiscence, z-scores.

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Key Points

- Necrotizing enterocolitis is a major cause of morbidity and mortality in premature infants.
- In a retrospective study, we reviewed the medical records of 91 infants to identify the clinical determinants and outcomes of cholestasis in preterm infants with surgical necrotizing enterocolitis. Sixty-two (62/91, 68.1%) infants with NEC developed cholestasis at any time following the onset of illness.
- Cholestasis was seen more frequently in those who had received ionotropic support at 24 hours following the diagnosis of surgical NEC, had higher C-reactive protein levels, 2 weeks after the diagnosis of NEC, had blood culture-positive sepsis, received parenteral nutrition for longer durations, had higher weight-for-length z-scores at 36 weeks postmenstrual age, had a longer length of hospital stay, had intestinal failure, and had more surgical complications.
- Cholestasis is seen in most infants recovering from surgical NEC. Intestinal failure and subsequent dependence on parenteral nutrition for long periods are important predictors.

Introduction

Necrotizing enterocolitis (NEC) affects 6–10% of very-low-birth-weight premature infants[1,2] and surgical disease remains a leading

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cause of death in almost 40–50% of these patients.[3] Nearly 13–45% of infants with surgical NEC develop intestinal failure,[4,5] which is associated with prolonged hospitalization and higher economic burden.[6]

Short bowel syndrome secondary to surgical NEC in preterm infants is associated with a longer hospital stay, growth failure, cholestasis, and liver injury.[7] Cholestasis is frequently seen in these infants, affecting 42–85%.[8–11] Bowel length and preservation of the ileocecal valve are the major predictors of weaning from PN.[5] The duration of parenteral nutrition (PN) following surgical NEC is an independent clinical risk factor for cholestasis.[8] Thus, while these are well-known risk factors for cholestasis following surgical necrotizing enterocolitis (sNEC), other clinical predictors of cholestasis after sNEC are not well-studied. African American infants show a higher prevalence of surgical NEC and its associated mortality,[12] although the clinical predictors of cholestasis in African American preterm infants with surgical NEC need further study.

We have previously published systemic morbidities and clinical outcomes in preterm infants with sNEC.[13–17] In these reports, we investigated the clinical determinants and outcomes of cholestasis in these patients. We compared clinical information in preterm infants with and without cholestasis in a sNEC cohort. The associations between clinical factors and outcomes were assessed with univariate and multivariable logistic regression analyses. We now compared the clinical determinants and outcomes of cholestasis in preterm infants with sNEC.

Methods

Study Design

The study was conducted at the University of Mississippi Medical Center (UMMC) Neonatal Intensive Care Unit, a Level IV unit with 900–1000 admissions yearly and referrals from the entire state. The UMMC Institutional Review Board approved the study with a waiver of informed parental consent. All infants admitted between January 2013 and December 31, 2018, with a diagnosis of NEC (Bell stage III), were included in the study.[18] Neonates diagnosed with medical NEC, isolated ileal perforation, kidney anomalies, congenital heart disease, and intestinal atresia were excluded from the analysis.

Clinical Information

Demographic data collected included birth weight (BW), gestational age (GA), appropriate for GA status (AGA), race, sex, mode of delivery, outborn status (referred from other hospitals), and Apgar score ≤6 at 5 minutes. Maternal information collected included clinically diagnosed chorioamnionitis, antenatal steroids, and pregnancy-induced hypertension (PIH). Neonatal data included patent ductus arteriosus (PDA), respiratory support, inotrope (dopamine) use 24 hours after NEC onset, hematological information, ibuprofen/indomethacin treatment (before NEC), and frequency of cholestasis (direct bilirubin >2 mg/dL) at any time after NEC diagnosis. Sepsis-related variables included blood culture-proven sepsis at NEC onset and duration/type of antibiotics.

NEC Information

The diagnosis of NEC was based on abdominal X-ray findings, including portal venous gas, pneumatosis, and pneumoperitoneum and the cases were classified using Bell's criteria.[18] Data on the age at NEC diagnosis and frequency of Bell stage III/surgical NEC were compiled.[18,19]

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Histopathological Evaluation

Hematoxylin- and eosin-stained resected intestinal tissue sections were evaluated by a team of a board-certified gastrointestinal pathologists and a senior pathology trainee for necrosis, inflammation, hemorrhage, and reparative changes.[20]

Cholestasis

We recorded the data on cholestasis (direct bilirubin >2 mg/dL) at the time of NEC onset[21] and every week up to 2 months thereafter. We defined mild–moderate cholestasis as a direct bilirubin between 2 and 5 mg/dL. Severe cholestasis was defined as a direct bilirubin >5 mg/dL.

Postoperative and Outcome Data

We also recorded information on intestinal failure (parenteral nutrition >90 days) and surgical morbidity. Postoperative information such as postoperative ileus days (defined as the number of days infants were NPO after bowel surgery), time to reach full enteral feeds (≥120 mL/kg/day), total parenteral nutrition days, length of stay, and hospital mortality were measured. We defined mortality as death due to any reason before hospital discharge. Surgical morbidity/complications were defined as stricture, fistula, wound dehiscence, surgical site infection (including abscess), adhesions, and perforations. If an infant had more than one abovementioned complication at any time following NEC were grouped into more than 1 surgical complication cohort.

Somatic Growth

We tracked anthropometric variables, including weight, height, weight-for-length, head circumference, and respective z-scores using sex-specific Fenton growth charts at 36 weeks postmenstrual age.

Brain Growth

Per our hospital practice, we obtained brain MRI without contrast in all VLBW infants when clinically indicated at a corrected age of 36 weeks or before discharge. The most common reason for not obtaining MRI was death or transfer to a different center for bowel transplantation. All term-equivalent age (TEA) MRI scans were scored independently by two pediatric neuroradiologists who were unaware of the initial MRI reading and the diagnosis of cholestasis. We used a 8-scale scoring system for white and gray matter injury developed by Woodward et al.[22]

Statistical Methods

Demographic and clinical information in preterm infants with and without cholestasis in the surgical NEC cohort were compared.

Table 1: Clinical information of surgical NEC infants with and without cholestasis

	N	*Total (N = 91)*	*No cholestasis (N = 29)*	*Cholestasis (N = 62)*	*p-value*
Prenatal information					
Chronic hypertension, *n* (%)	75	12 (16.0)	4 (17.4)	8 (15.4)	0.83
Antenatal steroid use, *n* (%)	88	65 (73.9)	18 (66.7)	47 (77.0)	0.31
Infant information					
Gestational age (weeks, mean ± SD)	91	27.2 (4.0)	27.8 (4.0)	27.0 (4.0)	0.35
Birth weight (gm, mean ± SD)	91	1011.0 (563.9)	1112.4 (610.3)	963.6 (539.4)	0.24
Male, *n* (%)	91	63 (69.2)	22 (79.5)	41 (66.1)	0.35
Ethnicity, *n* (%)	91				0.23
African American		21 (23.1)	10 (34.5)	11 (17.7)	
Caucasian		66 (72.5)	48 (77.4)	18 (62.1)	
Latino		2 (2.2)	1 (3.4)	1 (1.6)	
Other		2(2.2)	0 (0.0)	2 (3.2)	
C-section, *n* (%)	91	62 (68.1)	22 (75.9)	40 (64.5)	0.28
Out born, *n* (%)	91	62 (68.1)	18 (62.1)	44 (71.0)	0.40
Ventilation following NEC, *n* (%)	88				0.08
Intubation		78 (88.6)	23 (82.1)	55 (91.7)	
CPAP		7 (8.0)	2 (7.1)	5 (8.3)	
High flow		1 (1.1)	1 (3.6)	0 (0.0)	
Room air		2 (2.3)	2 (7.1)	0 (0.0)	
Patent ductus arteriosus, *n* (%)	91	57 (62.6)	15 (51.7)	42 (67.7)	0.14
Pressor support 24 h after NEC, *n* (%)	91	71 (78.0)	17 (58.6)	54 (87.1)	***0.002***
Indomethacin use, *n* (%)	91	12 (13.2)	1 (3.4)	11 (17.7)	0.06

The presence of bold and italic values signified $p < 0.05$

Continuous data were summarized as median (1st quartile, 3rd quartile) with Mann–Whitney *U* or Kruskal–Wallis tests for differences. Categorical data were summarized as numerical counts and percentages. Variability was quantified using standard deviations (SDs). Group differences were tested with Chi-squared or Fisher's exact tests. Variables with significant association (*p*-value less than 0.05) in univariate analysis were candidates for the multivariable models.

A multinomial logistic regression was conducted to assess the potential risk of cholestasis associated with the following variables: pressor support 24 hours after NEC, indomethacin use, time to surgery from NEC onset, TPN days, postoperative ileus days, and time to reach full feeds. Simple linear regression was conducted to assess the predictors for persistent cholestasis at 2 months following the surgical NEC with the following continuous variables: length of stay, time to reach full feeds, TPN days, and length of postoperative ileus. A generalized linear regression using a binomial distribution was conducted on mortality, time to reach full feeds, intestinal failure, surgical complication, a single-surgical complication, more than one surgical complication, and white matter injury. A p-value < 0.05 was considered statistically significant for all the analyses. All analyses were performed in SPSS and SAS 9.4.

Results

Risk Factors for Cholestasis after sNEC and Outcomes of Cholestasis in sNEC

In our cohort of 91 infants with surgical NEC, 62 (62/91, 68.1%) infants developed cholestasis at some time following the onset of NEC. The patients had a gestational age of 27.2 ± 4 weeks (mean ± SD) and birth weight of 1011 ± 563.9 gms. The majority were male infants (63/91, 69.2%) and of African American ancestry (66/91, 72.5%). Infants with cholestasis received inotropic support more frequently at 24 hours following surgical NEC (87.1% vs 58.6%; $p = 0.002$), had higher mean CRP levels at 2 weeks after the onset of surgical NEC (6.26 ± 5.70 vs 2.23 ± 1.57; $p = 0.009$), and had positive blood culture sepsis more often than those without cholestasis (25 (40.3%) vs 4 (13.8%), $p = 0.011$).

Infants who developed cholestasis received parenteral nutrition (PN) for longer periods (108.4 ± 56.6 days vs 97.56 ± 56 days; $p = 0.007$), had higher weight for length z-scores at 36 weeks postmenstrual age [–1.0 (–1.73, –0.12) vs –1.32 (–1.76, –0.76); $p = 0.025$], and had a longer length of hospital stay (153.7 ± 77.5 days vs 112.51 ± 85 days; $p = 0.024$) when compared with infants with no cholestasis. Infants with cholestasis developed intestinal failure more often (35 (61%) p 6 (25%), $p = 0.003$), had more surgical complications following NEC (31 (50%) vs 8 (27.6%), $p = 0.044$), and had >1 complication (13 (21%) vs 1 (3.4%), $p = 0.031$) than those without cholestasis. The data are summarized in Tables 1 to 3. There was no significant difference in intestinal histopathology, length of bowel resected, and the white matter injury on the brain MRI nor mortality in the two groups.

On multivariable logistic regression modeling, the duration of PN (OR 1.026; CI 1.004–1.050; $p = 0.0235$) and the need for inotropic support for 24 hours following NEC (OR 6.68; CI 1.374–32.562; $p = 0.0186$) were independent risk factors for cholestasis. The data are summarized in Table 4.

Table 2: NEC disease features in infants with and without cholestasis

	N	*Total (N = 91)*	*No cholestasis (N = 29)*	*Cholestasis (N = 62)*	*p-value*
NEC disease features					
NEC age of onset (days, median ± SD)	91	17.2 (15.6)	14.7 (15.4)	18.4 (15.7)	0.30
Time to surgery from NEC onset (hours, mean ± SD)	91	243.3 (507.8)	124.0 (407.1)	299.1 (542.6)	0.13
Radiologic findings, *n* (%)	91				
Pneumatosis		51 (56.0)	18 (62.1)	33 (53.2)	0.43
Portal venous gas		6 (6.6)	0 (0.0)	6 (9.7)	0.08
Pneumoperitoneum		45 (49.5)	17 (58.6)	28 (45.2)	0.23
Penrose drain, *n* (%)	87	24 (39.1)	7 (25.9)	27 (45.0)	0.09
Presence of ileocecal valve, *n* (%)	90	61 (67.8)	22 (75.9)	39 (63.9)	0.26
Region of bowel resected *n* (%)	88				0.50
Small bowel		56 (63.6)	19 (70.4)	37 (60.7)	
Large bowel		2 (2.3)	0 (0.0)	2 (3.3)	
Combined large and small bowel		30 (34.1)	8 (29.6)	22 (36.1)	
Length of bowel resected (cm, mean ± SD)	91	23.3 (24.2)	23.6 (26.6)	23.2 (23.2)	0.94
Necrosis grade (mean ± SD)	91	1.6 (1.3)	1.6 (1.3)	1.6 (1.3)	0.81
Inflammation grade (mean ± SD)	91	1.9 (1.0)	1.7 (1.0)	2.0 (1.0)	0.09
Hemorrhage grade (mean ± SD)	91	2.3 (1.2)	2.5 (1.0)	2.2 (1.2)	0.24
Healed, *n* (%)	91	41 (45.1)	10 (34.5)	31 (50.0)	0.12
Sepsis variables					
Positive blood culture sepsis, n (%)	91	29 (31.9)	4 (13.8)	25 (40.3)	**0.01**
CRP on the day of NEC (mg/dL, mean ± SD)	77	7.8 (8.7)	5.7 (7.3)	8.8 (9.2)	0.13
CRP 24 hours after NEC (mg/dL, mean ± SD)	72	12.6 (11.3)	8.6 (9.6)	14.5 (11.6)	**0.039**
CRP 48 hours after NEC (mg/dL, mean ± SD)	65	15.0 (11.7)	12.8 (12.8)	16.0 (11.1)	0.32
CRP 96 hours after NEC (mg/dL, mean ± SD)	67	11.4 (11.4)	9.6 (7.8)	11.9 (12.2)	0.50
CRP 1 week after NEC (mg/dL, mean ± SD)	65	9.0 (9.6)	6.6 (6.4)	9.7 (10.3)	0.27
CRP 2 weeks after NEC (mg/dL, mean ± SD)	64	5.3 (5.3)	2.2 (1.6)	6.3 (5.7)	**0.009**
Central line days (days, mean ± SD)	84	60.7 (41.3)	50.4 (34.6)	65.0 (43.4)	0.14

The presence of bold values signified $p < 0.05$

Risk Factors and Outcomes of Cholestasis at 2 Months Following NEC

About 52 infants were eligible for the cholestasis analysis at 2 months following surgical NEC. In total, 15/52 (28.8%) infants had complete resolution of cholestasis. Out of 37 infants with persistent cholestasis, 22/52 (42.3%) had direct bilirubin levels between 2 and 5 mg/dL (mild–moderate) and 15/52 (28.8%) had direct bilirubin levels more than 5 mg/dL (severe cholestasis).

Those with resolved cholestasis at 2 months following the onset of surgical NEC had higher birth weight (1192.6 ± 623.8 vs 829±456 gms; $p = 0.024$), higher CRP levels at 48 and 96 hours ($p < 0.05$), and required small bowel resected less often [5/51 (9.8%) vs 28/51 (54.9%); $p = 0.004$] following surgical NEC. The gestational age, age of surgical NEC onset, length of bowel resection, surgical morbidities, and death were not statistically significant in infants with and without resolved cholestasis at 2 months following onset of the surgical NEC. The data are summarized in Supplementary Table 1.

On multinominal logistic regression, infants with surgical NEC had longer durations of postoperative ileus (11.9, CI 1.1, 22.8; $p = 0.03$), which was independently associated with direct bilirubin levels between 2 and 5 mg/dL (mild–moderate cholestasis) at 2 months of age. The duration of total PN was independently associated with direct bilirubin >5 mg/dL (severe cholestasis) at 2 months of age in infants (OR 37.14; 4.26, and 70.03; $p = 0.0269$). The data are summarized in Table 5.

Discussion

In our cohort, almost 68% of cases had cholestasis at any time following surgical NEC. Infants with cholestasis were sicker at the time of disease onset as evidenced by the need for inotropic support at 24 hours and the frequency of blood culture-proven sepsis. Infants with cholestasis had a higher incidence of intestinal failure (56.5% vs 20.7%), received PN for longer durations, and were more likely to have >1 surgical complication. Those with cholestasis stayed in the hospital almost 6 weeks longer than those without, although there was no overall increase in mortality than these controls. Unlike other reports,[8] we saw no significant differences in gestational age and birthweight in infants with and without cholestasis. In our cohort of surgical NEC, we also did not find significant differences in the presence of an ileocecal valve, bowel histopathology, and the length of bowel resection. However,

Table 3: Postoperative intestinal and outcomes information in infants with and without cholestasis

	N	*Total (N = 91)*	*No cholestasis (N = 29)*	*Cholestasis (N = 62)*	*p-value*
Postoperative intestinal features					
Time to reach full feeds (days, mean ± SD)	66	71.3 (45.6)	58.1 (47.8)	77.1 (44.0)	0.12
Days of starting feeds (days, mean ± SD)	80	19.3 (17.0)	14.0 (10.0)	21.5 (18.8)	0.08
Days of TPN (days, mean ± SD)	90	97.6 (56.1)	74.7 (48.1)	108.4 (56.6)	**0.007**
Postoperative ileus (days, mean ± SD)	81	17.6 (15.5)	13.4 (10.0)	19.2 (17.0)	0.13
Surgical complication, *n* (%)	91	39 (42.9)	8 (27.6)	31 (50.0)	**0.044**
Single complication, *n* (%)	91	23 (25.3)	6 (20.7)	17 (27.4)	0.49
>1 complication, *n* (%)	91	14 (15.4)	1 (3.4)	13 (21.0)	**0.031**
Wound dehiscence, *n* (%)	91	15 (16.5)	2 (6.9)	13 (21.0)	0.09
Wound infection, *n* (%)	91	8 (8.8)	1 (3.4)	7 (11.3)	0.22
Adhesions, *n* (%)	91	20 (22.0)	4 (13.8)	16 (25.8)	0.20
Fistula, *n* (%)	91	5 (5.5)	0 (0.0)	5 (8.1)	0.12
Intestinal failure, *n* (%)	83	42 (50.6)	6 (25.0)	36 (61.0)	**0.003**
Outcomes					
Weight *z*-scores @36 weeks	72	−1.67 (−2.1, −0.88)	−1.68 (−2.04, −1.05)	−1.54 (−2.11, −0.87)	0.38
Length *z*-scores @36 weeks	72	−1.92 (−3.26, −1.30)	−1.67 (−3.66, −1.19)	−2.04 (−3.26, −1.35)	0.30
Weight-for-length z-scores @36 weeks	72	−1.11 (−1.74, −0.194)	−1.32 (−1.76, −0.76)	−1.0 (−1.73, −0.12)	**0.025**
Head circumference z-scores @36 weeks	72	−2.16 (−2.72, −0.98)	−1.92 (−2.82, −0.942)	−2.39 (−2.77, −0.92)	0.30
White-matter injury, n (%)	60	28 (46.7)	9 (50.0)	19 (45.2)	0.74
Length of stay (days, mean ± SD)	91	140.5 (81.6)	112.4 (84.2)	153.7 (77.5)	**0.024**
Death	91	22 (24.2)	6 (20.7)	16 (25.8)	0.60

The presence of bold values signified $p < 0.05$

Table 4: Regression analysis

N = 65	*Exp (B)*	*95% CI*	*Significance*
Pressor support 24 hours after NEC	6.689	1.374–32.562	**0.0186**
Indomethacin use	4.783	0.352–64.991	0.2397
Time to surgery from NEC onset	1.001	0.999–1.003	0.4012
TPN days	1.026	1.004–1.050	**0.0235**
Days of starting feeds	1.109	0.996–1.235	0.0596
Time to reach full feeds	0.982	0.959–1.005	0.1213
Intercept	0.148		0.1099

patients with cholestasis (direct bilirubin >2 mg/dL) had a higher incidence of bloodstream infections following surgical NEC; in sepsis-associated liver injury, bacterial toxins may have induced pro-inflammatory cytokines and caused ischemic liver injury.[23]

In a retrospective study of 225 infants with NEC/SIP from Finland, investigators found intestinal failure-associated cholestasis (IFAC) in 42% of cases.[9] In multivariate logistic regression analysis, IFAC development was associated with septicemia and repeated surgical procedures. However, there was no increase in overall mortality.[9] We observed similar findings in our cohort; patients with cholestasis had more surgical complications following NEC and a larger number of infants had >1 complication. Infants who needed multiple surgical procedures required PN support for a longer duration with increased risk for cholestasis.

A recent multicenter observational study of 465 preterm infants assessing the risk factors associated with cholestasis indicated that the maximum dose of amino acids, extra uterine growth restriction, feeding intolerance, surgically treated NEC, and longer total hospital stay were independent risk factors for the development of PN-associated cholestasis (PNAC).[24] soybean oil–medium chain triglycerides–olive oil–fish oil (SMOF®) and breastfeeding were protective factors for PNAC. In comparison, in our cohort, the infants with any cholestasis following surgical NEC had longer length of stay on univariate analysis alone. We observed higher weight-for-length ratio most likely due to consistent adequate calories and proteins provided by the PN. However, at our center, we used the Intralipids® as a fat source that may have contributed to the cholestasis frequency observed. We did not collect data on the maximum dose of amino acid and dextrose concentration used in preterm infants with cholestasis.

A recent metanalysis by Zou et al.[25] indicated that fish oil-containing lipid emulsion significantly reduced the occurrence of PNAC with a risk ratio (RR) = 0.53, 95% confidence interval (CI) 0.36–0.80, $p = 0.002$. In mice, macrophage-derived interleukin (IL)-1β seems to play a key role in PNAC, activating hepatocyte nuclear factor-kappa B (NF-κB), which in turn interferes with farnesoid X and liver X-receptor signaling to suppress the transcription of bile and sterol transporters, thereby causing cholestasis.[26] Hepatic macrophages and related IL-1β and NF-κB signaling may be new targets for restoring bile and sterol transport to treat or prevent PNAC.

Similar to our study, Duro et al. reported cholestasis in 70% of cases in a predominantly male cohort with a median gestational age of 26 weeks.[8] They identified small-bowel resection or creation of jejunostomy (odds ratio [OR] 4.96, 95% confidence interval [CI] 1.97–12.51, $p = 0.0007$) and duration of PN in weeks (OR 2.37, 95% CI

Table 5: Bivariate analysis of resolved cholestasis

	Direct bilirubin at 2 months of age ≤5 [3]			*Direct bilirubin at 2 months of age >5* [3]			
	β	*95% CI*	*p-value*	*β*	*95% CI*	*p-value*	*n*
Length of stay[1]	8.39	−34.30, 51.09	0.7000	38.80	−8.18, 85.78	0.1055	53
Mortality[2]	0.74	−1.62, 3.11	0.5385	1.95	−0.35, 4.24	0.0966	53
Achievement of full feeds[2]	−1.79	−4.03, 0.45	0.1174	−1.25	−3.64, 1.14	0.3044	50
Time to reach full feeds[1]	20.54	−8.50, 49.59	0.1657	14.74	−16.92, 46.4	0.3615	43
Days of starting feeds[1]	15.42	3.71, 27.13	**0.0099**	0.67	−12.10, 13.43	0.9185	52
TPN days[1]	21.40	−8.60, 51.40	0.1620	37.14	4.26, 70.03	0.0269	52
Short gut syndrome[2]	1.16	−0.36, 2.68	0.1347	0.72	−0.83, 2.28	0.3627	50
Post-op ileus[1]	11.95	1.10, 22.80	**0.0309**	0.60	−11.23, 12.43	0.9208	52
Surgical complication[2]	0.05	−1.26, 1.35	0.9442	0.54	−0.91, 1.99	0.4656	53
Single complication[2]	0.56	−0.99, 2.11	0.4780	0.98	−0.65, 2.61	0.2392	53
More than 1 complication[2]	−0.55	−2.12, 1.03	0.4957	Low sample size			53
White-matter injury[2]	−0.68	−2.23, 8.88	0.3930	−0.15	−1.92, 1.61	0.8640	38

[1]Continuous outcome uses linear regression; [2]Binary outcome uses logistic regression; [3]Reference level direct bilirubin at 2 months of age <2

1.56–3.60, $p < 0.0001$) as independent risk factors for PN-associated liver disease (PNALD) in preterm infants with surgical NEC.[8] Just as in our cohort, the duration of PN was independently associated with cholestasis.

Our study has some important limitations. First, this was a single-center experience, with predominantly African American patients reducing the study's generalizability. Second, the retrospective study design and a small sample size limited our power to detect associations between clinical factors, NEC, and outcomes. Further, the small sample size may have resulted in type-I errors from multiple comparisons. Finally, most of the neonates with surgical NEC were African American. While this is partly due to race distribution in Mississippi, this may also be related to adverse social determinants of health and/or genetic risk for surgical NEC.

In summary, cholestasis is a common morbidity following surgical NEC and it is most likely secondary to intestinal failure and PN dependence for a longer period. We speculate that identification of risk factors such as sepsis and surgical complication following NEC surgery may allow the development of preventive strategies for cholestasis and improve outcomes. There is a need for large prospective multicenter clinical and translational studies to fully understand the mechanisms, risk factors for, and impact of cholestasis on health and outcomes in premature infants.

Author's Contributions

PMG, PPG, and AM designed the study. PMG, IP, JY, VGW, RJR, ML, CW, MHP, PPG, AGM, JLL, and AM analyzed the data and wrote the paper. All the authors contributed and approved the paper.

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Supplementary Materials

All the Supplementary Table is available online on the website of https://www.newbornjournal.org/.

References

1. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med 2011;364(3):255–264. DOI: 10.1056/NEJMra1005408.
2. Sankaran K, Puckett B, Lee DS, et al. Variations in incidence of necrotizing enterocolitis in Canadian neonatal intensive care units. J Pediatr Gastroenterol Nutr 2004;39(4):366–372. DOI: 10.1097/00005176-200410000-00012.
3. Blakely ML, Lally KP, McDonald S, et al. Postoperative outcomes of extremely low birth-weight infants with necrotizing enterocolitis or isolated intestinal perforation: A prospective cohort study by the NICHD Neonatal Research Network. Ann Surg 2005;241(6):984–989. DOI: 10.1097/01.sla.0000164181.67862.7f.
4. Wales PW, de Silva N, Kim JH, et al. Neonatal short bowel syndrome: A cohort study. J Pediatr Surg 2005;40(5):755–762. DOI: 10.1016/j.jpedsurg.2005.01.037.
5. Spencer AU, Neaga A, West B, et al. Pediatric short bowel syndrome: Redefining predictors of success. Ann Surg 2005;242(3):403–409. DOI: 10.1097/01.sla.0000179647.24046.03.
6. Mowitz ME, Dukhovny D, Zupancic JAF. The cost of necrotizing enterocolitis in premature infants. Semin Fetal Neonatal Med 2018;23(6):416–419. DOI: 10.1016/j.siny.2018.08.004.
7. Duggan CP, Jaksic T. Pediatric intestinal failure. N Engl J Med 2017;377(7):666–675. DOI: 10.1056/NEJMra1602650.
8. Duro D, Mitchell PD, Kalish LA, et al. Risk factors for parenteral nutrition-associated liver disease following surgical therapy for necrotizing enterocolitis: A Glaser Pediatric Research Network Study [corrected]. J Pediatr Gastroenterol Nutr 2011;52(5):595–600. DOI: 10.1097/MPG.0b013e31820e8396.
9. Karila K, Anttila A, Iber T, et al. Intestinal failure associated cholestasis in surgical necrotizing enterocolitis and spontaneous intestinal perforation. J Pediatr Surg 2019;54(3):460–464. DOI: 10.1016/j.jpedsurg.2018.10.043.
10. Smazal AL, Massieu LA, Gollins L, et al. Small proportion of low-birth-weight infants with ostomy and intestinal failure due to short-bowel syndrome achieve enteral autonomy prior to reanastomosis. JPEN J Parenter Enteral Nutr 2021;45(2):331–338. DOI: 10.1002/jpen.1847.
11. Fatemizadeh R, Gollins L, Hagan J, et al. In neonatal-onset surgical short bowel syndrome survival is high, and enteral autonomy is related to residual bowel length. JPEN J Parenter Enteral Nutr 2022;46(2):339–347. DOI: 10.1002/jpen.2124.
12. Jammeh ML, Adibe OO, Tracy ET, et al. Racial/ethnic differences in necrotizing enterocolitis incidence and outcomes in premature very

low birth weight infants. J Perinatol 2018;38(10):1386–1390. DOI: 10.1038/s41372-018-0184-x.
13. Garg PM, Britt AB, Ansari MAY, et al. Severe acute kidney injury in neonates with necrotizing enterocolitis: Risk factors and outcomes. Pediatr Res 2021. DOI: 10.1038/s41390-020-01320-6.
14. Garg PM, Paschal JL, Zhang M, et al. Brain injury in preterm infants with surgical necrotizing enterocolitis: Clinical and bowel pathological correlates. Pediatr Res 2021.
15. Garg PM, O'Connor A, Ansari MAY, et al. Hematological predictors of mortality in neonates with fulminant necrotizing enterocolitis. J Perinatol 2021;41(5):1110–1121. DOI: 10.1038/s41372-021-01044-3.
16. Garg PM, Bernieh A, Hitt MM, et al. Incomplete resection of necrotic bowel may increase mortality in infants with necrotizing enterocolitis. Pediatr Res 2021;89(1):163–170. DOI: 10.1038/s41390-020-0975-6.
17. Garg PM, Hitt MM, Blackshear C, et al. Clinical determinants of postoperative outcomes in surgical necrotizing enterocolitis. J Perinatol 2020;40(11):1671–1678. DOI: 10.1038/s41372-020-0728-8.
18. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187(1):1–7. DOI: 10.1097/00000658-197801000-00001.
19. Lambert DK, Christensen RD, Baer VL, et al. Fulminant necrotizing enterocolitis in a multihospital healthcare system. J Perinatol 2012;32(3):194–198. DOI: 10.1038/jp.2011.61.
20. Remon JI, Amin SC, Mehendale SR, et al. Depth of bacterial invasion in resected intestinal tissue predicts mortality in surgical necrotizing enterocolitis. J Perinatol 2015;35(9):755–762. DOI: 10.1038/jp.2015.51.
21. Premkumar MH, Carter BA, Hawthorne KM, et al. Fish oil-based lipid emulsions in the treatment of parenteral nutrition-associated liver disease: An ongoing positive experience. Adv Nutr 2014;5(1):65–70. DOI: 10.3945/an.113.004671.
22. Woodward LJ, Anderson PJ, Austin NC, et al. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med 2006;355(7):685–694. DOI: 10.1056/NEJMoa053792.
23. Geier A, Fickert P, Trauner M. Mechanisms of disease: mechanisms and clinical implications of cholestasis in sepsis. Nat Clin Pract Gastroenterol Hepatol 2006;3(10):574–585. DOI: 10.1038/ncpgasthep0602.
24. Wang YS, Shen W, Yang Q, et al. Analysis of risk factors for parenteral nutrition-associated cholestasis in preterm infants: A multicenter observational study. BMC Pediatr 2023;23(1):250. DOI: 10.1186/s12887-023-04068-0.
25. Zou TT, Li JR, Zhu Y, et al. Fish oil-containing lipid emulsions prevention on parenteral nutrition-associated cholestasis in very low birth weight infants: A meta-analysis. World J Pediatr 2022;18(7):463–471. DOI: 10.1007/s12519-022-00536-2.
26. El Kasmi KC, Vue PM, Anderson AL, et al. Macrophage-derived IL-1β/NF-κB signaling mediates parenteral nutrition-associated cholestasis. Nat Commun 2018;9(1):1393. DOI: 10.1038/s41467-018-03764-1.

REVIEW ARTICLE

Extrauterine Growth Restriction: Need for an Accurate Definition

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Abstract

Neonates show considerable variation in growth that can be recognized through serial measurements of basic variables such as weight, length, and head circumference. If possible, measurement of subcutaneous and total body fat mass can also be useful. These biometric measurements at birth may be influenced by demographics, maternal and paternal anthropometrics, maternal metabolism, preconceptional nutritional status, and placental health. Subsequent growth may depend on optimal feeding, total caloric intake, total metabolic activity, genetic makeup, postnatal morbidities, medications, and environmental conditions. For premature infants, these factors become even more important; poor *in utero* growth can be an important reason for spontaneous or induced preterm delivery. Later, many infants who have had intrauterine growth restriction (IUGR) and are born small for gestational age (SGA) continue to show suboptimal growth below the 10th percentile, a condition that has been defined as extrauterine growth restriction (EUGR) or postnatal growth restriction (PNGR). More importantly, a subset of these growth-restricted infants may also be at high risk of abnormal neurodevelopmental outcomes. There is a need for well-defined criteria to recognize EUGR/PNGR, so that correctional steps can be instituted in a timely fashion.

Keywords: Body fat mass, Cohort of Indonesian PreTerm infants for long-term Outcomes study, Corrected gestational age, Delta-Z, Demographic factors, Extra-uterine growth restriction, Failure to thrive, Fenton growth chart, Genetic make-up, growth charts, Infant growth, Intra-uterine growth restriction, Intergrowth 21st charts, Infant feeding, Linear growth velocity, Maternal metabolism, Maternal and paternal anthropometrics, Medications, Newborn, Neonate, Neurodevelopmental outcomes, Neonatal morbidities, Placental health, Postnatal growth restriction, Postnatal malnutrition, Pre-conceptional nutritional status, Postnatal morbidities, Postnatal growth, Small for gestation, Term corrected age, Total caloric intake, Total metabolic activity, Weight gain velocity, Z-scores.

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Highlights

- Neonates show considerable variation in growth; assessment requires serial measurement of basic parameters such as weight, length, and head circumference.
- Biometric parameters at birth may reflect demographic factors, maternal and paternal anthropometrics, maternal metabolism, preconceptional nutritional status, and placental health. Postnatal determinants of growth include feeding, total caloric intake, metabolic activity, genetic factors, morbidities, and environmental conditions.
- Infants who have had intrauterine growth restriction (IUGR) and are born small for gestational age (SGA) may have low growth potential. Many have suboptimal neurodevelopmental outcomes.
- There is a need to accurately define extrauterine growth restriction (EUGR) so that correctional steps can be instituted in a timely fashion.

Introduction

Advancements in the field of neonatology over last two decades has led to improved survival of premature and low birth weight infants.[1,2] However, the growth of these premature and critically ill neonates remains a cause for concern. To define and monitor the growth faltering of these infants, many terminologies has been used in literature such as EUGR and PNGR,[3,4] failure to thrive,[4] and postnatal malnutrition.[5] Many definitions have been suggested for these terminologies and attempts have been made

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Table 1: Currently available identification tools for EUGR

Criteria	*Mild EUGR*	*Moderate EUGR*	*Severe EUGR*	*When to apply?*
1. Weight-for-age *Z*-scores[a]	Decline of 0.8–1.2 SD	Decline of >1.2–2 SD	Decline >2 SD	Not appropriate for first 2 weeks of life
2. Weight gain velocity[b]	<75% of expected weight gain for that particular age	<50% of expected weight gain for that particular age	<25% of expected weight gain for that particular age	Not appropriate for first 2 weeks of life
3. ≥2 of the following				Not appropriate for first 2 weeks, can be used subsequently in conjunction with other parameters if accurate length measurement is available.
• Length-for-age *Z*-scores[a]	Decline of 0.8–1.2 SD	Decline of >1.2–2 SD	Decline >2 SD	
• Length gain velocity[b]	<75% of expected length gain for that particular age 15–18 days	<50% of expected length gain for that particular age 19–21 days	<25% of expected length gain for that particular age	
• Days to regain birth weight (in conjugation with nutrient intake)	(>3–5 consecutive days of <75% intakes of estimated protein/calorie)	(>5–7 consecutive days of <75% intakes of estimated protein/calorie)	>21 days (>7 consecutive days of <75% intakes of estimated protein/calorie)	Preferred for first 2 weeks of life

[a]Expected *Z*-score for weight for age and length for age. [b]Weight gain velocity and linear growth velocity were estimated using online calculator (www.peditools.org). In this calculator, weight gain velocity is estimated by using the World Health Organization (WHO) methods; weight increments are classified by birth-weight category presented in 1-week and 2-weeks intervals from birth to 60 days.[21]

to correlate these with neurodevelopmental and other clinical outcomes,[3,6–8]

Infant growth rates have been followed on charts such as the Fenton,[9] British,[10] and Italian.[11] Growth parameters have been studied in greater detail at some time points such as at a postnatal age of 28 days, postnatal and/or corrected gestational ages of 36–40 weeks, or at the time of discharge from NICU. Similar to full-term infants, preterm infants also grow along these growth curves.[12,13] The growth trajectories may get altered during periods of high-acuity illness, which might cause one or more anthropometric parameters to drop in terms of centile ranks at discharge or at term corrected age.[14,15]

Many studies have shown that drops in weight centiles may predict suboptimal neurodevelopmental outcomes.[4,6,7] Altered length[16,17] and head circumference[14,18–20] at corrected 36 weeks, at discharge, and/or and poor weight gain post-discharge have also been associated with poor developmental outcomes. However, we still have not been able to identify critical thresholds of these parameters. There is a need to define EUGR in terms of weight alone or in combination with length, head circumference, body composition, and genetic markers, and genetic potential based on parental anthropometric indices. Growth monitoring is also important for interpretation of postnatal weight loss and loss of growth centiles during high-acuity illness; we currently interpret our findings by comparing with the reference fetus and arbitrary statistical growth percentile cut offs. The objective of this article is to extensively review the current literature and provide uniform definition of EUGR postnatally,[21,22] while answering few important questions which lead the way.

We Still Need to Agree on a Single Definition of Extrauterine Growth Restriction

To assess the appropriate medical and nutritional interventions and to predict auxological long term outcomes, a consensus definition of EUGR is still needed. We recommend rectification, not only in the criteria to define EUGR but also the method and tool for growth monitoring. Until a consensus defines EUGR, the recommendations from "Identifying Malnutrition in Preterm and Neonatal Populations: Recommended Indicators" (Table 1)[5] and "Extrauterine Growth Restriction: Definitions and Predictability of Outcomes in a Cohort of Very Low Birth Weight Infants or Preterm Neonates,"[23] which defines EUGR as longitudinal (if the weight loss is more than one standard deviation (SD) between birth and a given *t*-time and cross sectional (if weight was below the 10th centile at a given *t*-time). A recent prospective cohort study from Jakarta, Indonesia [the Cohort of Indonesian PreTerm infants for long-term Outcomes (CIPTO) study] to study preterm infants born at the Cipto Mangunkusumo General Hospital has also provided important information.[24] They defined EUGR (as in Table 1) as a decline in the weight-for-age *Z*-score of above or equal to 1.2 and have reported related outcomes.

Are we Using Appropriate Metrics to Define Extrauterine Growth Restriction?

We are not sure if it is appropriate to assess growth using a single-point, single-parameter measurement such as weight. Weight measurements show high variability, and we have still not identified one growth chart as better than others for plotting growth of preterm infants. We are also not certain whether a specific set of growth charts can better assess the initial postnatal weight loss and post discharge catch-up. These questions are important in identification of EUGR.

Most studies still use a single point, single-parameter measurement such as weight at corrected 36 weeks' gestation or at discharge.[25–29] This is a convenient way to define EUGR but many studies have identified that there is a good catch-up between 36–40 weeks' gestation;[11,30,31] EUGR has been defined in literature using the following:

- Percentile ranks (<3rd and <10th percentiles) at 36 weeks/discharge,[32]
- The *Z*-scores (*Z*-score of 1 or 2) for weight loss from that at birth,[33]
- The *Z*-score at discharge of < –1.5 of intrauterine growth or standard postnatal growth,[26,34,35]

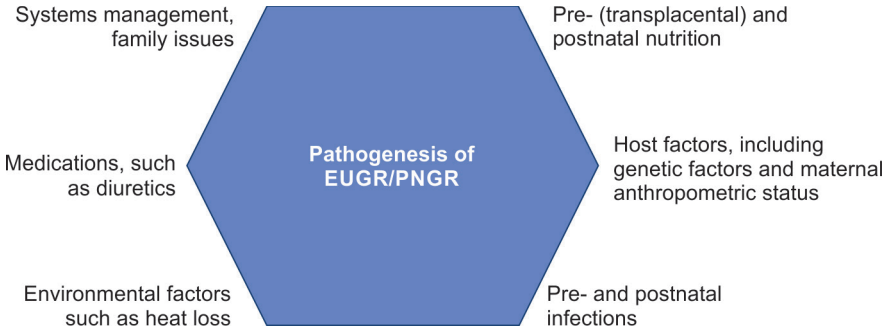

Fig. 1: Multiple factors are likely involved in the pathogenesis of EUGR/PNGR

- Drop in *Z*-score (delta-Z) from birth to 36 weeks corrected gestational age or at discharge.[36,37]

Shah et al.[6] compared the definitions related to both percentiles (<3rd and <10th percentiles) at 36 weeks' discharge, and *Z*-score (1 or 2 *Z*-scores) losses from birth weight. Zozaya et al.[7] compared *Z*-scores at discharge of below −1.5 of intrauterine growth or standard postnatal growth and drop in *Z*-score (delta-*Z*) from birth to corrected 36 weeks' gestational age or at discharge. Both studies concluded that the drop in *Z*-scores has a higher predictive value in relation with neurodevelopment outcome than a single time point measurement of weight less than 10th percentile.

Currently there is no consensus about which growth monitoring tool is better for assessment of growth in preterm infants during postnatal period. There are two following standard growth charts available: (A) the Fenton growth chart is a reference chart based on a cross-sectional study population[9] and (B) the Intergrowth 21st charts (IG-21)[38] that are based on a postnatal longitudinal study population. In accordance with the available literature, growth failure defined as a *Z*-score drop of >1 from birth to discharge in terms of weight, length and head circumference[7,23,39] has shown that that PNGR was less common with IG-21 as compared to Fenton[40–45] and is strongly associated with poor long-term outcome. Larger studies are still required to identify the most optimal growth assessment tool.

We Need to Consider Body Composition in Addition to the Conventional Anthropometric Measurements to Define Extrauterine Growth Restriction/Postnatal Growth Restriction

Weight gain, as an isolated index, may not be the most appropriate method to assess growth because weight is an indirect indicator of body composition (lean body mass + fat tissue + body fluid).[22] The lean body mass is likely to be more accurate as a predictor, and fat tissue may be the least important. In a systematic review and meta-analysis, Johnson et al.[46] and Gianni et al.[47] showed that preterm infants at corrected term gestational age of 40 weeks had a higher proportion of body fat than comparable full-term infants. The preterm infants in this cohort had less lean body mass, and this continued to be a matter of concern until 5 years of age. In another consideration, all preterm infants show a variable degree of physiological weight loss in the first few days after birth due to loss of extracellular fluid. This is reflected in growth charts as loss of growth percentiles.[12] This fluid loss is important for hemodynamic and physiological stability of these infants.[48,49] If a preterm infant is discharged from the hospital during this period of physiological weight loss, these changes will be documented as EUGR but Rochow et al.[12] showed that they subsequently regain normal growth trajectories. The WHO recommends body mass index (BMI) and weight-for-length as better standards for monitoring growth during childhood,[50] but these guidelines cannot be readily extrapolated for preterm infants. In these patients, the body composition will remain concerning even if they gain weight because the length will likely not change proportionately.[51,52] We believe that instead of using a single-point, single-parameter measurement such as weight, following the three most commonly used anthropometric parameters (weight, length and head circumference) over time might be better.

The Impact of Suboptimal Growth goes Beyond Somatic Consequences

In premature infants, neurodevelopmental outcomes are an important indicator of the quality of care. Many recent studies emphasize the effect of nutrition on neurodevelopmental outcome of premature infants.[53–55] Others suggest that preterm infants with multiple morbidities grow slower than controls who have been relatively healthy.[14,15,56] Hence, optimization of nutrition can potentially improve both growth and developmental outcomes. However, weight below 10th percentile at a single time point (36 or 40 weeks' corrected gestational age, or at discharge) is not the only growth indicator that is associated with poor developmental outcome;[4,6,7] length[16,17] and head circumference[16,18–20,57–59] may also be important predictors.

Infants who are born SGA[60] have shown slower growth during their hospital stay.[7,14,57–59] They are at increased risk of multiple neonatal morbidities,[5,56] neurological injury such as intraventricular hemorrhage and periventricular leukomalacia,[14] and are at risk of developmental delay. However, these are complex issues that extend beyond infant health; parental cognitive capacity, involvement, education, and socioeconomic status are also important predictors of developmental outcome.[61–63] A cursory look at the host–infections–environment–therapy–nutrition–systems management hexagon that we have been using in this journal to study disease pathogenesis suggests that there is a clear possibility of multifactorial origin (Fig. 1).[64] There is a need for an in-depth, careful analysis to determine the relative weightage of each of these nodes.

Conclusion

Extrauterine growth restriction/PNGR is an important problem in recovering premature/critically ill infants and cannot be ignored. To define EUGR appropriately is the need of the hour and growth monitoring of preterm infants using appropriate growth charts should be encouraged to identify early deviance in growth trajectories. Only then we will be able to institute relevant interventions in a timely fashion. The association with neurodevelopmental outcomes increases its importance even further; it may enrich our currently used single-point, single-parameter measurement at 36 weeks or at corrected term gestational age. If we do not have an optimum way of measurement, it will remain difficult to compare the impact of many prophylactic/therapeutic interventions.

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References

1. Euser AM, de Wit CC, Finken MJ, et al. Growth of preterm born children. Horm Res 2008;70(6):319–328. DOI: 10.1159/000161862.
2. Bagga N, Reddy KK, Mohamed A, et al. Quality improvement initiative to decrease extrauterine growth restriction in preterm neonates. Nutr Clin Pract 2021;36(6):1296–1303. DOI: 10.1002/ncp.10735.
3. Fenton TR, Chan HT, Madhu A, et al. Preterm infant growth velocity calculations: A systematic review. Pediatrics 2017;139(3):e20162045. DOI: 10.1542/peds.2016-2045.
4. Hack M, Merkatz IR, Gordon D, Jet al. The prognostic significance of postnatal growth in very low birth weight infants. Am J Obstet Gynecol 1982;143(6):693–699. DOI: 10.1016/0002-9378(82)90117-x.
5. Goldberg DL, Becker PJ, Brigham K, et al. Identifying malnutrition in preterm and neonatal populations: Recommended indicators. J Acad Nutr Diet 2018;118(9):1571–1582. DOI: 10.1016/j.jand.2017.10.006.
6. Shah PS, Wong KY, Merko S, et al. Postnatal growth failure in preterm infants: Ascertainment and relation to long-term outcome. J Perinat Med 2006;34(6):484–489. DOI: 10.1515/JPM.2006.094.
7. Zozaya C, Diaz C, de Pipaon MS. How should we define postnatal growth restriction in preterm infants? Neonatology 2018;114(2): 177–180. DOI: 10.1159/000489388.
8. Tudehope DI, Burns Y, O'Callaghan M, et al. The relationship between intrauterine and postnatal growth on the subsequent psychomotor development of very low birthweight (VLBW) infants. Aust Paediatr J 1983;19(1):3–8. DOI: 10.1111/j.1440-1754.1983.tb02041.x.
9. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59. DOI: 10.1186/1471-2431-13-59.
10. Cole TJ, Williams AF, Wright CM, et al. Revised birth centiles for weight, length and head circumference in the UK-WHO growth charts. Ann Hum Biol 2011;38(1):7–11. DOI: 10.3109/03014460.2011.544139.
11. Bertino E, Coscia A, Mombro M, et al. Postnatal weight increase and growth velocity of very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2006;91(5):F349–F356. DOI: 10.1136/adc.2005.090993.
12. Rochow N, Raja P, Liu K, et al. Physiological adjustment to postnatal growth trajectories in healthy preterm infants. Pediatr Res 2016;79(6):870–879. DOI: 10.1038/pr.2016.15.
13. Cole TJ, Statnikov Y, Santhakumaran S, et al. Birth weight and longitudinal growth in infants born below 32 weeks' gestation: A UK population study. Arch Dis Child Fetal Neonatal Ed 2014;99(1): F34–F40. DOI: 10.1136/archdischild-2012-303536.
14. Franz AR, Pohlandt F, Bode H, et al. Intrauterine, early neonatal, and postdischarge growth and neurodevelopmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. Pediatrics 2009;123(1):e101–e109. DOI: 10.1542/peds.2008-1352.
15. Ehrenkranz RA, Younes N, Lemons JA, et al. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 1999;104 (2 Pt 1):280–289. DOI: 10.1542/peds.104.2.280.
16. Belfort MB, Gillman MW, Buka SL, et al. Preterm infant linear growth and adiposity gain: Trade-offs for later weight status and intelligence quotient. J Pediatr 2013;163(6):1564.e2–1569.e2. DOI: 10.1016/j.jpeds.2013.06.032.
17. Dusick AM, Poindexter BB, Ehrenkranz RA, et al. Growth failure in the preterm infant: Can we catch up? Semin Perinatol 2003;27(4):302–310. DOI: 10.1016/s0146-0005(03)00044-2.
18. Raghuram K, Yang J, Church PT, et al. Head growth trajectory and neurodevelopmental outcomes in preterm neonates. Pediatrics 2017;140(1):e20170216. DOI: 10.1542/peds.2017-0216.
19. Georgieff MK, Hoffman JS, Pereira GR, et al. Effect of neonatal caloric deprivation on head growth and 1-year developmental status in preterm infants. J Pediatr 1985;107(4):581–587. DOI: 10.1016/s0022-3476(85)80028-7.
20. Sammallahti S, Pyhala R, Lahti M, et al. Infant growth after preterm birth and neurocognitive abilities in young adulthood. J Pediatr 2014;165(6):1109.e3–1115.e3. DOI: 10.1016/j.jpeds.2014.08.028.
21. Nitasha Bagga, Nalinikant Panigrahay, Akhil Maheshwari. Extrauterine growth restriction in preterm infants. Newborn 2022;1(1): 67–73. DOI: 10.5005/jp-journals-11002-0019.
22. Fenton TR, Cormack B, Goldberg D, et al. "Extrauterine growth restriction" and "postnatal growth failure" are misnomers for preterm infants. J Perinatol 2020;40(5):704–714. DOI: 10.1038/s41372-020-0658-5.
23. Peila C, Spada E, Giuliani F, et al. Extrauterine growth restriction: Definitions and predictability of outcomes in a cohort of very low birth weight infants or preterm neonates. Nutrients 2020;12(5):1224. DOI: 10.3390/nu12051224.
24. Rohsiswatmo R, Kaban RK, Sjahrulla MAR, et al. Defining postnatal growth failure among preterm infants in Indonesia. Front Nutr 2023;10:1101048. DOI: 10.3389/fnut.2023.1101048.
25. Shlomai NO, Reichman B, Lerner–Geva L, et al. Population-based study shows improved postnatal growth in preterm very-low-birthweight infants between 1995 and 2010. Acta Paediatr 2014;103(5):498–503. DOI: 10.1111/apa.12569.
26. Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. Pediatrics 2003;111(5 Pt 1):986–990. DOI: 10.1542/peds.111.5.986.
27. Cooke RJ, Ainsworth SB, Fenton AC. Postnatal growth retardation: A universal problem in preterm infants. Arch Dis Child Fetal Neonatal Ed 2004;89(5):F428–F430. DOI: 10.1136/adc.2001.004044.
28. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: An inevitable consequence of current recommendations in preterm infants? Pediatrics 2001;107(2):270–273. DOI: 10.1542/peds.107.2.270.
29. Roggero P, Gianni ML, Amato O, et al. Postnatal growth failure in preterm infants: recovery of growth and body composition after term. Early Hum Dev 2008;84(8):555–559. DOI: 10.1016/j.earlhumdev.2008.01.012.
30. Fenton TR, Nasser R, Eliasziw M, et al. Validating the weight gain of preterm infants between the reference growth curve of the fetus and the term infant. BMC Pediatr 2013;13:92. DOI: 10.1186/1471-2431-13-92.
31. Niklasson A, Albertsson–Wikland K. Continuous growth reference from 24th week of gestation to 24 months by gender. BMC Pediatr 2008;8:8. DOI: 10.1186/1471-2431-8-8.
32. Berry MA, Abrahamowicz M, Usher RH. Factors associated with growth of extremely premature infants during initial hospitalization. Pediatrics 1997;100(4):640–646. PMID: 9310518.
33. Carlson SJ, Ziegler EE. Nutrient intakes and growth of very low birth weight infants. J Perinatol 1998;18(4):252–258. PMID: 9730193.

34. Martin CR, Brown YF, Ehrenkranz RA, et al. Nutritional practices and growth velocity in the first month of life in extremely premature infants. Pediatrics 2009;124(2):649–657. DOI: 10.1542/peds.2008-3258.
35. Villar J, Giuliani F, Barros F, et al. Monitoring the postnatal growth of preterm infants: A paradigm change. Pediatrics 2018;141(2):e20172467. DOI: 10.1542/peds.2017-2467.
36. Horbar JD, Ehrenkranz RA, Badger GJ, et al. Weight growth velocity and postnatal growth failure in infants 501 to 1500 grams: 2000–2013. Pediatrics 2015;136(1):e84–e92. DOI: 10.1542/peds.2015-0129.
37. Radmacher PG, Looney SW, Rafail ST, et al. Prediction of extrauterine growth retardation (EUGR) in VVLBW infants. J Perinatol 2003;23(5):392–395. DOI: 10.1038/sj.jp.7210947.
38. Papageorghiou AT, Kennedy SH, Salomon LJ, et al. The INTERGROWTH-21st fetal growth standards: Toward the global integration of pregnancy and pediatric care. Am J Obstet Gynecol 2018;218(2S):S630–S640. DOI: 10.1016/j.ajog.2018.01.011.
39. Salas AA, Bhatia A, Carlo WA. Postnatal growth of preterm infants 24 to 26 weeks of gestation and cognitive outcomes at 2 years of age. Pediatr Res 2021;89(7):1804–1809. DOI: 10.1038/s41390-020-01158-y.
40. Tuzun F, Yucesoy E, Baysal B, et al. Comparison of INTERGROWTH-21 and Fenton growth standards to assess size at birth and extrauterine growth in very preterm infants. J Matern Fetal Neonatal Med 2018;31(17):2252–2257. DOI: 10.1080/14767058.2017.1339270.
41. Kim YJ, Shin SH, Cho H, et al. Extrauterine growth restriction in extremely preterm infants based on the Intergrowth-21st Project Preterm Postnatal Follow-up Study growth charts and the Fenton growth charts. Eur J Pediatr 2021;180(3):817–824. DOI: 10.1007/s00431-020-03796-0.
42. Reddy KV, Sharma D, Vardhelli V, et al. Comparison of Fenton 2013 growth curves and Intergrowth-21 growth standards to assess the incidence of intrauterine growth restriction and extrauterine growth restriction in preterm neonates ≤32 weeks. J Matern Fetal Neonatal Med 2021;34(16):2634–2641. DOI: 10.1080/14767058.2019.1670795.
43. Liu S, Metcalfe A, Leon JA, et al. Evaluation of the INTERGROWTH-21st project newborn standard for use in Canada. PLoS One 2017;12(3):e0172910. DOI: 10.1371/journal.pone.0172910.
44. Samarani M, Restom G, Mardini J, et al. Comparative study between Fenton and intergrowth 21 charts in a sample of Lebanese premature babies. BMC Pediatr 2020;20(1):74. DOI: 10.1186/s12887-020-1968-7.
45. Yitayew M, Chahin N, Rustom S, et al. Fenton vs. Intergrowth-21st: Postnatal growth assessment and prediction of neurodevelopment in preterm infants. Nutrients 2021;13(8):2841. DOI: 10.3390/nu13082841.
46. Johnson MJ, Wootton SA, Leaf AA, et al. Preterm birth and body composition at term equivalent age: A systematic review and meta-analysis. Pediatrics 2012;130(3):e640–e649. DOI: 10.1542/peds.2011-3379.
47. Gianni ML, Roggero P, Piemontese P, et al. Boys who are born preterm show a relative lack of fat-free mass at 5 years of age compared to their peers. Acta Paediatr 2015;104(3):e119–e123. DOI: 10.1111/apa.12856.
48. Heimler R, Doumas BT, Jendrzejczak BM, et al. Relationship between nutrition, weight change, and fluid compartments in preterm infants during the first week of life. J Pediatr 1993;122(1):110–114. DOI: 10.1016/s0022-3476(05)83502-4.
49. Lorenz JM, Kleinman LI, Ahmed G, et al. Phases of fluid and electrolyte homeostasis in the extremely low birth weight infant. Pediatrics 1995;96(3 Pt 1):484–489.
50. de Onis M. The use of anthropometry in the prevention of childhood overweight and obesity. Int J Obes Relat Metab Disord 2004;28 (Suppl. 3):S81–S85. DOI: 10.1038/sj.ijo.0802810.
51. Lorch SA. The clinical and policy implications of new measures of premature infant growth. Pediatrics 2015;135(3):e703–e704. DOI: 10.1542/peds.2014-3774.
52. Al-Theyab NA, Donovan TJ, Eiby YA, et al. Fat trajectory after birth in very preterm infants mimics healthy term infants. Pediatr Obes 2019;14(3):e12472. DOI: 10.1111/ijpo.12472.
53. O'Connor DL, Gibbins S, Kiss A, et al. Effect of supplemental donor human milk compared with preterm formula on neurodevelopment of very low-birth-weight infants at 18 months: A randomized clinical trial. JAMA 2016;316(18):1897–1905. DOI: 10.1001/jama.2016.16144.
54. Makrides M, Gibson RA, McPhee AJ, et al. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: A randomized controlled trial. JAMA 2010;304(15):1675–1683. DOI: 10.1001/jama.2010.1507.
55. Keim SA, Boone KM, Klebanoff MA, et al. Effect of docosahexaenoic acid supplementation vs placebo on developmental outcomes of toddlers born preterm: A randomized clinical trial. JAMA Pediatr 2018;172(12):1126–1134. DOI: 10.1001/jamapediatrics.2018.3082.
56. Regev RH, Arnon S, Litmanovitz I, et al. Association between neonatal morbidities and head growth from birth until discharge in very-low-birthweight infants born preterm: A population-based study. Dev Med Child Neurol 2016;58(11):1159–1166. DOI: 10.1111/dmcn.13153.
57. Belfort MB, Rifas–Shiman SL, Sullivan T, et al. Infant growth before and after term: Effects on neurodevelopment in preterm infants. Pediatrics 2011;128(4):e899–e906. DOI: 10.1542/peds.2011-0282.
58. Ehrenkranz RA, Dusick AM, Vohr BR, et al. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006;117(4):1253–1261. DOI: 10.1542/peds.2005-1368.
59. Ong KK, Kennedy K, Castaneda–Gutierrez E, et al. Postnatal growth in preterm infants and later health outcomes: A systematic review. Acta Paediatr 2015;104(10):974–986. DOI: 10.1111/apa.13128.
60. Corpeleijn WE, Kouwenhoven SM, van Goudoever JB. Optimal growth of preterm infants. World Rev Nutr Diet 2013;106:149–155. DOI: 10.1159/000342584.
61. Weisglas–Kuperus N, Hille ET, Duivenvoorden HJ, et al. Intelligence of very preterm or very low birthweight infants in young adulthood. Arch Dis Child Fetal Neonatal Ed 2009;94(3):F196–F200. DOI: 10.1136/adc.2007.135095.
62. Pineda RG, Stransky KE, Rogers C, et al. The single-patient room in the NICU: Maternal and family effects. J Perinatol 2012;32(7):545–551. DOI: 10.1038/jp.2011.144.
63. Benavente–Fernandez I, Synnes A, Grunau RE, et al. Association of socioeconomic status and brain injury with neurodevelopmental outcomes of very preterm children. JAMA Netw Open 2019;2(5): e192914. DOI: 10.1001/jamanetworkopen.2019.2914.
64. Maheshwari A, Lui K, Motta M. Understanding the impact of maternal health on neonatal disease: A new horizon. Newborn 2023;1(4):iv–vi. DOI: 10.5005/newborn-1-4-iv.

REVIEW ARTICLE

Point-of-care Ultrasound to Diagnose and Monitor the Course of Necrotizing Enterocolitis

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Abstract

Context: Neonatal gut ultrasound (US) is an emerging clinical tool for quick diagnosis and prognosis in various abdominal pathologies. In this review, we summarize normal gut US findings and concentrate on the specifications of diagnosing necrotizing enterocolitis.

Evidence: A comprehensive literature search was conducted across numerous sources with relevant keywords along with the specified age group of 0–28 days of life.

Findings: This review describes the normal gut US picture with the basic technicalities needed to master the art of point-of-care (POC) abdominal US. This modality is gaining importance due to its accuracy, applicability, safety, and affordability. Key findings include altered bowel perfusion, decreased peristalsis, and bowel wall thickening with better precision compared to abdominal X-ray (AXR). Many meta-analyses and narrative reviews have already demonstrated their usefulness. 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.

Conclusion: Emerging evidence and expertise in the field of abdominal US will make it a valuable tool for early diagnosis and prognosis of necrotizing enterocolitis.

Keywords: Gut signature, Necrotizing enterocolitis, Point-of-care abdominal ultrasound.

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Highlights

- Neonatal gut ultrasound (US) is an emerging tool for quick diagnosis and prognosis in various abdominal pathologies such as necrotizing enterocolitis.
- The abdomen is examined for fluid or free-air collection, portal venous gas, intestinal echotexture, gut wall thickness, pneumatosis intestinalis, and peristaltic movements.
- The normal intestine shows a characteristic gut signature in abdominal US with alternating hyperechoic and hypoechoic layers. Peristalsis can be seen as a worm-like motion. In necrotizing enterocolitis (NEC), the inflamed intestine shows increased wall thickness due to ischemia and necrosis.
- Intestinal intramural gas escaping through the mesenteric vessels to the portal veins can be detected as echogenic foci in the portal venous system or the distal parenchymal liver tissue.
- The term "pneumatosis intestinalis" refers to gas entrapped in the damaged layers of the bowel wall in NEC. Most gas bubbles are seen as echogenic dots in the intestinal wall.

Introduction

Necrotizing enterocolitis (NEC), an acute inflammatory condition of the gut, is a dreaded complication in premature and critically ill term infants. It is seen in about 5–10% of very-low-birth-weight (VLBW) infants with mortality rates ranging between 20 and 40%.[1–3] The mortality is inversely proportional to gestation and birth weight.[3,4] There is some information that timely diagnosis of NEC can improve the outcomes in these patients.

Early diagnosis of NEC is often difficult because clinical features such as feeding intolerance, abdominal distension, and gastrointestinal hemorrhages are non-specific and so are the routine laboratory tests. Abdominal X-ray (AXR) evaluation has been considered a gold standard for diagnosing NEC and in assessing its severity, such as in the modified Bell's staging.[5,6] The ease of access, cost-effectiveness, and the short learning curve have made it an integral part of both the diagnosis and monitoring of NEC. However, AXR has important limitations; the findings of dilated gut loops, air-fluid levels, and ascites can be non-specific, and others such as

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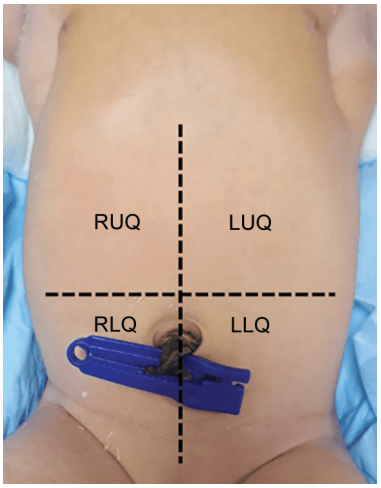


Fig. 1: Four quadrants of the abdomen are to be studied in POC abdominal US

LLQ, Left lower quadrant; LUQ, Left upper quadrant; RLQ, Right lower quadrant; RUQ, Right upper quadrant

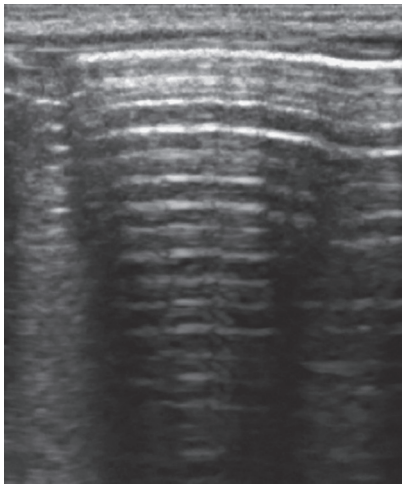


Fig. 2: Gas reverberation artifacts commonly seen in POC abdominal US

pneumatosis, portal venous gas, and fixed bowel loops are seen only in about half of all cases with confirmed disease.[7] Therefore, there is a need for diagnostic tools that are accurate, easy to apply, and yet affordable. Point-of-care (POC) abdominal ultrasound (US) can fulfill all these criteria; it is inexpensive, portable, not too uncomfortable for the patient, has a fast turnaround time, can be repeated for monitoring the course of the disease, and there is no radiation exposure.

The POC abdominal US was first proposed in the 1980s for diagnosis and subsequent monitoring of NEC.[8,9] Since then, many studies have supported its role in the assessment/clinical management of NEC.[10–15] Even though AXR remains a first-line modality with more than 90% of neonatologists still relying on it to diagnose and manage NEC,[16] POC abdominal US is gaining importance. Ahle et al.[16] conducted a survey and showed that POC abdominal US was used in combination with AXR for managing NEC in about 58% of all centers. Abdominal US was done most frequently when the AXR findings were inconclusive. Many studies have shown that POC abdominal US was better than AXR in diagnosing NEC.[12,13,15,17] However, abdominal US remains underutilized and there is a need for better awareness and training of neonatologists for early diagnosis and treatment of NEC, which will likely improve the outcomes.[7,18]

Technique

The imaging of the gastrointestinal tract in POC abdominal US requires a standardized, structured format. Faingold[19] published a detailed protocol for doing POC abdominal US for diagnosing NEC. High-frequency linear probes of 8–20 Hz are recommended for clear visualization of the gut wall. Lower-frequency curvilinear probes may be more useful for imaging free fluid in deeper spaces and in detecting portal venous gas.

Images of all four quadrants of the abdomen should be obtained (Fig. 1) with the probe placed in the two perpendicular planes—transverse and longitudinal. The procedure is often easier to perform by nesting or swaddling the infant, who should be monitored for vital signs during the evaluation. Gas reverberation artifacts (Fig. 2) are seen frequently while doing POC abdominal US. These can be reduced with gentle compression of the probe and turning the infant to one side.

The infant should be carefully assessed before placing the sonographic probe(s) as NEC is frequently associated with abdominal tenderness; there might be a need for analgesics/conscious sedation. The abdomen should be examined for (A) fluid or free-air collection and portal venous gas using a lower-frequency curvilinear probe; and (B) findings in the gastrointestinal tract in grayscale and color Doppler mode. In the grayscale, the intestines should be evaluated for echotexture, gut wall thickness, dilatation, pneumatosis intestinalis, and peristaltic movements. These findings may each need to be examined for at least one minute in each view for changes with peristaltic movements. In the color Doppler mode, the gut wall vascularity should be assessed in comparison with adjacent bowel loops. The color Doppler may need to be examined at a velocity of 0.029–0.11 m/seconds with the lowest possible pulse repetition frequency without aliasing, and with a low wall filter and the highest Doppler gain settings without flash artifacts. These tools help in better delineation of intestinal blood flow.[15,19] Observations of each quadrant should be documented; the inability to assess specific region(s) due to artifacts should be recorded for examination at later time points. Follow-up assessments are frequently performed every 12–24 hours in view of the dynamic nature of the disease and because gut wall abnormalities may be missed in some scans because of frequently seen artifacts.

Normal Gut Appearance in Point-of-care Abdominal Ultrasound

Gut Signature

The gut wall on POC abdominal US appears as alternate hyper- and hypo-echoic layers (Figs 3 and 4). The intestinal wall shows the following five layers from within outward: The mucosa (hyperechoic), muscularis mucosae (hypoechoic), submucosa (hyperechoic), muscularis propria (hypoechoic) and serosa (hyperechoic). This alternating hyperechoic and hypoechoic layers on abdominal US is called the "gut signature".[20,21] The appearance of these five layers depends on the resolution of the probe, the quality of the sonogram, and the depth of the gut being studied. In neonates, three layers are more easily discernible, the most prominent being the hypoechoic

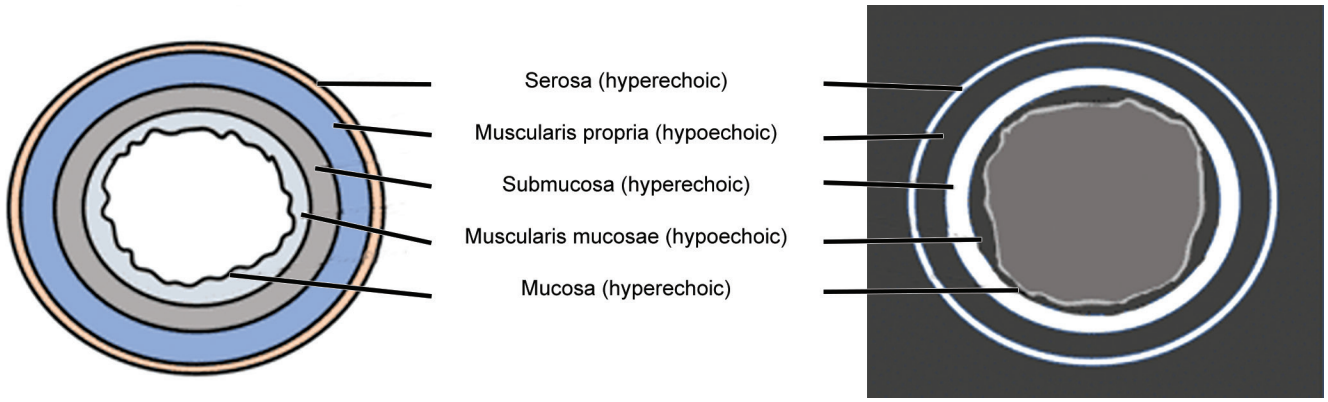


Fig. 3: Diagrammatic representation of alternating hypoechoic and hyperechoic layers of gut wall seen on POC abdominal US (gut signature)

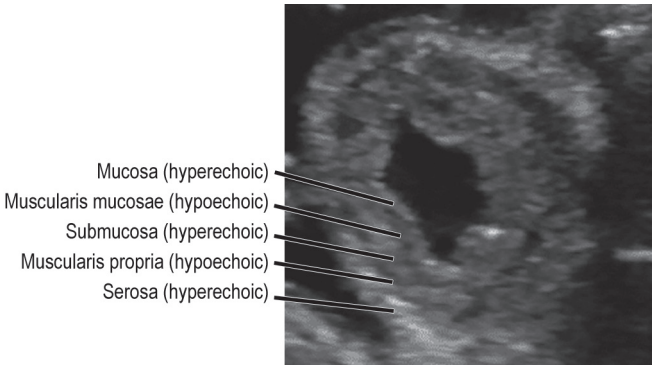


Fig. 4: Gut signature in POC abdominal US

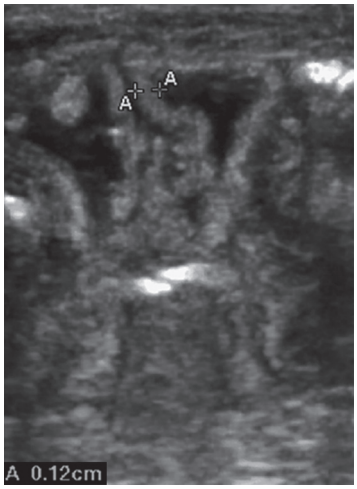


Fig. 5: Calipers measuring gut wall thickness. Normal gut wall thickness in neonates is 1–2.6 mm

muscularis propria. The loss of this gut signature indicates bowel pathology.

Gut Wall Thickness

Gut wall thickness is age dependent.[22] In neonates, the normal gut wall thickness varies between 1–2.6 mm (Fig. 5).[15,23] In NEC, most inflamed intestinal segments show increased wall thickness. Some segments with ischemia and necrosis are relatively thin.[7,24]

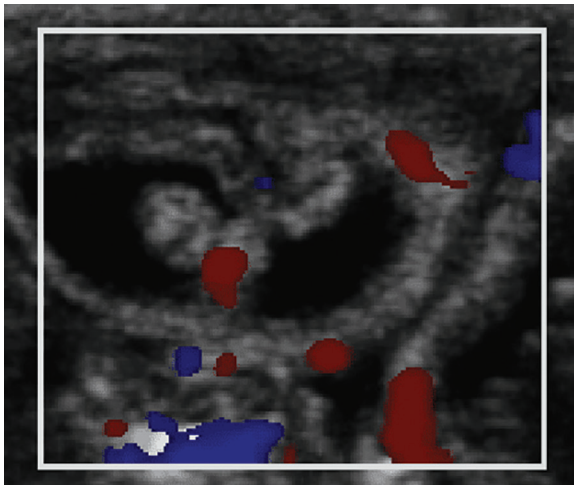


Fig. 6: Normal gut perfusion was assessed by putting a color Doppler and counting the signal dots per sq. cm

Perfusion of Normal Gut

Gut wall perfusion can be assessed by placing color Doppler in the gut wall. Normally, 1–9 color signal dots can be detected per sq. cm at a color Doppler velocity of 0.029–0.11 m/s with the lowest possible pulse repetition frequency without aliasing. The highest Doppler gain settings without flash artifacts indicate normal physiological bowel wall perfusion (Fig. 6).[15] Abnormalities of gut perfusion show no color dots even at the lowest velocity. However, some segments can show increased dots or there might be abnormal patterns.[7,15,24]

Peristalsis in Normal Gut

When POC abdominal US is used for real-time monitoring, peristalsis can be seen as a worm-like motion; some segments may show displacement of echogenic fluid in the opening/closing gut lumen. Normal bowel usually shows at least 10 peristaltic movements per minute.[15]

Intraluminal Gas Shadows

In the normal intestine, intraluminal gas shadows show as echogenic dots (Fig. 7). These dots should be differentiated from the echogenic dots present in the intestinal wall indicating intramural pneumatosis intestinalis.[7]

Point-of-care Abdominal Ultrasound in Necrotizing Enterocolitis

Probe Tenderness

When an US probe is placed, signs of tenderness, even though non-specific, may indicate early NEC. Administration of analgesics may provide some comfort to these patients.

Portal Venous Gas

Echogenic intestinal intramural gas can often be seen escaping from the mesenteric vessels into the portal venous system in hepatic parenchyma (Fig. 8). On real-time POC abdominal US assessment, these echogenic foci are typically seen moving distally. These are seen as sharp bidirectional spikes superimposed on the underlying waveform on spectral Doppler. Even though these echogenic foci are usually transient and have low sensitivity, these are highly specific for the recognition of NEC.[23] The observers should note that insertion/manipulation of an umbilical venous catheter(s) can also be seen as echogenic foci.

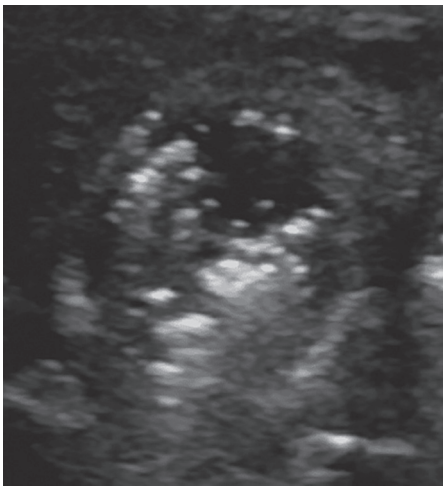


Fig. 7: Echogenic dots present in the lumen of the normal intestine

Free Fluid Collection

Neonates with NEC may have ascites, which show as anechoic areas in the abdominal cavity between the gut and the surrounding intraperitoneal structures. It can be of two types—simple and complex (Fig. 9). Small amounts of simple free fluid can also present physiologically.[15] Complex ascites are more often echogenic and can show loculations. These findings may indicate intestinal perforation and a need for surgical intervention.[25]

Free Air Collection

Pneumoperitoneum, a sign of intestinal perforation, is seen on US as a hyperechoic line posterior to the anterior abdominal wall. It is easiest to visualize between the anterior surface of the liver and the abdominal wall (Fig. 10). However, the examiners should be cautious and not compress the probe as this might displace any air present in the space between the liver and the abdominal wall.

Loss of Gut Signature

Changes in gut wall echotexture with the loss of gut signature usually indicate bowel wall pathology. Increased intestinal echogenicity with a loss of the hypoechoic muscularis signal is a characteristic sign (Fig. 11). This should be differentiated from the pneumatosis intestinalis, which is usually associated with posterior shadowing.[26]

Gut Wall Thickness

The gut should be visualized with measurements of bowel wall thickness in all four quadrants (Fig. 12A). In the initial stages of NEC, inflammation and edema are seen as increased bowel wall thickness (>2.5-2.7 mm) (Fig. 12B).[15,23] Later, disease progression with ischemia and necrosis may reduce bowel wall thickness (typically <1 mm) (Fig. 12C).[7,15,23,24] In a meta-analysis, neonates with low gut wall thickness were at higher risk of requiring surgery or of death [odds ratio (OR): 7.1, 1.6–32.3] compared to those with increased thickness (OR: 3.9, 2.4–6.1).[25]

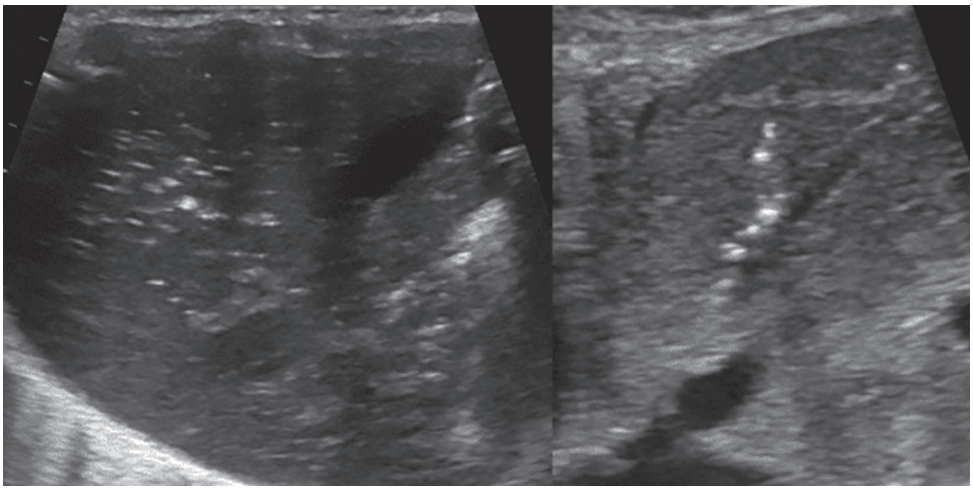
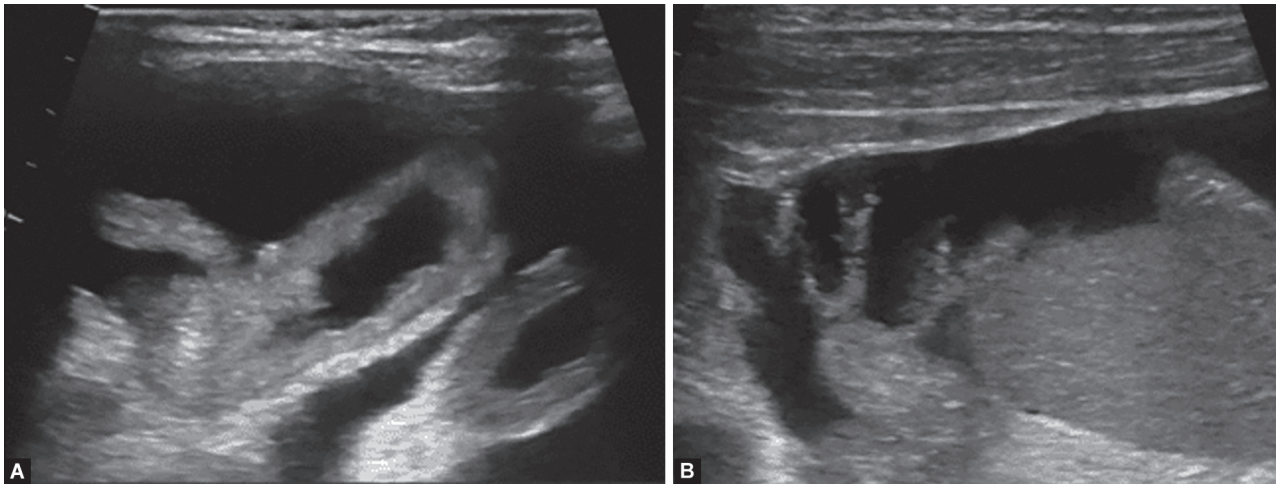


Fig. 8: Portal venous gas—echogenic foci in the portal vein system



Figs 9A and B: Free fluid collection. (A) Simple free fluid—anechoic area between the gut walls; (B) Complex free fluid collection—echogenic material is seen in between the anechoic areas suggestive of debris

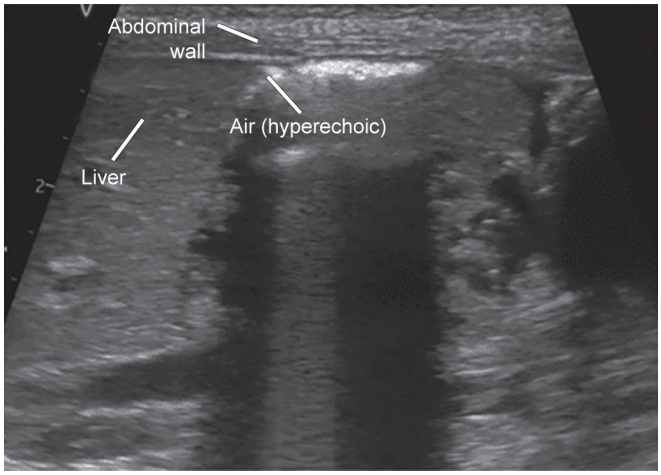


Fig. 10: Pneumoperitoneum—hyperechoic line can be seen between the anterior surface of the liver and the abdominal wall

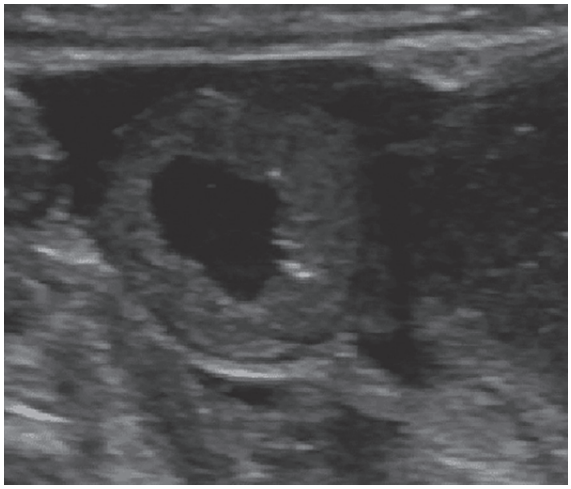
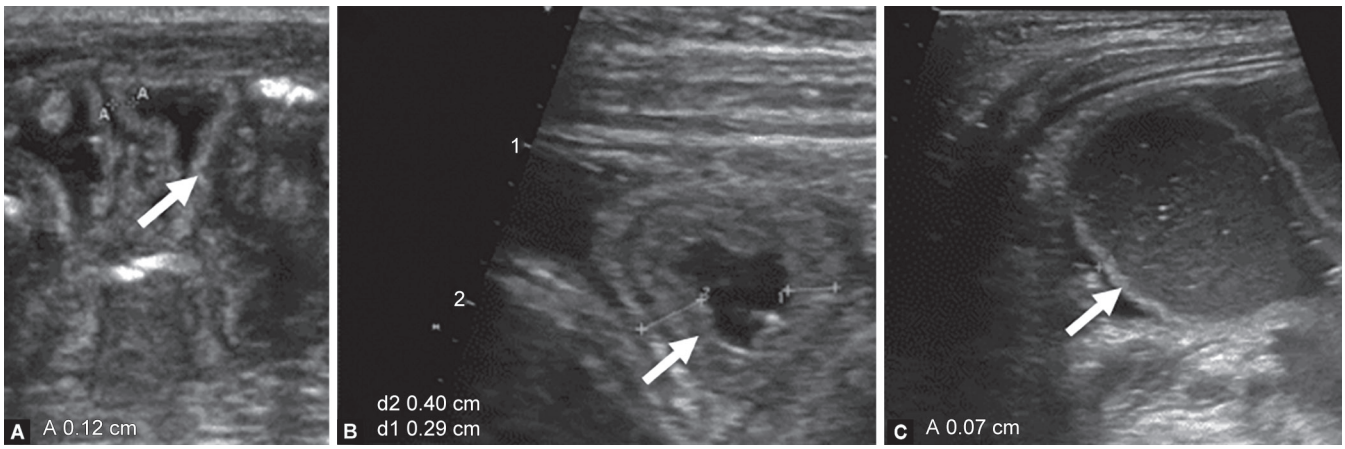


Fig. 11: Loss of gut signature



Figs 12A to C: Gut wall thickness. (A) Normal gut wall thickness; (B) Increased gut wall thickness; (C) Decreased gut wall thickness

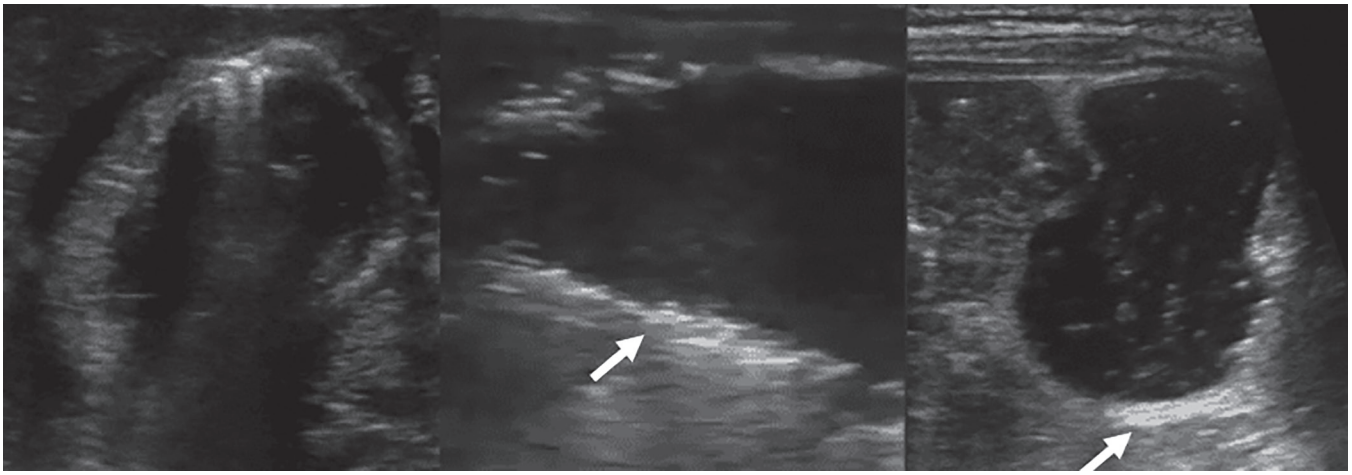
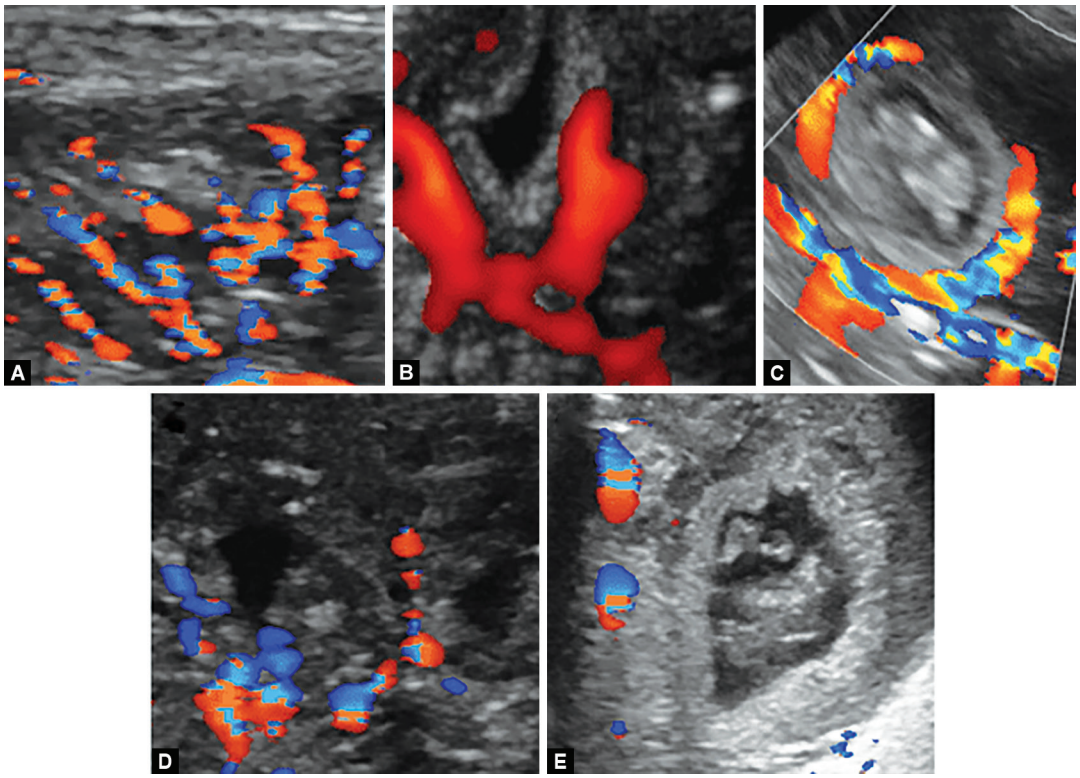


Fig. 13: Pneumatosis intestinalis—echogenic dots in the wall of the gut



Figs 14A to E: Pathological perfusion of gut wall. (A) Zebra pattern; (B) Y-shaped pattern; (C) Ring-shaped pattern; (D) Increased color dots; (E) Decreased perfusion of gut wall in NEC

Loss of Peristalsis

The normal gut has peristaltic movements. Gut pathology in NEC leads to decreased or absent peristaltic movements (<10/min).[15] These findings might be missed if the bowel is not examined for adequate periods of time.

Pneumatosis Intestinalis

The term pneumatosis intestinalis refers to gas entrapped in the damaged layers of the bowel wall in NEC. These gases are produced due to bacterial fermentation of static gut contents in the inflamed bowel and are seen as echogenic dots in the intestinal wall.[27] These dots can range from a few, interspersed hyperechoic lesions in the gut wall to a large circumferential cloud-like layer that surrounds the bowel wall (circle sign) (Fig. 13).

Pneumatosis is often a transient finding in NEC and may require repeated POC abdominal US scans.[23] In addition to low diagnostic sensitivity, it also does not aid in predicting the need for surgery or the eventual outcome in these patients.[25] As mentioned above, the intramural dots of pneumatosis should be differentiated from the normally seen intraluminal echogenic dots (Fig. 7). Unlike the intramural *pneumatosis* that can be seen anywhere along the bowel wall, the intraluminal gas shadows are usually seen in the

non-dependent part of the intestine and get displaced on changing the position of the baby or on the application of pressure with the probe.

Abnormal Bowel Perfusion

After assessing the gut on a grayscale, further evaluation of vascularity and bowel perfusion can be performed using color Doppler. Inflamed segments of the bowel in NEC frequently show hyperemia with increased vascularity. These changes show characteristic US signatures such as the zebra pattern (increased vascularity at the mucosal folds of the small intestine resulting in multiple, parallel color lines) (Fig. 14A), Y-shaped patterns (subserosal and mesenteric vessels) (Fig. 14B), ring-shaped patterns (increased blood flow over the entire circumference of the bowel wall) (Fig. 14C), or as increased color dots, more than the normal (Fig. 14D).[7,15,24,26] The ensuing bowel ischemia and necrosis result in decreased and then absent perfusion of the gut (Fig. 14E). The loss of perfusion frequently indicates a need for surgery or a fatal outcome.[25] Comparison of the diseased segments of the intestine with the surrounding normal gut might provide important insights into the extent of altered perfusion.

Utility of Point-of-care Abdominal Ultrasound in Necrotizing Enterocolitis

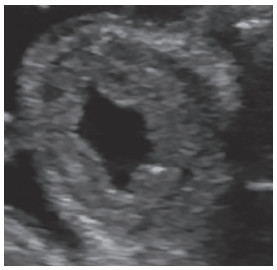
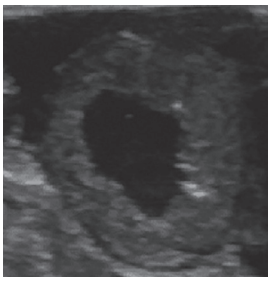
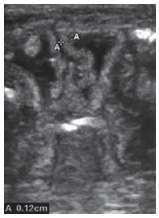
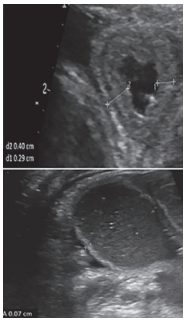
We know that AXR has limitations in the diagnosis of NEC.[7,28] The diagnosis is frequently feasible only when pneumatosis and/or portal venous gas are seen. The sensitivity of these radiological markers can be even lower in mildly-afflicted cases.[29] Bowel wall dilation is a sensitive finding but is not specific to NEC.[7] Other non-specific findings include ascites, air-fluid levels, and bowel wall thickening. An important clinical difficulty arises in the low specificity of the sensitive signs and low sensitivity for the specific signs.[7,28,30,31]

Many meta-analyses and narrative reviews have shown that abdominal US is useful in the diagnosis of NEC.[7,12,25,32,33] Compared to AXR, US seems to be more sensitive for early detection of NEC; it can detect early markers such as altered bowel perfusion, decreased peristalsis, and bowel wall thickening, and helps in the timely initiation of management before the onset of advanced disease marked by ileus, loss of bowel perfusion, and bowel wall thinning (Tables 1 and 2).[10,11,25] Even though abdominal US may not detect NEC in every single case, it can confirm the absence of findings of NEC where AXR is equivocal.[34,35] The detection of pneumatosis and/or portal venous gas can also help in differentiating perforated NEC from other causes of intestinal perforation like spontaneous intestinal perforation.[36] Compared to abdominal radiography, US is more sensitive in detecting pneumatosis and/or portal venous gas.[37]

Unfortunately, both AXR and abdominal US seem to be inadequate as stand-alone diagnostic tests for NEC. A non-diagnostic AXR cannot nullify a suspicious abdominal US in a preterm infant with suspicion of NEC. Abdominal US is more informative than AXR in the evaluation for NEC, but its sensitivity and negative predictive value are low. A negative abdominal US scans should be interpreted with caution, particularly in at-risk preterm infants. In a cohort of 100 infants with suspected NEC and a hypothetical overall prevalence of about 50%, Cuna et al.[23] showed that 25–40 infants with a negative US evaluation could have had NEC (false negatives).

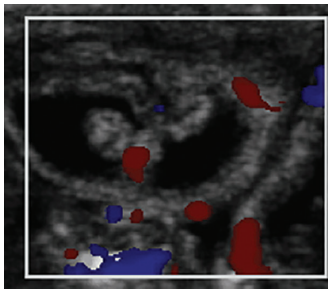
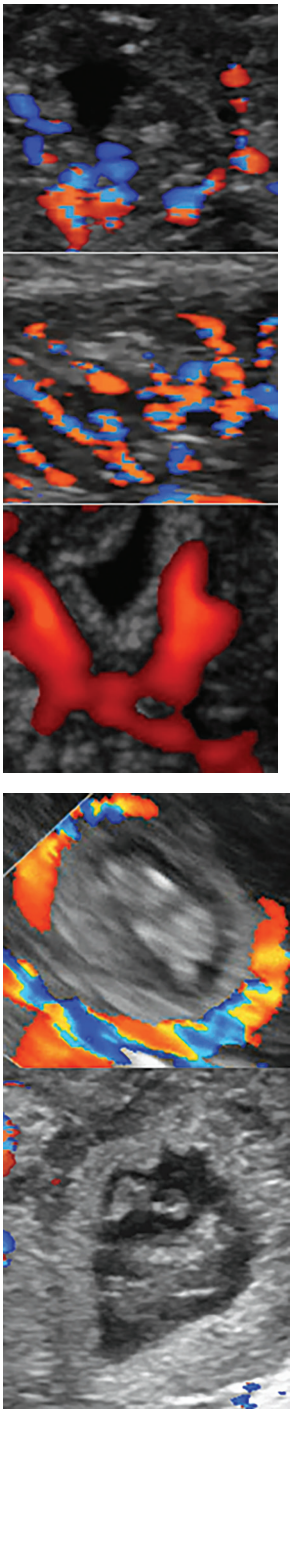
A meta-analysis[23] of studies of infants with probable NEC showed US as having high specificity and positive predictive value

Table 1: Summary of POC abdominal US findings in a normal gut and NEC

	Normal gut		*NEC*	
Probe tenderness	*Absent*		*Present*	
Gut wall echotexture	5 layers of alternating hyperechoic and hypoechoic layers – gut signature		Loss of gut signature	
Gut wall thickness	1–2.6 mm		Increased thickness – >2.6 mm Later stages – decreased thickness <1 mm	

(Contd...)

Table 1: *(Contd...)*

	Normal gut		*NEC*	
Probe tenderness	*Absent*		*Present*	
Peristalsis	At least 10 peristaltic movements per minute		Less than 10 peristaltic movements per minute	
Gut wall perfusion	1–9 color signal dots detected per sq. cm		Increased perfusion – >9 color signal dots detected per sq. cm Specific patterns – zebra pattern Y-shaped pattern Ring-shaped pattern Later stages – decreased or absent perfusion	

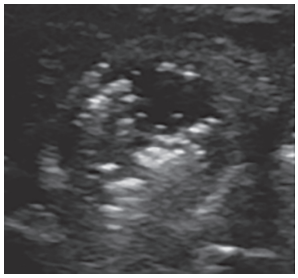
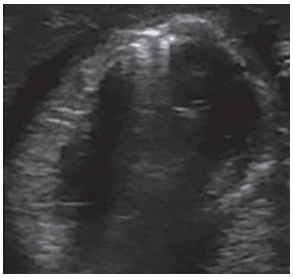
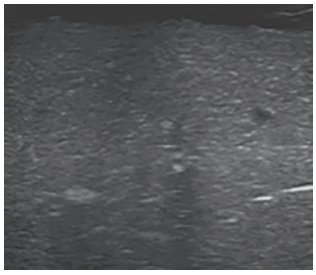
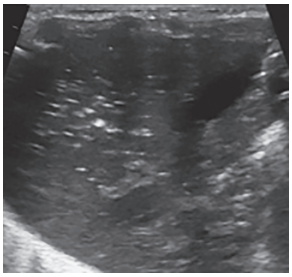
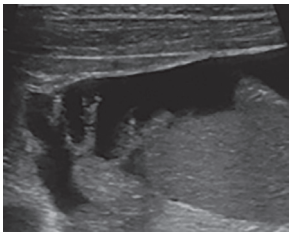
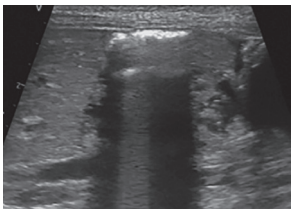
Pneumatosis intestinalis	Absent (intraluminal gas may be present)		Present	
Portal venous gas	Absent		Present	
Fluid collection	Absent (small amount of simple free fluid can be present physiologically)		Present Complex free fluid is always pathological	
Free air collection	Absent		Hyperechoic line posterior to the anterior abdominal wall – easiest to visualize between the anterior surface of the liver and the abdominal wall	

Table 2: Format for POC abdominal US

	LLQ	*LUQ*	*RUQ*	*RLQ*
Phase I (using lower frequency curvilinear probe – 4–8 Hz)				
Portal venous gas				
Tenderness				
Fluid collection				
Free air collection				
Phase II (using high-frequency linear probe – 8–20 Hz)				
Gut wall echotexture				
Gut wall thickness				
Peristalsis*				
Pneumatosis intestinalis				
Perfusion				

*For assessing peristalsis, the gut must be observed for at least 1 minute. For each quadrant, the examination should be done in two planes—transverse and longitudinal. LLQ, left lower quadrant; LUQ, left upper quadrant; RLQ, right lower quadrant; RUQ, right upper quadrant

for NEC diagnosis. Classic signs of NEC on abdominal US (portal venous gas, pneumatosis, and free air) had pooled sensitivities ranging from 0.27 to 0.48 and pooled specificities ranging from 0.91 to 0.99. Bowel wall thinning and absent peristalsis had overall low sensitivity (0.22 and 0.30) but high specificity (0.96 and 0.96) for NEC. Detection of abdominal fluid, which included ascites and focal fluid collection, also had overall low sensitivity and high specificity (simple ascites—0.45 and 0.92; focal fluid collection—0.19 and 0.98). Hence, sonographic evaluation may have low sensitivity and high specificity for the diagnosis of NEC. The absence of the findings in a single sonographic examination does not exclude NEC in a patient.

Abdominal US can help in prognostication in NEC. Focal fluid collections, complex ascites, absent peristalsis, pneumoperitoneum, bowel wall echogenicity, bowel wall thinning, absent perfusion, bowel wall thickening, and dilated bowel have been associated with the combined outcome of the need for surgery or death.[25] Therefore, when positive, US can help in earlier, timely decision-making for surgical management in NEC, when AXRs might still be equivocal.

Limitations

Further work is needed for increasing the acceptance of abdominal US as a standard modality for the diagnosis of NEC. There is limited experience in settings with low incidence of NEC. Also, the steep learning curve, the higher financial burden of the machine, interobserver variability, the perception of neonatologists toward US, and the common artifacts faced, hinder its widespread use. Clinical instability due to overzealous use of abdominal US leading to desaturation, apnea, and bradycardia can be present. These can be overcome by training and emphasis on the protocol-based approach of the POC abdominal US examination with special emphasis on the most important diagnostic pointers toward NEC. Using a large quantity of gel with minimum possible pressure on the abdomen may prevent stress to the neonate.

Conclusion

Necrotizing enterocolitis, a nightmare for neonatologists, continues to have poor outcome. Early diagnosis of NEC and timely surgical intervention can hugely improve the prognosis of these neonates. POC abdominal US along with clinical evaluation and AXR has the potential to become the gold standard for the evaluation of these neonates, which not only can diagnose early signs of NEC but also may differentiate NEC from other causes of feed intolerance. With the growing evidence about the benefits of abdominal US, and the clinicians getting accustomed to sonography, it will go a long way in managing such babies.

References

1. Alsaied A, Islam N, Thalib L. Global incidence of necrotizing enterocolitis: A systematic review and meta-analysis. BMC Pediatr 2020;20(1):344. DOI: 10.1186/s12887-020-02231-5.
2. Zozaya C, González IG, Avila–Alvarez A, et al. Incidence, treatment, and outcome trends of necrotizing enterocolitis in preterm infants: A multicenter cohort study. Front Pediatr 2020;8:188. DOI: 10.3389/fped.2020.00188.
3. Han SM, Hong CR, Knell J, et al. Trends in incidence and outcomes of necrotizing enterocolitis over the last 12 years: A multicenter cohort analysis. J Pediatr Surg 2020;55(6):998–1001. DOI: 10.1016/j.jpedsurg.2020.02.046.
4. Fitzgibbons SC, Ching Y, Yu D, et al. Mortality of necrotizing enterocolitis expressed by birth weight categories. J Pediatr Surg 2009;44(6):1072–1075; Discussion 1075–1076. DOI: 10.1016/j.jpedsurg.2009.02.013.
5. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187(1):1–7. DOI: 10.1097/00000658-197801000-00001.
6. Walsh MC, Kliegman RM. Necrotizing enterocolitis: Treatment based on staging criteria. Pediatr Clin North Am 1986;33(1):179–201. DOI: 10.1016/s0031-3955(16)34975-6.
7. Epelman M, Daneman A, Navarro OM, et al. Necrotizing enterocolitis: Review of state-of-the-art imaging findings with pathologic correlation. Radiographics 2007;27(2):285–305. DOI: 10.1148/rg.272055098.
8. Merritt CR, Goldsmith JP, Sharp MJ. Sonographic detection of portal venous gas in infants with necrotizing enterocolitis. AJR Am J Roentgenol 1984;143(5):1059–1062. DOI: 10.2214/ajr.143.5.1059.
9. Robberecht EA, Afschrift M, De Bel CE, et al. Sonographic demonstration of portal venous gas in necrotizing enterocolitis. Eur J Pediatr 1988;147(2):192–194. DOI: 10.1007/BF00442221.
10. Garbi–Goutel A, Brévaut–Malaty V, Panuel M, et al. Prognostic value of abdominal sonography in necrotizing enterocolitis of premature infants born before 33 weeks gestational age. J Pediatr Surg 2014;49:508–13. DOI: 10.1016/j.jpedsurg.2013.11.057.
11. He Y, Zhong Y, Yu J, et al. Ultrasonography and radiography findings predicted the need for surgery in patients with necrotising enterocolitis without pneumoperitoneum. Acta Paediatr 2016;105:e151–5. DOI: 10.1111/apa.13315.
12. Dilli D, Suna Oğuz S, Erol R, et al. Does abdominal sonography provide additional information over abdominal plain radiography for diagnosis of necrotizing enterocolitis in neonates? Pediatr Surg Int 2011;27:321–7. DOI: 10.1007/s00383-010-2737-8.
13. Shebrya NH, Amin SK, El-Shinnawy MA, et al. Abdominal ultrasonography in preterm necrotizing enterocolitis. Is it superior to plain radiography? Egyptian J Rad Nuclear Med 2012;43(3):457–463. DOI: 10.1016/j.ejrnm.2012.06.001.
14. Kim WY, Kim WS, Kim IO, et al. Sonographic evaluation of neonates with early-stage necrotizing enterocolitis. Pediatr Rad 2005;35(11):1056–1061. DOI: 10.1007/s00247-005-1533-4.
15. Faingold R, Daneman A, Tomlinson G, et al. Necrotizing enterocolitis: Assessment of bowel viability with color Doppler US. Radiology 2005;235(2):587–594. DOI: 10.1148/radiol.2352031718.
16. Ahle M, Ringertz HG, Rubesova E. The role of imaging in the management of necrotising enterocolitis: A multispecialist survey and a review of the literature. Eur Radiol 2018;28(9):3621–3631. DOI: 10.1007/s00330-108-5362-x.
17. Chen S, Hu Y, Liu Q, et al. Comparison of abdominal radiographs and sonography in prognostic prediction of infants with necrotizing enterocolitis. Pediatr Surg Int 2018;34(5):535–541. DOI: 10.1007/s00383-018-4256-y.
18. Abdullah F, Zhang Y, Camp M, et al. Necrotizing enterocolitis in 20,822 infants: Analysis of medical and surgical treatments. Clin Pediatr 2010;49(2):166–171. DOI: 10.1177/0009922809349161.
19. Faingold R. Technical aspects of abdominal ultrasound and color Doppler assessment of bowel viability in necrotizing enterocolitis. Pediatr Radiol 2018;48(5):617–619. DOI: 10.1007/s00247-018-4077-0.
20. Heyder N, Kaarmann H, Giedl J. Experimental investigations into the possibility of differentiating early from invasive carcinoma of the stomach by means of ultrasound. Endoscopy 1987;19(06):228–232. DOI: 10.1055/s-2007-1013019.
21. Wilson SR. Gastrointestinal tract sonography. Abdom Imaging 1996;21(1):1–8. DOI: 10.1007/s002619900001.
22. Haber HP, Stern M. Intestinal ultrasonography in children and young adults: Bowel wall thickness is age dependent. J Ultrasound Med 2000;19(5):315–321. PMID: 10811404.
23. Cuna AC, Lee JC, Robinson AL, et al. Bowel ultrasound for the diagnosis of necrotising enterocolitis. Ultrasound Q 2018; 34:113–118. DOI: 10.1097/RUQ.0000000000000342.
24. van Druten J, Khashu M, Chan SS, et al. Abdominal ultrasound should become part of standard care for early diagnosis and management of necrotising enterocolitis: A narrative review. Arch Dis Child Fetal Neonatal Ed 2019;104(5):F551–F559. DOI: 10.1136/archdischild-2018-316263.
25. Cuna AC, Reddy N, Robinson AL, et al. Bowel ultrasound for predicting surgical management of necrotizing enterocolitis: A systematic review and meta-analysis. Pediatr Radiol 2018;48(5):658–666. DOI: 10.1007/s00247-017-4056-x.
26. Alexander KM, Chan SS, Opfer E, et al. Implementation of bowel ultrasound practice for the diagnosis and management of necrotising enterocolitis. Arch Dis Child Fetal Neonatal Ed 2021;106(1):96–103. DOI: 10.1136/archdischild-2019-318382.
27. Priyadarshi A, Rogerson S, Hinder M, et al. Neonatologist performed point-of-care bowel ultrasound: Is the time right? Australas J Ultrasound Med 2018;22(1):15–25. DOI: 10.1002/ajum.12114.

28. Buonomo C. The radiology of necrotizing enterocolitis. Radiol Clin North Am 1999;37(6):1187–1198. DOI: 10.1016/s0033-8389(05)70256-6.
29. Tam AL, Camberos A, Applebaum H. Surgical decision making in necrotizing enterocolitis and focal intestinal perforation: Predictive value of radiologic findings. J Pediatr Surg 2002;37(12):1688–1691. DOI: 10.1053/jpsu.2002.36696.
30. Kosloske AM, Musemeche CA, Ball WS, et al. Necrotizing enterocolitis: Value of radiographic findings to predict outcome. AJR Am J Roentgenol 1988;151(4):771–774. DOI: 10.2214/ajr.151.4.771.
31. Daneman A, Woodward S, de Silva M. The radiology of neonatal necrotizing enterocolitis (NEC). A review of 47 cases and the literature. Pediatr Radiol 1978;7(2):70–77. DOI: 10.1007/BF00975674.
32. Bohnhorst B. Usefulness of abdominal ultrasound in diagnosing necrotising enterocolitis. Arch Dis Child Fetal Neonatal Ed 2013;98(5):F445–F450. DOI: 10.1136/archdischild-2012-302848.
33. Lok JM, Miyake H, Hock A, et al. Value of abdominal ultrasound in management of necrotizing enterocolitis: A systematic review and meta-analysis. Pediatr Surg Int 2018;34(6):589–612. DOI: 10.1007/s00383-018-4259-8.
34. Cotten CM, Taylor S, Stoll B, et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics 2009;123(1):58–66. DOI: 10.1542/peds.2007-3423.
35. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: The experience of the NICHD neonatal research network. Pediatrics 2002;110(2 Pt 1):285–291. DOI: 10.1542/peds.110.2.285.
36. Pumberger W, Mayr M, Kohlhauser C, et al. Spontaneous localized intestinal perforation in very-low-birth-weight infants: a distinct clinical entity different from necrotizing enterocolitis. J Am Coll Surg 2002;195:796–803. DOI: 10.1016/s1072-7515(02)01344-3.
37. Prithviraj D, Sandeep B, Suresh A, et al. Comparison between X-ray and abdominal ultrasound findings of necrotizing enterocolitis, its usefulness in early diagnosis, prognosis, and to assess, is this is the time to change our view of surgeon's intervention according to the Bell's criteria. Int J Sci Study 2015;3(4):119–130. DOI: 10.17354/ijss/2015/319.

REVIEW ARTICLE

Umbilical Cord Blood Gases: Sampling, Evaluation, and Application for Clinicians

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Abstract

Predicting the severity of birth asphyxia-related brain injury in newborn infants is a difficult task. Cord blood gases can be useful indices in the assessment of the impact of peripartum events. Cord blood gas parameters are particularly important because, despite all the progress in fetal monitoring, the time gap between the onset of fetal heart rate (FHR) abnormalities and birth asphyxia-related brain injury has remained difficult to predict. In this paper, we have focused on cord blood gas values in understanding the degree of compromise. These data can help determine the timing of fetal compromise prior to labor, and whether these precipitating events were acute or prolonged. When combined with some adverse clinical markers, the accuracy of low-cord pH in predicting neonatal mortality and morbidity can be even higher. Low-cord pH or eucapnic neonatal pH can also help in the surveillance of at-risk infants and in timely institution of neuroprotective therapies. We present a detailed review on sampling, evaluation, and application of cord blood gas values for clinicians.

Keywords: Arterio-venous difference, '20, 30, 40, 50 rule', Maternal hypoxemia, Base deficit, Birth asphyxia, Brain injury, Carbonic acid, Cerebral palsy, Cord blood gas, Eucapnic pH, pH qu 40, Hypercapnia, Hypoxic–ischemic encephalopathy, Maternal positioning, Neonatal encephalopathy, Nuchal cord, Organic acids, Oxygen-carrying capacity, Peripartum events, Placenta, Rectal temperature, Regional anesthesia, Respiratory acidosis, Stillbirth, Surveillance, Umbilical arteries, Umbilical venous blood, Vascular zone, Universal cord blood gas analysis.

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Key Points

- Cord blood gas values can be useful indices in the assessment of the impact of peripartum events.
- In combination with adverse clinical markers, cord pH can be a useful predictor of neonatal mortality; serial measurements of cord pH or eucapnic neonatal pH can help in the surveillance of at-risk infants.
- An uneventful first stage of labor can show a base deficit of 3 mM/L, which further drops at a rate of 1 mM/L per hour during the second stage of labor. In contrast, prolonged uterine contractions may be associated with fetal heart decelerations, and the base deficit may drop by 1 mM/L every 30 minutes.
- Low umbilical arterial pH <7 has been associated with a 10-fold higher risk of 1-min Apgar score of <4, 5-min Apgar score of <7, and 7.6-times higher risk of acute NE.
- Increasing information suggests that universal cord blood gas analysis can provide useful predictors of adverse neurocognitive outcomes.

Introduction

The umbilical cord is the critical conduit in the womb between the mother and her growing fetus; any insult or injury to this supply line can disrupt fetal oxygenation. In clinical units, the materno-fetal unit is routinely monitored for changes in maternal heart rate and blood pressure, fetal heart rate (FHR), FHR variability, and fetal movements during pregnancy and labor. Unfortunately, manual methods to monitor these are cumbersome and may not be cost-effective. To circumvent these difficulties, external and internal electronic fetal heart monitoring came into vogue and these are now the standard of care during labor.[1]

Recent years have brought increasing recognition that despite all the advances made in fetal monitoring, we still face a time lag between the detection of FHR abnormalities and the delivery of the infant. This sometimes jeopardizes fetal circulation and results in birth asphyxia. Measurement of cord blood gas values can help determine the degree of compromise and whether the precipitating event was acute or prolonged, and its timing prior to the onset of labor. Umbilical cord blood gas, a marker of neonatal vitality, is now increasingly accepted as the standard of care in all high-risk deliveries.[2] Hence, it is important for those who manage newborn babies to be familiar with the practice of obtaining and interpreting cord blood gas values.[3]

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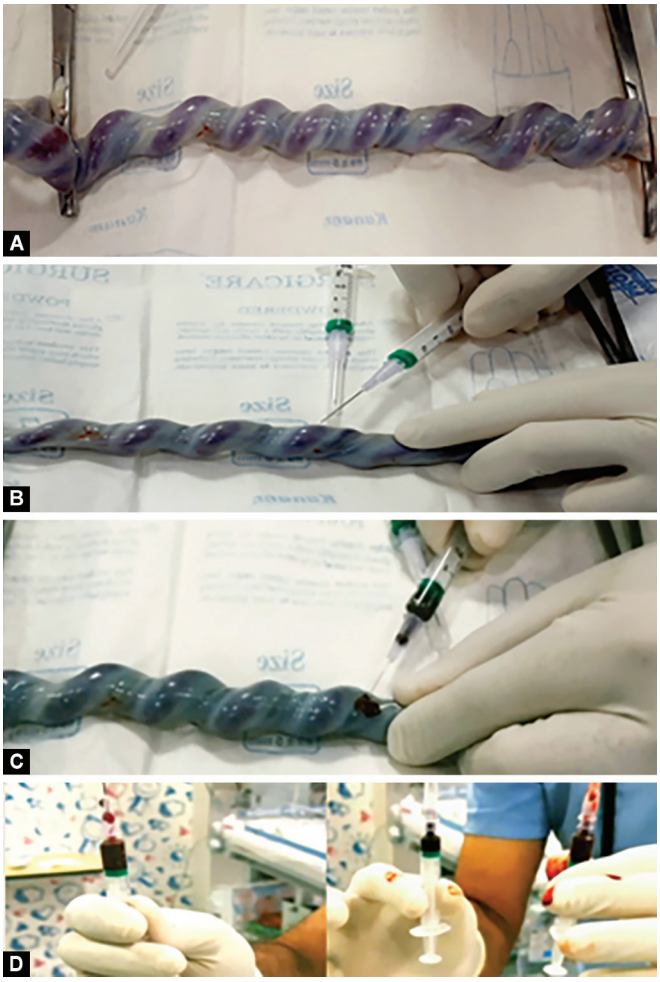
Physiology of Placental Circulation

The placenta is a vascular zone where gas/nutrient exchange between maternal and fetal circulation occurs. There is one large umbilical vein that carries oxygenated blood and nutrients to the fetus. Following tissue extraction of gases and nutrients, fetal blood returns to the placenta in two small umbilical arteries. Hence, umbilical artery blood primarily reflects fetal metabolism, while umbilical venous blood represents placental functions.[4] Normal fetal metabolism produces volatile (carbonic acid) and nonvolatile



Figs 1A to D: Cord blood gas sampling procedure essentials. (A) Double clamp, a 20-cm long segment of cord. (B) Differentiate umbilical artery from vein Take 2 heparinized syringes for paired samples. (C) Sample umbilical artery first at 45°. (D) Do not contaminate the sample with air remove air bubbles, label both samples correctly transport and analyze within 30 minutes

A brief description of the umbilical cord blood gas sampling procedure can be viewed in the video available on its journal website at https://www.newbornjournal.org/

acids (lactate and organic acids). These are neutralized by buffer bases (bicarbonate and hemoglobin) to maintain the fetal pH within a narrow range.[5] However, unlike newborn infants, the fetus is unable to compensate for acidemia by respiratory and renal responses. The placenta can help maintain the bicarbonate pool, but biocarbonate depletion eventually manifests as base deficit.[6]

Cord Blood Gas Sampling Procedure

The accuracy of cord blood gas (CBG) analysis is improved by double clamping of the cord on either side to isolate a 20 cm-long portion, ideally before the baby's first breath. Clamping of the cord arrests the umbilical circulation; analysis of a sample drawn soon thereafter gives an estimate of the acid–base status of the infant at the time of birth. However, if the cord is not clamped to isolate its blood circulation from that of the placenta, the ongoing placental metabolism may alter the acid–base status in cord blood.[7] There may be a progressive decline in pH and base excess, increase in pCO_2 and lactate; these changes have been described as "hidden acidosis", which might just reflect a transient effect of initiation of neonatal breathing and give a false impression of significant acidosis at birth.[8] In other cases, cord blood gas values may remain unchanged for up to an hour after isolating the cord from maternal/neonatal circulation.

In most infants, umbilical arterial blood gas values may represent fetal metabolism, and if abnormal, may predict neonatal morbidity. In many cases, blood drawn from a relatively superficial umbilical vein can show less-accurate values. Hence, both arterial and venous blood should be sampled. Blood can be drawn into preheparinized syringes by needle aspiration, taking precautions to exclude air bubbles before capping the syringe, and should be analyzed within 30 minutes of sampling (Fig. 1). Contamination of the syringe with air has no effect on pH, pCO_2, or bicarbonate but can significantly elevate pO_2 values when there is more than 37.5% residual air in the syringe.[9–11] The validation of paired (arterial and venous) sample is based on minimum arterio-venous (A-V) difference for pH and pCO_2. The pH difference should be >0.02 units, and the PCO_2 difference should be >3.75 mm Hg. If the minimum A-V difference is documented, it can be safely assumed that the two samples are from different vessels, and the one with lower pH and higher pCO_2 is from the artery.[12] With the practice of placental transfusion gaining universal acceptance, concerns about

its effects on cord blood gas seem unfounded even after delayed cord clamping of up to 2 minutes.[13]

Interpretation of Cord Gas Values in Practice

In clinical practice, the following key questions need to be considered about CBG values:

(A) Normal Values

In CBG analysis, pH, PCO_2, and PO_2 are measured, whereas base deficit (BD) is calculated. The normal ranges for umbilical pH and blood gases which are broad and overlapping (shown in Table 1). It is often difficult to assign it to the umbilical artery or vein.[14,15] Ross and Gala.[16] recommend using the "20, 30, 40, 50 rule" as a simple tool for remembering normal CBG values (Table 2). Umbilical arterial PO_2 is typically lower than umbilical venous PO_2, at 20- and 30-mm Hg, respectively. PCO_2 value is higher in the umbilical artery than the umbilical vein, thus, 50 mm Hg denotes umbilical artery value, and 40 mm Hg indicates the umbilical vein value.

A normal uneventful first stage of labor leads to a base deficit of 3 mM/L, which further drops at a rate of 1 mM/L per hour during the second stage of labor. In contrast, prolonged uterine contractions may be associated with fetal heart decelerations, and the base deficit may drop by 1 mM/L every 30 minutes. The most severe fetal compromise, as seen in sudden cord compression or uterine rupture, may increase the base deficit by 1 mM/L every 2–3 minutes. In these situations, the obstetric team may have only 10–15 minutes to deliver the baby.[17]

pH_{UA} is typically lower than the umbilical vein pH, reflecting its higher PCO_2 and lactate levels. As the base deficit increases during labor, the pH falls. Brief rise in CO_2 levels (respiratory acidosis) may cause some fluctuations in pH, but this does not usually cause a significant insult and normalizes within a few minutes.[18]

Table 1: Normal cord blood gas values

	Umbilical artery	*Umbilical vein*
pH	7.18–7.38	7.25–7.45
PO_2	5.6–30.4 mm Hg	17.4–41.0 mm Hg
pCO_2	32.4–66.0 mm Hg	27.0–49.4 mm Hg
BD mean (SD)	4.79 (3.46) mmol/L	4.0 (3.5) mmol/L

Table 2: The "20, 30, 40, 50 rule" cord blood gases rule

Value mm Hg	*Cord gas value depicted*
20	Umbilical artery PO_2
30	Umbilical vein PO_2
40	Umbilical vein PCO_2
50	Umbilical artery PCO_2

(B) Factors Affecting Fetal Acid–Base Metabolism

Several factors have been associated with impaired fetal oxygenation and cord blood metabolic acidosis (Table 3). Maternal hypoxemia (respiratory diseases, seizures) and reduced oxygen-carrying capacity (anemia) may result in low maternal, and consequently, low fetal PO_2. Decreased uterine blood flow due to hypotension (shock, sepsis, regional anesthesia, and maternal positioning) and impaired perfusion on the maternal side of the placenta (abruptio) can be seen as narrowed arterio-venous differences in CBGs.[19] However, partial or complete restriction of umbilical blood flow (cord prolapse or entanglement, nuchal cord) may be seen as progressive widening of the umbilical artery and venous blood gas values. An arterio-venous pH difference of more than 0.15 units can differentiate reliably between cord prolapse and placental abruption. By virtue of being thin walled, during cord compression, the umbilical vein is significantly more compressed as compared with the umbilical arteries, reducing the supply of blood from the placenta to the fetus. A hypoxic fetus extracts most of the oxygen and generates more CO_2, making the arterial pH more acidotic, while umbilical venous pH is maintained by a normally functioning placenta.[20] Apgar scores and umbilical venous samples in such infants alone may be misleading, and it is crucial to confirm the diagnosis by documenting acidosis in the umbilical arterial blood.[21]

Rarely, despite severe intrapartum asphyxia in cord accidents (prolapse, true knot, and tight nuchal cord), the cord blood gas

Table 3: Factors affecting fetal acid base metabolism

Maternal factors	*Utero-placental factors*	*Fetal factors*
Maternal hypoxia	Uterine hyperstimulation	Umbilical cord factors
• Respiratory diseases	• Oxytocic drugs	• Oligohydramnios
• Respiratory depression	• Prolonged labor	• Cord prolapse/compression
• Trauma, seizures	• Instrumental delivery	• Nuchal cord
• Smoking	• Placental abruption	• Knots/entanglement
Maternal reduced oxygen-carrying capacity	Utero-placental dysfunction	Decreased fetal oxygen-carrying capacity
• Anemia	• Abruptio placenta	• Anemia: isoimmunization
• Carboxy hemoglobin	• Infarction	Vasa previa
	• Dysfunction: reversal or reduction of flow	• Carboxy hemoglobinemia
	• Premature rupture of membranes	• Twin-to-twin transfusion
Reduced perfusion of placenta	Uterine infection	
• Hypotension (shock/sepsis)	• Chorioamnionitis	• Shoulder dystocia
• Regional anesthesia		• Congenital malformations
• Maternal positioning		• Genetic abnormalities
• Preeclampsia		• Errors of metabolism
• Diabetes		• Cardiac abnormalities
• Heart disease		• Multiple births

values may be absolutely normal. Isolated cord segment on account of complete obstruction of the umbilical vessels reflects blood gas values unaffected by anaerobic fetal metabolism. On restoration of circulation, blood gas taken after 30 minutes reveals true disturbed fetal metabolism. In cases with intrapartum fetal death (fresh stillbirth), normal cord gases suggest sudden fetal cardiac arrest.[22] Infants born by elective cesarean section and those born to multiparous mothers have CBG values closer to normal adult values.[23] In twin deliveries, the second twin exhibits a time-bound precipitous fall in cord pH.[24] Abnormal umbilical cord morphology, length, vascular coils per centimeter, and true knots seem to have a very weak correlation with low-cord pH.[25,26] Although placental infection like chorioamnionitis with or without funisitis is associated with cerebral palsy, the mechanism appears independent of a hypoxic–ischemic insult.[27] Helwig et al.,[28,29] in their study of 15,000 vigorous newborn infants, showed that the cord arterial pH dropped more in term/post-term than in preterm infants. This trend was attributed to a shorter duration of labor in those born prior to term and increased placental oxygen consumption with advancing maturity.

(C) Evaluation of Fetal Hypoxia and Acidosis

Cord blood gas provides the most accurate and objective evidence of asphyxia at the time of birth. It complements routine clinical assessment of the baby at birth using the APGAR scoring system.[16,30] Cord blood gas is an indicator of fetal oxygenation – a measure of fetal well-being and perhaps an indicator of the quality of obstetric care. Deranged cord gases suggest possible birth asphyxia, a term that summarizes a lack of pulse, oxygen supply, and carbon dioxide washout. One can question about the mechanisms by which the fetus can thrive in the relatively hypoxic state *in utero*, but the predominance of fetal hemoglobin, Bohr's effect, and the still state of the fetus are plausible protective factors. Low umbilical artery pH (pH_{UA}) is an established marker of hypoxia and can help in early identification of asphyxia. The umbilical artery base deficit (BD_{UA}) may be a more linear measure of the accumulation of metabolic acids. Cord blood metabolic acidosis differs from cord blood respiratory acidosis, which results in only minimal reduction in pH with no base deficit.[31] Isolated respiratory acidosis at birth suggests an impaired gas exchange of short duration, resulting in minimal hypoxia and moderate hypercapnia. It is a relatively transient state of little significance that resolves soon after the newborn starts to breathe. If hypoxia is prolonged, the ensuing anaerobic metabolism produces lactic acidosis, which neutralizes the buffer bases, ultimately resulting in metabolic acidosis and base deficit.[32–34]

Hypoxic–Ischemic Encephalopathy as a Cause of Neonatal Encephalopathy

Cord arterial pH <7.0 and base deficit >12 mM/L is considered as reflecting significant neonatal metabolic acidemia and is seen in around 1% of all childbirths. This degree of fetal acid–base imbalance is associated with risk of hypoxic brain cell injury and consequent hypoxic–ischemic encephalopathy (HIE) and its long-term complications, such as cerebral palsy and neurodevelopmental abnormalities.[35]

Newborn infants who present with poor feeding, respiratory difficulties, seizures, tone abnormalities, and altered levels of consciousness are described as having neonatal encephalopathy (NE).[36] Neonatal encephalopathy is just a clinical condition that can result from several antenatal and/or perinatal factors. The most common causes of NE are HIE, perinatal infections, placental abnormalities, metabolic disorders, coagulopathies, and neonatal vascular stroke. However, in more than 50% of cases of NE, the cause remains unidentified.[37] The interchangeable use of the terms, HIE and NE, is controversial, as we often do not know when hypoxia–ischemia is indeed the cause of NE. It is proposed that in symptomatic newborns with no identifiable sentinel event, the term NE may be used, as we do not need etiologic labels for disease entities. All current parameters like pH, base deficit, and seizures are non-specific. The pattern of brain injuries produced by hypoxia–ischemia also does not prove that all NE is caused by HIE. Hence, for medico-legal clarity, attributing a cause (hypoxia–ischemia) to the disorder (encephalopathy) without documenting reduced cerebral blood flow should be avoided.[38,39] The incidence of NE is 1/10th (1.5/1,000 live birth) of significant cord blood acidosis (1/100 live births). Also, NE is not an inevitable consequence of significant fetal acidosis; nearly 75% of these acidotic babies do not show any neurological signs of NE. However, a diagnosis of HIE as the cause of NE in part depends upon demonstrating significant cord blood acidosis. A normal cord arterial pH and base deficit usually eliminate asphyxia as a cause of neurological manifestations in a newborn. In fact, the incidence of asphyxia contributing to cerebral palsy is relatively small at 10% of all causes.[40]

In 1990, a multidisciplinary International Cerebral Palsy Task Force set out criteria for retrospective labeling of an intrapartum hypoxic event as sufficient to cause cerebral palsy. These criteria were then updated in 2003 by the Task Force on Neonatal Encephalopathy and Cerebral Palsy, a joint effort of the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics, and were further modified in the year 2014 (Table 4).[41,42] Based on these criteria, the Joint Task Force Committee suggested that the pathway from intrapartum hypoxic–ischemic injury to subsequent cerebral palsy must progress through NE. Any neurological damage, including cerebral palsy, cannot be attributed to birth asphyxia in the absence of NE. Past assumption of HIE causing all NE was misplaced and was the reason behind this changed approach to search for other genetic, metabolic, and developmental causes contributing to neurological damage. This also has medico-legal significance in the court of law in resolving disputes related to brain damage sustained during childbirth.[43] This approach was released as a safety document meant to identify some of the above factors operating even before the onset of labor, where NE can be anticipated and minimized by offering therapeutic hypothermia.[42]

Therapeutic hypothermia (controlled cooling of infants >36 weeks to a rectal temperature of 34°C for 48–72 hours) is the only effective neuroprotective intervention in asphyxiated babies, and its efficacy in a baby with HIE depends upon initiating it within 6 hours of birth. A cord blood pH <7 and a base deficit >16 mM/L is one of the inclusion criteria for the application of this therapy.[44]

Pathological Acidosis and Neurological Outcome

Acidosis is generally well-tolerated by the fetus without adverse neurological sequelae until it reaches a pathological threshold. A practical pH threshold for significant neonatal academia is an umbilical artery pH <7, a value below which adverse clinical events begin to be seen frequently.[45] Evidence in support of this threshold value was derived from a 2010 meta-analysis of 51 cohort and case-controlled studies of over 480,000 infants, indicating a

Table 4: International consensus criteria to determine a severe acute hypoxic event as a potential cause of cerebral palsy

(A) Essential criteria (all mandatory)

- Metabolic acidosis CBGUA (pH<7 and BD 12 mmol/L or more).
- Onset of moderate-to-severe neonatal encephalopathy within 72 hours of birth in a baby 34 weeks gestation or more.
- Cerebral palsy of spastic quadriplegic or dyskinetic type.
- Exclusion of other known causes of cerebral palsy, e.g., genetic disorders, infections, intrapartum fever, antepartum hemorrhage, prematurity, growth-restricted babies, tight cord around the neck and as a result of complication of multiple pregnancy.

(B) Nonspecific criteria that collectively suggest a significant intrapartum acute or chronic insult

- A sentinel event severe enough to cause sudden hypoxia in a healthy fetus occurring immediately before or during labor, e.g., cord prolapse, antepartum hemorrhage, and ruptured uterus.
- A sudden and sustained fetal bradycardia from that sentinel event.
- Apgar scores of less than 4 beyond 5 minutes.
- Onset of multisystem organ involvement within 72 hours of birth.
- Early imaging study (within 5 days) showing evidence of edema and intracranial hemorrhage.

strong association with neonatal mortality at pH <7 and neonatal morbidity at pH <7.1.[16,46,47] In a cohort study of 8,700 term infants, pH_{UA} <7 was a strong predictor of all adverse outcomes, including NE or death. These outcomes were seen in 2.3% of all acidemic babies and 8.5% of infants with severe acidemia.[48]

Most infants with a cord pH <7 who appear well at birth and are free of any cardiovascular compromise do not require admission in the neonatal unit or extensive investigation simply based on low-cord pH. These babies did not develop neurological problems after birth, even when followed for 6.5 years.[49] Universally, a cord pH_{UA} <7 is considered significant neonatal metabolic academia and if associated with other short-term markers, is a reliable indicator of acute peripartum events and a good predictor of adverse neurocognitive outcomes.[46,50–52] Cord pH is widely used as an outcome measure in obstetric clinical trials and is a measure of the quality of obstetric care.[53] However, based on the cord pH value without clinical signs and symptoms of NE, there is substantial uncertainty in the management and neurocognitive prognosis of neonates.[53]

Neonates with pH_{UA} <7 have shown 10-fold higher risk of 1-min Apgar score of <4, 5-min Apgar score of <7, and 7.6-times higher risk of acute NE. Also, multiparous women had higher risks of low Apgar score and NE as compared with nulliparas.[54] Shoulder dystocia and women with urological problems had a statistically higher risk of delivering a baby with a low 5-min Apgar score.[34] In their series of 3506 infants, Goldaber et al.[55] observed neonatal death to be more likely at pH <7, and seizures as more likely at pH <7.05. Worsening acidosis predisposed to increased morbidity due to HIE with 12% of infant being symptomatic at cord pH <7 to 80% at cord pH <6.8%. No infants were born alive at pH <6.6.[34,56] Using a scoring system for renal, central nervous system, and respiratory and cardiovascular morbidity, Low et al.[57] showed that significant acidosis (base deficit >12 mM/L) was a good predictor of multi-organ involvement.

As an isolated finding, neonatal metabolic acidemia is a poor predictor of the risk of HIE. However, when combined with other clinical parameters such as non-reassuring fetal heart tracings, need for continued resuscitation/intubation beyond 5 minutes, low 5-min Apgar score, early occurrence of seizures, and development of moderate HIE, the risk of neuro-cognitive impairment is strong.[58,59] Cord blood lactate levels are an additional parameter included in numerous new-generation blood gas analyzers. Lactate, a product of anaerobic metabolism, barely diffuses across the placenta and is the main metabolite responsible for fall in cord pH, and base buffers.[60] Considering its fetal origin, lactate should be a much more reliable predictor of poor neonatal outcomes than other tests such as the cord arterial pH and base deficit.[61,62] The presence of high lactate levels >4.1 mM/L and lactate/pyruvate ratios <22 is predictive of neonatal encephalopathy with a 100% sensitivity and 95% specificity.[63]

In a study of 4910 term infants, high mean lactate levels (6.49 mmol/L compared with 3.26 mM/L, $p < 0.001$) correlated well with composite neonatal morbidity (1.1%) as compared with pH (7.19 compared with 7.29, $p < 0.001$).[64] High umbilical cord lactate is thus a reliable method to quantify acidosis and is more prognostic of neonatal morbidity than pH.[65,66] In 2014, the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy[42] stated: "To elucidate the different causal pathways leading to HIE and CP, it is important that a reliable and readily available assessment of fetal status is possible and that more specific markers of an intrapartum insult be developed." The existing association between cord arterial pH and/or BD and short-/long-term neurocognitive outcomes reveals that traditionally accepted cutoff values to define significant neonatal acidemia still need more investigations.[67,68]

Sailing and Schmidt[69] and Sigaard-Andersen[70] noted very high pCO_2 levels, much higher than those seen in adults, in neonatal acidemia. These respiratory abnormalities usually corrected with appropriate ventilation. Hence, it is crucial to identify respiratory acidosis in the neonatal period from NMA to select newborns with mixed or predominantly metabolic acidosis to be admitted in the NICU for close monitoring and treatment. Scientists have now proposed calculated neonatal eucapnic pH (pH euc-n), which includes nonrespiratory pH, reduced pH, standard pH, or pH qu 40 (base required to bring the pH to 7.40 and pCO_2 at 40 mm Hg), as reflecting the metabolic component of pH due to nonrespiratory acid–base balance as a specific marker for neonatal metabolic acidosis (NMA) rather than currently used biomarkers (pH or base deficit).[71] A pH euc-n > 7.11 derived after appropriate correction of hypercapnia reconciled to the fetal *milieu interior* predicts that the infant will likely remain asymptomatic and have an uneventful course. p-euc-n values < 7.11 are more often associated with NE. pH euc-n is easy to calculate at the bedside (Blickstein method) by adding 0.08 to ua pH value for every 10 mm Hg rise of pCO_2 above the threshold of 50 mm Hg from the routine blood gas reports and provides valuable objective defense for obstetricians in allegations of professional liability.[72] It also informs neonatologists about the need for therapeutic hypothermia.[69]

Cord Blood Gas Analysis: Selective or Universal

Universal cord blood gas analysis (UCBGA) was first advocated 60 years back to assess the metabolic condition of a newborn infant at birth. The costs of UCBGA are justified as these can reduce the need for neonatal ICU admissions. Considering the temporal relationship between cord blood acidemia and adverse neurocognitive outcomes, many international associations have recommended UCBGA. This transition from selective to UCBGA has reduced the frequency of cord arterial acidemia and improved perinatal outcomes. These changes in obstetric practice have improved fetal/neonatal outcomes. The financial costs and emotional burden arising from perinatal hypoxic–ischemic injuries (cerebral palsy) provide a much more compelling societal perspective than the added cost of UCBGA.[73] Thorp and Rushing.[74] have summarized their views on the pros and cons of selective vs UCBGA.

Advantages of UCBGA

A cord blood value will be available for all babies who become symptomatic sometime after birth (crucial for management of a baby and future medico-legal disputes).

- The team becomes adept at sampling and processing the CBG sample.
- Omission to perform a CBG in an emergency is avoided.
- Provides insight into the interpretation of electronic fetal heart monitoring for safe and effective intervention strategies.

Disadvantages of UCBGA

- Added costs to obstetric care;
- Need for additional staff that might not be available at all units;
- A low-cord pH in a vigorous newborn baby might pose a potential medicolegal concern because it falsely suggests birth asphyxia.

Universal cord blood gas analysis can be used to audit the quality of fetal monitoring and intervention strategies used by the obstetric team to prevent significant fetal acidemia and its associated neonatal morbidity and mortality.[53]

Conclusion

Cord blood gas analysis is frequently used at birth to assess the effects of peripartum events in a newborn. Neonatal and childhood neuro-cognitive morbidities, including cerebral palsy, are often attributed to fetal acidemia. Existing associations between cord pH and adverse outcomes are conflicting. Low-cord pH along with some adverse clinical markers reliably predicts neonatal mortality and morbidity. Hence, it is justified to enhance surveillance of infants born with a low-cord pH or, more specifically, neonatal eucapnic pH so that those who fulfill the required criteria be offered various neuroprotective therapies. The obstetric and neonatal teams should be well-versed with the CBG sampling procedure and its evaluation. Future studies should assess the use of CBG across neonatal populations and explore the cost-effectiveness of universal screening. Meanwhile, the search for an absolute reliable marker of NMA should be the focus for future research.

Author's Contributions

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: MH, IK, and SG.
- Drafting the work or revising it critically for important intellectual content: MH and IK.
- Final approval of the version to be published: MH.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: MH.

References

1. Royal College of Obstetricians and Gynaecologists Clinical Effectiveness Support Unit. The use of electronic fetal monitoring: The use and interpretation of cardiotocography in intrapartum fetal surveillance. London: RCOG [cited 2001]. Available from: http://www.rcog.org.uk.
2. ACOG Committee Opinion No. 348. Umbilical cord blood gas and acid-base analysis. Obstet Gynecol 2006;108(5):1319–1322. DOI: 10.1097/00006250-200611000-00058.
3. Ross MG. How and when umbilical cord gas analysis can justify your obstetric management. OBG Manag 2017;29(3):38–44, 46. Available from: https://cdn.mdedge.com/files/s3fs-public/obgm0290338.pdf.
4. Cantu J, Szychowski JM, Li X, et al. Predicting fetal academia using umbilical venous cord gas parameters. Obstet Gynecol 2014;124(5):926–932. DOI: 10.1097/AOG.0000000000000517.
5. Blechner JN. Maternal–fetal acid–base physiology. Clin Obstet Gynecol 1993;36(1):3–12. DOI: 10.1097/00003081-199303000-00004.
6. Aarnoudse JG, Ilsley NP, Penfold P, et al. Permeability of human placenta to bicarbonate: In vitro perfusion studies. Br J Obstet Gynaecol 1984;91:1096. DOI: 10.1111/j.1471-0528.1984.tb15083.x.
7. Ullrich JR, Ackerman BD. Changes in umbilical artery blood gas values with the onset of respiration. Biol Neonate 1972;20(5):466–474. DOI: 10.1159/000240488.
8. Mokorami P, Wiberg N, Olofsson P. Hidden acidosis: An explanation of acid-base and lactate changes occurring in umbilical cord blood after delayed sampling. BJOG 2013;120(8):996–1002. DOI: 10.1111/1471-0528.12234.
9. Armstrong L, Stenson B. Effect of delayed sampling on umbilical cord arterial and venous lactate and blood gases in clamped and unclamped vessels. Arch Dis Child Fetal Neonatal 2006;91(5):F342–F345. DOI: 10.1136/adc.2005.086744.
10. Gaskins JE, Goldkrand JW. Air contamination in umbilical cord blood gas sampling. Am J Obstet Gynecol 1994;171(6):1546–1549. DOI: 10.1016/0002-9378(94)90399-9.
11. Armstrong L, Stenson B. Use of umbilical cord blood gas analysis in the assessment of the newborn. Arch Dis Child Fetal Neonatal 2007;92(6):430–434. DOI: 10.1136/adc.2006.099846.
12. Westgate J, Garibaldi J, Greene K. Umbilical cord blood gas analysis at delivery: A time for quality data. Br J Obstet Gynaecol 1994;101(12):1054–1063. DOI: 10.1111/j.1471-0528.1994.tb13581.x.
13. Nudelman MJR, Belogolovsky E, Jegatheesan P, et al. Effect of delayed cord clamping on umbilical blood gas values in term newborns. Obstet Gynecol 2020;135(3):576–582. DOI: 10.1097/AOG.0000000000003663.
14. Yeomans ER, Hauth JC, Gilstrap LC III, et al. Umbilical cord pH, PCO_2, and bicarbonate following uncomplicated term vaginal deliveries. Am J Obst Gynecol 1985;151(6):798–800. DOI: 10.1016/0002-9378(85)90523-x.
15. Wiberg N, Källén K, Olofsson P. Base deficit estimation in umbilical cord blood is influenced by gestational age, choice of fetal fluid compartment, and algorithm for calculation. Am J Obstet Gynecol 2006;195(6):1651–1656. DOI: 10.1016/j.ajog.2006.05.043.
16. Ross MG, Gala R. Use of umbilical artery base excess: Algorithm for the timing of hypoxic injury. Am J Obstet Gynecol 2002;187(1):1–9. DOI: 10.1067/mob.2002.123204.
17. Low JA, Pancham SR, Piercy WN, et al. Intrapartum fetal asphyxia: Clinical characteristics, diagnosis, and significance in relation to pattern of development. Am J Obstet Gynecol 1977;129(8):857–872. DOI: 10.1016/0002-9378(77)90519-1.

18. Hagelin A, Leyon J. The effect of labor on the acid-base status of the newborn. Acta Obstet Gynecol Scand 1998;77(8):841–844. PMID: 9776598.
19. Duerbeck NB, Chaffin DG, Seeds JW. A practical approach to umbilical artery pH and blood gas determinations. Obstet Gynecol 1992;79(6):959–962. PMID: 1579322.
20. Johnson JW, Richards DS. The etiology of fetal acidosis as determined by umbilical cord acid-base studies. Am J Obstet Gynecol 1997;177(2):274–282. DOI: 10.1016/s0002-9378(97)70187-x.
21. Martin GC, Green RS, Holzman IR. Acidosis in newborns with nuchal cords and normal Apgar scores. J Perinatol 2005;25(3):162–165. DOI: 10.1038/sj.jp.7211238.
22. Nakamura KT, Smith BA, Erenberg A, et al. Changes in arterial blood gases following cardiac asystole during fetal life. Obstet Gynecol 1987;70(1):16–17. PMID: 3110712.
23. Thorp JA, Sampson JE, Parisi VM, et al. Routine umbilical cord blood gas determinations? Am J Obstet Gynecol 1989;161(3):600–605. DOI: 10.1016/0002-9378(89)90362-1.
24. Leung TY, Lok IH, Tam WH, et al. Deterioration in cord blood gas status during the second stage of labour is more rapid in the second twin than in the first twin. BJOG 2004;111(6):546–549. DOI: 10.1111/j.1471-0528.2004.00133.x.
25. Atalla RK, Abrams K, Bell SC, et al. Newborn acidbase status and umbilical cord morphology. Obstet Gynecol 1998;92(5):865–868. DOI: 10.1016/s0029-7844(98)00316-0.
26. Maher JT, Conti JA. A comparison of umbilical cord blood gas values between newborns with and without true knots. Obstet Gynecol 1996;88(5):863–866. DOI: 10.1016/0029-7844(96)00313-4.
27. Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy: A meta-analysis. JAMA 2000;284(11):1417–1424. DOI: 10.1001/jama.284.11.1417.
28. Helwig JT, Parer JT, Kilpatrick SJ, et al. Umbilical cord blood acid-base state: What is normal? Am J Obstet Gynecol 1996;174(6):1807–1812;1812–1814. DOI: 10.1016/s0002-9378(96)70214-4.
29. Weiner CP, Sipes SL, Wenstrom K. The effect of fetal age upon normal fetal laboratory values and venous pressure. Obstet Gynecol 1992;79(5 (Pt 1)):713–718. PMID: 1565354.
30. HN Simhan. Umbilical cord blood gas analysis at delivery – UpToDate 2020. Available at: https://www.uptodate.com/.
31. Martí Gamboa S, Pascual Mancho J, Rodrigo Rodríguez M, et al. pH, base deficit or lactate. Which is better for predicting neonatal morbidity? J Matern Fetal Neonatal Med 2017;30(19):2367–2371. DOI: 10.1080/14767058.2016.1248936.
32. Low JA, Panagiotopoulos C, Derrick EJ. Newborn complications after intrapartum asphyxia with metabolic acidosis in the term fetus. Am J Obstet Gynecol 1994;170(4):1081–1087. DOI: 10.1016/s0002-9378(94)70101-6.
33. Van den Berg PP, Nelen WL, Jongsma HW, et al. Neonatal complications in newborns with an umbilical artery pH, 7.00. Am J Obstet Gynecol 1996;175(5):1152–1157. DOI: 10.1016/s0002-9378(96)70021-2.
34. Goodwin TM, Belai I, Hernandez P, et al. Asphyxial complications in the term newborn with severe umbilical acidemia. Am J Obstet Gynecol 1992;167(6):1506–1512. DOI: 10.1016/0002-9378(92)91728-s.
35. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev 2010;86(6):329–38. DOI: 10.1016/j.earlhumdev.2010.05.010.
36. Volpe JJ. Neonatal encephalopathy: An inadequate term for hypoxic-ischemic encephalopathy. Ann Neurol 2012;72(2):156–166. DOI: 10.1002/ana.23647.
37. Graham EM, Ruis KA, Hartman AL, et al. A systematic review of role of the intrapartum hypoxia-ischemia in causation of neonatal encephalopathy. Am J Obstet Gynecol 2008;199(6):587–595. DOI: 10.1016/j.ajog.2008.06.094.
38. Molloy EJ, Bearer C. Neonatal encephalopathy versus hypoxic-ischemic encephalopathy. Pediatr Res 2018;84(5):574. DOI: 10.1038/s41390-018-0169-7.
39. Dammann O, Ferriero D, Gressens P. Neonatal encephalopathy or hypoxic-ischemic encephalopathy? Appropriate terminology matters Pediatr Res 2011;70(1):1–2. DOI: 10.1203/PDR.0b013e318223f38d.
40. Nelson KB, Leviton A. How much of neonatal encephalopathy is due to birth asphyxia? Am J Dis Child 1991;145(11):1325–1331. DOI: 10.1001/archpedi.1991.02160110117034.
41. American College of Obstetricians and Gynecologists (ACOG) and American Academy of Pediatrics (AAP). Neonatal encephalopathy and neurologic outcome, Second Edition. ACOG, Obstet Gynecol 2014;123(4):896–901. Available at: https://www.acog.org/clinical/clinical-guidance/task-force-report/articles/2014/neonatal-encephalopathy-and-neurologic-outcome.
42. MacLenan AH, Thompson SC. Cerebral palsy: Causes, pathways and the role of genetic variants. Am J Obstet Gynecol 2015;213(6):779–788. DOI: 10.1016/j.ajog.2015.05.034.
43. Perlman J. Intrapartum hypoxic-ischemic cerebral injury and subsequent cerebral palsy. Pediatrics 1997;99(6):851–859. DOI: 10.1542/peds.99.6.851.
44. Peliowski-Davidovich A. Hypothermia for newborns with hypoxic ischemic encephalopathy. Paediatr Child Health 2012;17(1):41–44. DOI: 10.1093/pch/17.1.41.
45. Yeh P, Emary K, Impey L. The relationship between umbilical cord arterial pH and serious adverse neonatal outcome: Analysis of 51,519 consecutive validated samples. BJOG 2012;119(7):824–831. DOI: 10.1111/j.1471-0528.2012.03335.x.
46. Malin GL, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: Systematic review and meta-analysis. BMJ 2010;340:c1471. DOI: 10.1136/bmj.c1471.
47. Svirko, Mellanby J, Impey L. The association between cord pH at birth and intellectual function in childhood. Early Hum Dev 2008;84(1):37–41. DOI: 10.1016/j.earlhumdev.2007.02.002.
48. King TA, Jackson GL, Josey AS, et al. The effect of profound umbilical artery acidemia in term neonates admitted to a newborn nursery. J Pediatr 1998;132(4):624–629. DOI: 10.1016/s0022-3476(98)70350-6.
49. Hafström M, Ehnberg S, Blad S, et al. Developmental outcome at 6.5 years after acidosis in term newborns: A population-based study. Pediatrics 2012;129(6):e1501–e1507. DOI: 10.1542/peds.2011-2831.
50. Sabol BA, Caughey AB. Acidemia in neonates with a 5-minute Apgar score of 7 or greater-What are the outcomes? Am J Obstet Gynecol 2016;215(4):486.e1–486.e6. DOI: 10.1016/j.ajog.2016.05.035.
51. Knutzen L, Svirko E, Impey L. The significance of base deficit in acidemic term neonates. Am J Obstet Gynecol 2015;213(03):373.e1–373.e7. DOI: 10.1016/j.ajog.2015.03.051.
52. Georgieva A, Moulden M, Redman CW. Umbilical cord gases in relation to the neonatal condition: the EveREst plot. Eur J Obstet Gynecol Reprod Biol 2013;168(02):155–160. DOI: 10.1016/j.ejogrb.2013.01.003.
53. Cottee C, Harding K. Risk management in obstetrics. Obstet, Gynaecol Reprod Med 2008;18:155–62. DOI: 10.1016/j.ogrm.2008.04.003.
54. Ferreira CS, Melo A, Fachada AH, et al. Umbilical cord blood gas analysis, obstetric performance and perinatal Outcome. Rev Bras Ginecol Obstet 2018;40(12):740–748. DOI: 10.1055/s-0038-1675187.
55. Goldaber KG, Gilstrap LC 3rd, Leveno KJ, et al. Pathologic fetal acidemia. Obstet Gynecol 1991;78(6):1103–1107. PMID: 1945216.
56. Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. Am J Obstet Gynecol 1997;177(6):1391–1394. DOI: 10.1016/s0002-9378(97)70080-2.
57. Low JA, Panagiotopoulos C, Derrick EJ. Newborn complications after intrapartum asphyxia with metabolic acidosis in the preterm fetus. Am J Obstet Gynecol 1995;172(3):805–810. DOI: 10.1016/0002-9378(95)90003-9.
58. Perlman JM, Risser R. Can asphyxiated infants at risk for neonatal seizures be rapidly identified by current high-risk markers? Pediatrics 1996;97(4):456–462. PMID: 8632928.
59. Piquard F, Schaefer A, Dellenbach P, et al. Is fetal acidosis in the human fetus maternogenic during labor? A reanalysis. Am J Physiol 1991;261:R1294–R1299. DOI: 10.1152/ajpregu.1991.261.5.R1294.
60. Kruger K, Kublickas M, Westgren M. Lactate in scalp and cord blood from fetuses with ominous fetal heart rate patterns. Obstet Gynecol 1998;92(6):918–922. DOI: 10.1016/s0029-7844(98)00347-0.
61. Natesan SR. Routine measurements of cord arterial blood lactate levels in infants delivering at term and prediction of neonatal outcome. Med J Malaysia 2016;71(3):131–133. PMID: 27495887.

62. Chou YH, Tsou Yau KI, Wang PJ. Clinical application of the measurement of cord plasma lactate and pyruvate in the assessment of high-risk neonates. Acta Paediatr 1998;87(7):764–768. DOI: 10.1080/080352598750013851.
63. Allanson ER, Waqar T, White C, et al. Umbilical lactate as a measure of acidosis and predictor of neonatal risk: A systematic review. BJOG 2017;124(4):584–594. DOI: 10.1111/1471-0528.14306.
64. Tuuli MG, Stout MJ, Shanks A, et al. Umbilical cord arterial lactate compared with pH for predicting neonatal morbidity at term. Obstet Gynecol 2014;124(4):756–761. DOI: 10.1097/AOG.0000000000000466.
65. Swanson K, Whelan AR, Grobman WA, et al. Can venous cord gas values predict fetal acidemia? Am J Obstet Gynecol 2017;217(3):364.e361–364.e365. DOI: 10.1016/j.ajog.2017.05.047.
66. Harris M, Beckley SL, Garibaldi JM, et al. Umbilical cord blood gas analysis at the time of delivery. Midwifery 1996;12(3):146–150. DOI: 10.1016/s0266-6138(96)90059-5.
67. Kelly R, Ramaiah S, Sheridan H, et al. Dose-dependent relationship between acidosis at birth and likelihood of death or cerebral palsy. Arch Dis Child Fetal Neonatal Ed 2018;103:F567–F572. DOI: 10.1136/archdischild-2017-314034.
68. Vesoulis ZA, Liao SM, Rao R, et al. Re-examining the arterial cord blood gas pH screening criteria in neonatal encephalopathy. Arch Dis Child Fetal Neonatal Ed 2018;103(4):F377–F382. DOI: 10.1136/archdischild-2017-313078.
69. Sailing E, Schmidt S. In response to the article by Racinet C et al. Neonatal acidosis at birth: In search of a reliable marker. Gynecol Obstet Fertil 2016;44:730–731. DOI: 10.1016/j.gyobfe.2016.04.005.
70. Andersen OS, Engel K. A new acid base nomogram. An improved method for calculation of the relevant blood acid base data. Scand J Clin Lab Invest 12960;12:177–186. DOI: 10.3109/00365516009062420.
71. Racinet C, Ouellet P, Muraskas J, et al. Neonatal cord blood eucapnic pH: A potential biomarker predicting the need for transfer to the NICU. Arch Pédiatr 2020;27(1):6–11. DOI: 10.1016/j.arcped.2019.10.013.
72. Blickstein I, Green T. Umbilical cord blood gases. Clin Perinatol 2007;34(3):451–459. DOI: 10.1016/j.clp.2007.05.001.
73. White CRH, Doherty DA, Henderson JJ, et al. Benefits of introducing universal cord blood gas and lactate analysis into an obstetric unit. Aust New Z J Obstet Gynaecol 2010;50(4):318–328. DOI: 10.1111/j.1479-828X.2010.01192.x.
74. Thorp JA, Rushing RS. Umbilical cord blood gas analysis. Obstet Gynecol Clin North Am 1999;26(4):695–709. DOI: 10.1016/s0889-8545(05)70107-8.

REVIEW ARTICLE

Respiratory Syncytial Virus Infections in Neonates: A Persisting Problem

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Abstract

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in young infants. It is an enveloped, single-stranded, nonsegmented, negative-strand RNA virus, a member of the family Pneumoviridae. Globally, RSV is responsible for 2.3% of deaths among neonates 0–27 days of age. Respiratory syncytial virus infection is most common in children aged below 24 months. Neonates present with cough and fever. Respiratory syncytial virus-associated wheezing is seen in 20% infants during the first year of life of which 2–3% require hospitalization. Reverse transcriptase polymerase chain reaction (RT-PCR) gives fast results and has higher sensitivity compared with culture and rapid antigen tests and are not affected by passively administered antibody to RSV. Therapy for RSV infection of the LRT is mainly supportive, and preventive measures like good hygiene and isolation are the mainstay of management. Standard precautions, hand hygiene, breastfeeding and contact isolation should be followed for RSV-infected newborns. Recent AAP guidelines do not recommend pavilizumab prophylaxis for preterm infants born at 29–35 weeks without chronic lung disease, hemodynamically significant congenital heart disease and coexisting conditions. RSV can lead to long-term sequelae such as wheezing and asthma, associated with increased healthcare costs and reduced quality of life.

Keywords: Arexvy, Bronchiolitis, Lower respiratory tract infection, Neonate, Nerve growth factor/TrkA receptor axis, Newborn, Nirsevimab, Palivizumab, Perinatal RSV infection, Pneumoviridae.

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Keypoints

- Respiratory syncytial virus (RSV) is transmitted by nasal and oral secretions; the incubation period is 4–6-days.
- Seasonal outbreaks of RSV in the Northern Hemisphere occur from October to April, with a peak in January or February. In the Southern Hemisphere, epidemics occur during the May–September wintertime, peaking in May or June.
- A Risk Scoring Tool (RST) has been developed. It includes three risk factors: (a) birth between 3 months before and 2 months after the aforementioned season start dates; (b) presence of smokers in the household and/or maternal smoking whil pregnant; and (c) having young siblings in the family and/or daycare attendance to accurately and reliably predict RSV hospitalization.
- Vertical RSV infection is associated with dysregulation of critical neurotrophic pathways, including the nerve growth factor (NGF)/TrkA receptor axis during fetal development, which promotes aberrant cholinergic innervation of the respiratory tract and increases airway reactivity after postnatal reinfection with RSV.
- Rapid antigen diagnostic tests (RADT) provide results in less than 30 minutes, but these are less sensitive than PCR.
- The American Academy of Pediatrics does not recommend routine use of ribavirin because of the possibility of (a) long-term need for aerosols and hospitalization; (b) potential for intoxication (bone marrow suppression); and of (c) high costs.
- A new RSV vaccine was recently approved for use in adults, which has brought new excitement about the possibilities for testing in infants.

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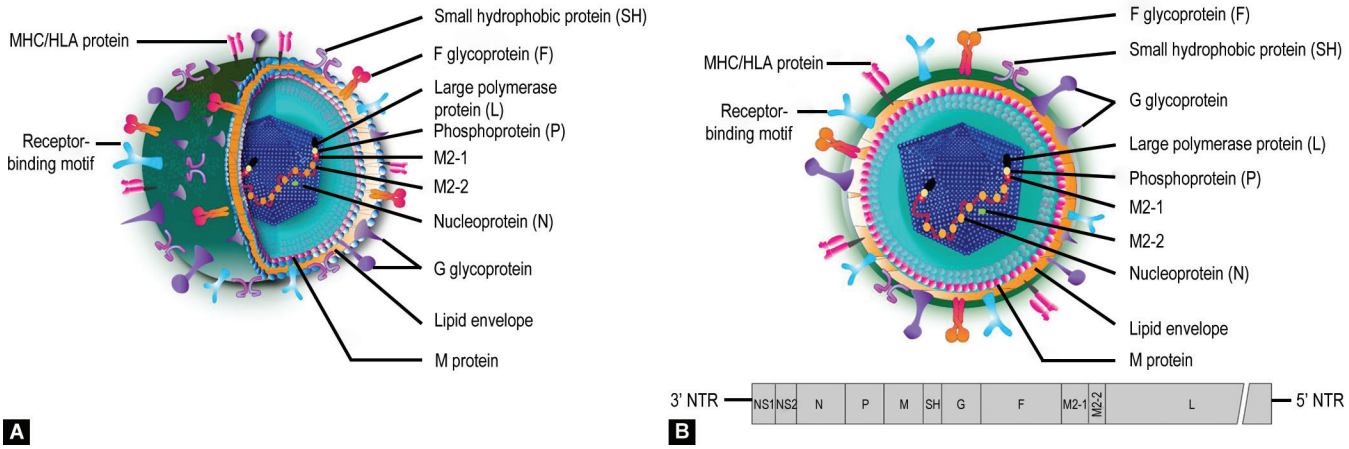
Introduction

Respiratory syncytial virus was isolated from primate carriers in 1956.[1] Despite major advances in our ability to prevent, diagnose, and treat RSV infections, this virus continues to be the most common cause of lower respiratory tract (LRT) infections in infants less than 1 year of age.[2] In this article, we present a review of the virus structure, epidemiology, clinical features, and management of infants infected with these viruses.



Figs 1A and B: Schematic diagrams showing (A) Surface and side dissection; and (B) Cross-section of the respiratory syncytial virus

Pathogenesis

Viral Structure

Respiratory syncytial virus is an enveloped, single-stranded, nonsegmented, negative-strand RNA virus (Fig. 1), a member of the family *Pneumoviridae* and order Mononegalevirales.[3] It is a pleiomorphic virus with an average diameter of 50–250 nm. The viral genome is 15.2 kb in size, has 10 genes and encodes 11 proteins: F and G envelope surface glycoproteins, M1, M2-1, and M2-2 matrix proteins, NS1 and NS2 virion proteins, SH protein and N, D, L nucleotide capsule proteins. The F protein promotes fusion of infected cell membranes with adjacent cells, leading to the formation of the eponymous syncytia.[4] The anti-RSV monoclonal antibody response mainly targets Fusion and G proteins. Two antigenic subgroups exist differing in the surface glycoproteins: A and B. Subgroup A infections are more common, severe, and contagious.[5–10] Table 1 outlines the major viral components.

Epidemiology

In a systematic review, the global annual rate of RSV hospitalization among children <5 years was 4.4 per 1000 with highest rates among children aged less than 6 months and preterm neonates.[11] Globally, RSV is responsible for 2.3% of deaths among neonates 0–27 days of age, 6.7% among infants 28–364 days, and 1.6% among children 1–4 years of age.[12] The mode of transmission is nasal and oral secretions.[13] The incubation period is 4–6 days (range 2–8 days).[14] Viremia typically lasts around 3–8 days, although it might be longer in the immunocompromised. The average duration of viral shedding is 11 days.[15] Viral shedding may last up to 4 weeks in young infants and several months in children with HIV infection.[16] Recurrent infections are seen frequently.

Respiratory syncytial virus infection is seen most frequently in children aged less than 24 months; the prevalence is 5.2/1000 (26/1000 in neonates during the first month after birth). Hospitalization rates are highest during the first 6 months.[17] Nearly, 80% of RSV infections are seen in infants because they have lower IgG levels approaching nadir at 3–6 months. Prematurity is a risk factor in view of lower IgG antibody titers and an immature neonatal immune system.

In the Northern Hemisphere, seasonal outbreaks of RSV occur from October to April, with a peak in January or February.[2,18,19] In contrast, wintertime epidemics are seen in the Southern Hemisphere from May to September, peaking in May or June. In tropical and semitropical climates, the seasonal outbreaks usually are seen during the rainy season, whereas the epidemic peaks are not as sharp in temperate climates. The COVID-19 pandemic was associated with marked reduction in RSV infections in children and were attributed to mitigation measures, such as the use of masks, social distancing, and temporary closure of schools.[20–27]

Patients at the highest risk for severe LRT disease include:

- Infants under 6 months of age,[28] attending daycare,[29,30] and those with older siblings who may harbour asymptomatic RSV.[31,32]
- Infants and children with chronic lung disease (bronchopulmonary dysplasia, cystic fibrosis)[33–35]
- Preterm infants less than 35 weeks gestational age.[28,32,36–38]
- Infants with congenital heart disease.[39]
- Infants exposed to second-hand smoke.[40–42]
- Human immunodeficiency virus (HIV)-exposed, uninfected infants.[43–45]
- Infants with Down syndrome.[34,46]

In a meta-analysis, 8 risk factors were identified to be associated with RSV-associated acute lower respiratory infection: prematurity, low birth weight, male gender, siblings, maternal smoking, history of atopy, and no breastfeeding and crowding.[47] A Risk Scoring Tool (RST) has been developed using three risk factor variables: (a) birth between 3 months before and 2 months after season start date; (b) smokers in the household and/or maternal smoking while pregnant; and (c) siblings and/or daycare attendance to accurately and reliably predict RSV hospitalization. It is a useful tool when opting for RSV prophylaxis; it helps determine the likely risk severity of infection and guide therapy in a cost-effective manner. Smoking in the household and daycare are modifiable risk factors. The chronological age at the beginning of RSV season, low birth weight, and birth order are neonatal risk factors for RSV LRT requiring hospitalization.[48]

Polymorphisms in cytokine and chemokine-related genes, namely, the interleukin (IL)-4, IL-8, IL-10, IL-13, and the chemokine receptor (CCR)5 predispose to severe RSV disease.[49–54] Severe disease is also predisposed by cell surface interactions or cell signaling genes, such as toll-like receptor (TL)-4, chemokine receptor 1 (CX3CR1), surfactant protein (SP)-A, and SP-D.[55–60]

Table 1: Major structural components of RSV

Structure	*Available information*
Lipid envelope	The nucleocapsid is surrounded by a lipoprotein envelope derived from the nuclear membrane of the infected host cell.[61] The RSV virions are pleomorphic consisting of both irregular spherical shape with sizes of 150–300 nm and also filamentous forms of the virions that are 60–100 nm in diameter and up to 10 µm in length.[62]
Glycoproteins	Viral glycoprotein spikes are attached to the lipid envelope and bind specific host receptors to facilitate attachment and entry of the virus. There are three transmembrane surface glycoproteins. The attachment glycoprotein (G) and the fusion (F) glycoprotein control the initial phases of infection. G glycoprotein targets the ciliated cells of the airways, and F-glycoprotein facilitates fusion of the virion membrane and target cell membrane. The F protein is pertinent to antiviral drug development, and G and F-glycoproteins are targeted by neutralizing antibodies induced by infection.[63] G (binding) protein is important for binding to the host cell and F (fusion) protein is responsible for fusion of the viral envelope with the cellular plasma membrane.
Receptor-binding motifs	Receptor-binding motifs are involved in virion attachment to cell surface receptors. RSV attachment (G) glycoprotein targets CX3CR1 receptor on primary human airway epithelial (HAE) cultures. The G protein contains a CX3C motif which is critical for its role in infection of HAE cultures.[64]
Envelope protein	RSV has three envelope proteins, namely, the small hydrophobic protein (SH), G protein, and F protein. The G protein facilitates binding of RSV to target cells while the function of SH is not known. F protein mediates virus-to-cell and cell-to-cell fusion, resulting in syncytia formation, after which the virus is named.[65]
Membrane protein	The F gene encodes a type I integral membrane protein, which is synthesized as a 574 amino acid inactive precursor, F_0. Three F_0 monomers assemble into a trimer and, while passing through the Golgi apparatus, these monomers get activated by a host protease.[63]
MHC or HLA proteins	RSV infection of lung epithelium induces RIG-I expression, leading to induction of a class I MHC transactivator, NLRC5, and subsequent upregulation of MHC-I. Suppression of RIG-I induction leads to blockage of RSV-induced NLRC5 expression and MHC-I upregulation. Increased MHC-I expression may exacerbate RSV infection by immunopathologic damage.[66]
Spike protein	Specific receptor binding is achieved by the RSV F protein, a spike protein required for attachment to specific receptors and membrane fusion.[67]
Surface tubules	RSV exploits cytoskeletal components to complete its life cycle, such as actin, affecting its entry into the host cell, formation of cell-associated virus, virus escape, and exacerbation of the infection and syncytium formation. The cell membranes of the RSV-infected cells lost their characteristic shape and the cytoskeleton was reduced and elongated.[68]
Palisade layer	Either not expressed or relevance unclear fetal/infantile disease.
Viral tegument	Either not expressed or relevance unclear fetal/infantile disease.
Lateral bodies	Either not expressed or relevance unclear fetal/infantile disease.
Capsid	RSV has a capsid which forms viral particles and packages the viral genomic RNA, leading to the rapid assembly of nucleocapsid cores in the cytoplasm. The RNA nucleocapsid of RSV is enclosed in a bilayer lipid sphere and the genome is a single strand of RNA encoding for 10 viral proteins.[69] The RSV genome encodes 11 proteins and is tightly encapsidated with the nucleocapsid, consisting of the nucleocapsid (N) protein, RNA polymerase (L) and its cofactor phosphoprotein (P) and M2-1 protein. The genome also encodes the envelope glycoproteins fusion protein (F), glycoprotein (G) and small hydrophobic protein (SH), two non-structural proteins (NS1 and NS2), the M2-2 protein, and the matrix protein (M).
Capsomeres	The proteins that compose the structural unit of the capsid may form three-dimensional structures known as capsomeres that are visible in an electron micrograph.
Core membrane	Either not expressed or relevance unclear fetal/infantile disease.
Protein core	The non-structural proteins help with viral replication within the infected host cell. The structural proteins have three functional groups. The HRSV protein core forms a trimer-of-hairpins structure. The complex is a six-helix bundle in which the HR-N peptides form a three-stranded, central coiled coil, and the HR-C peptides pack in an antiparallel manner into hydrophobic grooves on the coiled-coil surface.[70]
Core fibrils	Either not expressed or relevance unclear fetal/infantile disease.
Matrix	The matrix consists of two membrane-associated proteins. The matrix (M) protein, a non-glycosylated phosphorylated protein located external to the nucleocapsid layer, acts as a bridge between the lipid bilayer envelope and the nucleocapsid. It drives the viral structural components to facilitate viral assembly. The RSV M also facilitates the transportation of newly synthesized ribonucleoprotein complexes (RNPs) to assembly sites, thereby leading to assembly at the cell surface. M protein associates with the RNPs to inhibit viral transcription and, thereby facilitating viral assembly.[71] The matrix protein (M) lays between the RNP and the envelope, acting as the cushion.[72]

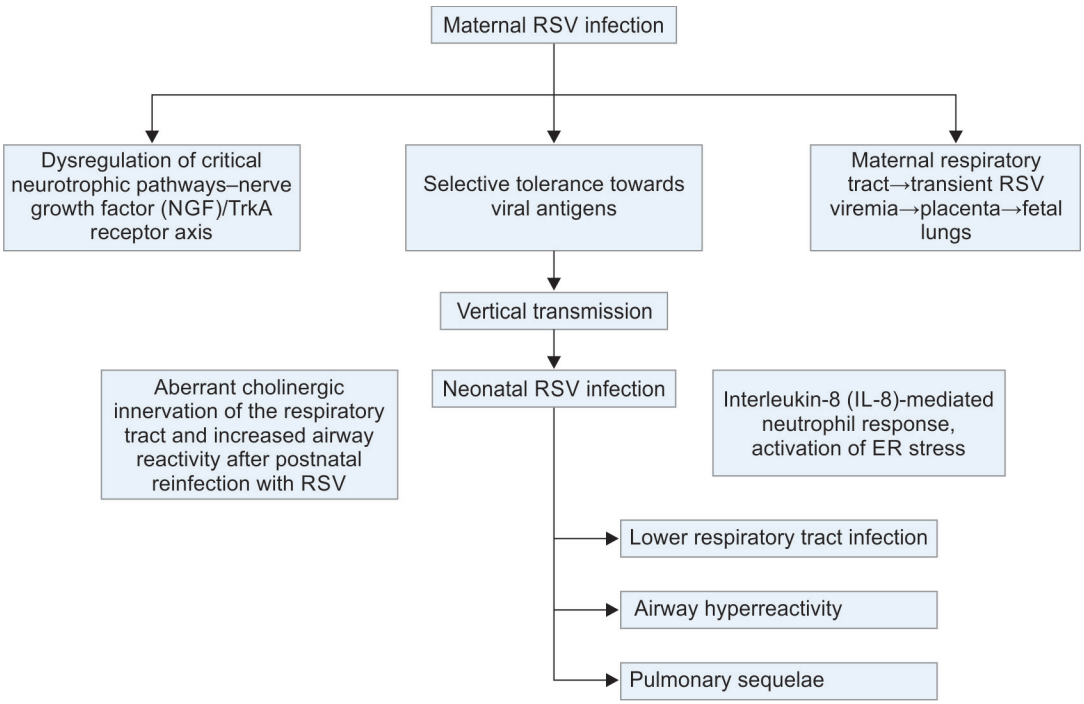
Enzymes	The L protein contains a polymerase domain associated with a polyribonucleotidyl transferase domain in its N-terminus, and a methyltransferase (MTase) domain followed by the C-terminal domain (CTD) enriched in basic amino acids at its C-terminus. These enzymatic activities are essential for efficient viral mRNA translation into proteins, and to prevent the recognition of viral RNA by innate immunity.[73]
RNA elements	Transcription and replication of RSV genome generate RNA intermediates that constitute pathogen-associated molecular patterns (PAMPs), which are sensed by pattern recognition receptors (PRRs) to trigger the interferon (IFN)-mediated antiviral response and the expression of proinflammatory cytokines.[74] RSV participates in viral RNA synthesis by RNA synthesis RNP complex, comprising four proteins, the nucleoprotein (N), the large protein (L), the phosphoprotein (P), and the M2-1 protein.[72]
Nucleus	Either not expressed or relevance unclear fetal/infantile disease.
Nucleosome	Either not expressed or relevance unclear fetal/infantile disease.
DNA	No DNA genome exists.
RNA	Respiratory syncytial virus (RSV) is a negative-sense (–) nonsegmented RNA virus and its RNA synthesis occurs by viral gene transcription and genome replication. Gene transcription includes the positive-sense (+) viral mRNA synthesis, 5′-RNA capping and methylation, and 3′ end polyadenylation. Genome replication includes positive-sense RNA antigenome and negative-sense RNA genome synthesis.[72]
Genome-associated polyprotein	Each RSV gene encodes an mRNA with the 5′ methylated cap and 3′ polyA tail to be translated into a single corresponding protein, except the M2 gene, which has two slightly overlapped open reading frames (ORFs) encoding two proteins: M2-1 and M2-2. RSV initiates viral infection by a virus-specific RNA synthesis RNP required for replication of the full-length genome along with transcription of individual genes.[75]
DNA polymerase	Either not expressed or relevance unclear fetal/infantile disease.
RNA polymerase	Transcription by the RNA-dependent-RNA-polymerase composed of L and P proceeds directly from the negative-sense (3′-5′) genome through the production of capped/polyA monocistronic mRNAs.[74] RNA synthesis is carried out by the RNA-dependent RNA polymerase (RdRp) complex, which consists of the catalytic core L and the cofactor P. L is a 250 kDa polypeptide facilitating synthesis of viral genomic or antigenomic RNAs and mRNA. It also catalyzes ribonucleotide polymerization, mRNA 5′ cap addition and cap methylation.[72]
Reverse transcriptase	Either not expressed or relevance unclear fetal/infantile disease.
Head	Either not expressed or relevance unclear fetal/infantile disease.
Base plate	Either not expressed or relevance unclear fetal/infantile disease.
Integrase	Either not expressed or relevance unclear fetal/infantile disease.
Tail	Either not expressed or relevance unclear fetal/infantile disease.
Tail fiber	Either not expressed or relevance unclear fetal/infantile disease.
Neck	Either not expressed or relevance unclear fetal/infantile disease.

The Canadian RST and the International RST are both validated, reliable, and show a similar level of good predictive accuracy (both show Area Under Curve–Receiver Operator Characteristic, AUC-ROC >0.75; as significant ($p < 0.001$) correlations apparent for risk scores and risk categories.[76] The RST used data from six prospective, observational studies – the: "Risk Factors Linked to Respiratory Syncytial Virus Infection Requiring Hospitalization in Premature Infants Study" (FLIP-2, Spain);[77] "RISK" (the Netherlands);[78] "Pediatric Investigators Collaborative Network on Infections in Canada" (PICNIC, Canada);[79] "Italian National Birth Cohort" (IBC, Italy);[80] "Respiratory Syncytial Virus (RSV) Respiratory Events Among Preterm Infants Outcomes and Risk Tracking Study" (REPORT, USA);[32] and "Predictors Associated with RSV Hospitalization in Nonprophylaxed, Premature Infants" (PONI, multinational).[81]

The RST predicts the risk of RSV hospitalization in 32–35^{+6} weeks' gestational age preterm infants. The RST can facilitate decision-making for clinicians, parents, and policy-makers regarding RSV prophylaxis. Two out of the five identified risk factors, including smoking in the household and daycare, are modifiable and can be used to educate parents.[82] The scoring is performed on a scale between 0 and 56; ≤19 is considered low, 20–45 is perceived as moderate and ≥50 as high-risk. The cumulative RSV hospitalization risk was 3.6% (484/13,475) in the pooled dataset. The combined moderate- and high-risk groups showed a score of 6.3%. The high-risk group had a score of 9.5%, and the very high-risk group showed a score of 11.9%.[82] The IMpact randomized controlled trial showed that prophylaxis with palivizumab reduced RSV hospitalization in 32–35-week gestational age infants by 80–85%. The number needed to treat was 12.[83,84]

The RST is an efficient way for deciding for selective prophylaxis, targeting only 18% of any birth cohort. The financial constraints make it difficult to provide prophylaxis to all infants. Notably, 41% of all LRT infection hospitalizations are in infants who did not receive RSV prophylaxis. RSV-infected children account for 40–60% of the total number of children hospitalized for LRT infections. Only 16% of the total number of hospitalizations due to LRT infections occur in those who have received RSV prophylaxis.[27]

Flowchart 1: Pathogenesis of perinatal RSV infection



Maternal-fetal Transmission

Respiratory syncytial virus spreads from the respiratory tract of the mother first to the placenta, and then to the developing fetal lungs during transient RSV viremia (Flowchart 1). It is detected postnatally in the lungs.[85] Vertical RSV infection is associated with dysregulation of critical neurotrophic pathways – the nerve growth factor (NGF)/TrkA receptor axis during fetal development, leading to aberrant cholinergic innervation of the respiratory tract and increased airway reactivity after postnatal reinfection with RSV.[86]

Respiratory syncytial virus does not induce persistent immunity in humans, reinfection of adult healthy humans causes community-acquired respiratory infections and seasonal epidemics; hence, post-infection of pregnant mothers, immune response is inadequate to prevent viremia and transplacental transmission. Prenatal RSV infection interferes with the NGF promoter via suppression of specific miRNAs (especially miR-221) and selective demethylation, which also manifests postnatally.

Intrauterine fetal RSV infections, before the establishment of immunological self-tolerance, induce selective tolerance toward viral antigens. Therefore, exposed newborns do not regard RSV as pathogenic and non-self during an early-life reinfection, in view of weak anti-RSV Th1 immunity and persistent post-RSV airway dysfunction in childhood.[86]

Respiratory syncytial virus-exposed fetal lungs display changes in critical molecular alterations with persistent functional consequences. Viral transmission and replication in the growing fetal lung tissues modulate expression of ion channels and receptors, predisposing to airway hyperreactivity in later life, supporting Barker's Fetal Programming hypothesis of the Developmental Origins of Health and Disease (DOHaD).

Perinatal RSV persists as an immunologically privileged sanctuary by causing latent infection in cells.[87] It is associated with dysregulation of neurotrophins, involved in neuronal survival and function.[88] The NGF controls the release and expression of major neurotransmitters from the peripheral neurons.[89] It is also associated with innate and adaptive immunity, and allergic inflammation.[90,91] NGF also increases the expression of the anti-apoptotic Bcl-2 family and promotes the longevity of infected bronchial epithelium to support viral replication.[92] Prenatal RSV infection interferes with the NGF promoter via suppression of specific miRNAs (such as miR-221) and selective demethylation.

Pathophysiology

Respiratory syncytial virus infects ciliated cells, epithelium of the small bronchioles and type 1 pneumocytes with infection being confined to the respiratory mucosa. Bronchial narrowing and interference in gas exchange occurs as a result of infiltration of the airway by inflammatory cells, necrosis of the respiratory tract epithelium, shedding of necrotic cells and impaired ciliary function.[93] Infection clearance is dependent on both humoral and cellular immunity. IL-8-mediated neutrophil response is the first response against RSV infection in the body, and correlates with disease severity. Viral clearance occurs by pulmonary $CD8^+$ T-cell response following systemic T-cell lymphopenia. B-cell-activating factors in the airway epithelium and interferon-gamma (IFN-γ) have a protective role.[94] Previous RSV infections do not appear to protect against reinfection.[95]

Humoral immunity reduces the severity of RSV infection, thereby making recurrent infections milder.[96] Higher transplacentally acquired RSV antibody titers are associated with milder symptoms restricted to the upper respiratory tract.[97] Lower antibody titers in cord blood are associated with increased risk of RSV hospitalization before 6 months of age.[98] RSV reaches the small bronchiolar epithelium from the nasopharynx, progressing to type 1 and 2 alveolar pneumocytes.[99,100]

Histopathologic findings of RSV are epithelial cell necrosis, bronchiolar epithelium proliferation, infiltration of monocytes,

T-cells and neutrophils.[100,101] This leads to airway obstruction, air trapping and neutrophilia in bronchoalveolar lavage.[102] RSV is generally restricted to the respiratory epithelium, although it may be occasionally recovered from extrapulmonary tissues, such as the liver,[103] cerebrospinal fluid,[104] or pericardial fluid.[105] IL-8, IL-6, tumor necrosis factor (TNF)-α, and IL-1β can be detected in RSV-infected airways.[106–108] IL-6 levels correlate with severity of the disease. Chemokines in respiratory tract secretions include chemokine ligand (CCL) 3 (macrophage inflammatory protein-1 alpha [MIP-1α]), CCL2 (monocyte chemoattractant protein-1 [MCP-1]), CCL11 (eotaxin), and CCL5 (RANTES [regulated on activation, normal T cell expressed and secreted]),[109,110] but only the β-chemokines, especially MIP-1α, are associated with severe disease.[109–111]

Respiratory syncytial virus infections can lead to endoplasmic reticulum (ER) dysfunction or ER stress in airway cells resulting in the UPR response to restore homeostasis by activating three transmembrane ER stress sensors: activated transcription factor 6 (ATF6), PKR-like ER kinase (PERK) and inositol-requiring enzyme 1 (IRE1). UPR response switches from being pro-survival to being pro-apoptotic if homeostasis is not achieved. Manipulation of the UPR response is used by many viruses to promote their translation. ER stress activation by RSV has been demonstrated in primary human tracheobronchial epithelial (HTBE) cells and in the A549 cell line.[74]

Clinical Presentations

Neonates present with cough and fever. On examination, rhinitis and pharyngitis, congestion of conjunctivae and tympanic membranes, tachypnea, wheezing, nasal flaring, and retractions are seen. On auscultation of the lungs, prolonged expiration, rales, inspiratory rhonchi, decreased lung sounds, and excessive aeration in the lung periphery may be found.[112] Apnea may be the presenting symptom in one-fifth of the cases hospitalized with RSV.[113–118] One cause of reflex apnea may be altered sensitivity of laryngeal chemoreceptors.[119] In a systematic review, the incidence of apnea in hospitalized infants with RSV was found to be between 1.2 and 23.8%. The risk of apnea was <5% in children without serious underlying disease. Overall, the incidence was higher in preterm than in term neonates.[113]

Infants are most susceptible between the ages of 6 weeks and 6 months. Genetic predisposition of the host, co-infection with other pathogens, viral phenotype, and viral load affect disease severity.[120,121]

Respiratory syncytial virus causes severe LRT disease, including bronchiolitis, bronchospasm, and pneumonia.[122] Primary infection usually causes LRT disease, while it is seen in around 50% of secondary infections.[96,123] Disease severity reduces with subsequent infections.[124] RSV-associated wheezing is seen in 20% infants during the first year of life of which 2–3% require hospitalization.[28,123] Some infants who require assisted ventilation may develop inappropriate secretion of antidiuretic hormone, which results in hyponatremia.[125–127] However, in most cases, RSV infection is a self-limited process without any long-term pulmonary sequelae. A few cases may show decreased pulmonary function and chronic obstructive pulmonary disease persisting into adulthood.[128]

Laboratory Diagnosis

Laboratory diagnosis is required in severe or atypical bronchiolitis or to decide for palivizumab prophylaxis, infection control, and additional clinical/laboratory evaluation.[129] Complete blood count is not specific, with a mild increase in C-reactive protein (CRP). Chest X-ray shows hyperinflation with flattening of the diaphragm, infiltrations, atelectasis, and increased peribronchial shadows; helps to rule out other differentials.

Nasal lavage, nasopharyngeal swab, throat swab can be used. Nasal lavage and nasopharyngeal aspirate samples are more sensitive in detecting viruses. Bronchoalveolar lavage and tracheal aspirate sampling is required in intubated patients because of severe LRT infections. Samples are obtained 3–4 days after symptom onset, carried on wet ice, and kept at 2–8°C in a refrigerator. Processing should be done within 48 hours; in case of delay, samples should be kept at −80°C.[130] Nasal lavage and nasopharyngeal aspirate samples are more sensitive in detecting viruses compared with the other methods. Bronchoalveolar lavage and tracheal aspirate sampling may be needed in intubated patients because of severe LRT infections. For the best results, samples should be obtained 3–4 days after symptom onset, carried with wet ice in the laboratory setting, and kept at 2–8°C in a refrigerator, if they are to be studies within 48 hours. If the test will be delayed, they should be kept at −80°C.[130]

Reverse Transcriptase Polymerase Chain Reaction

Reverse transcriptase polymerase chain reaction (RT-PCR) gives rapid, reliable results with higher sensitivity compared with culture and rapid antigen tests and are not affected by passively administered antibody to RSV.[131,132] Drawbacks are high cost and the needs for maintenance of equipment and training of personnel.[133]

PCR-based assays typically are included as part of a multiplex PCR assay that can detect multiple respiratory pathogens.[134] Multiplex PCR-based assays are more expensive than rapid antigen diagnostic tests (RADT). They also usually have a longer turnaround time than RADT, but some commercially available PCR-based assays provide results in <3 hours.[135] In a prospective study, RSV was noted to be more prevalent in children with community-acquired pneumonia (CAP) than in asymptomatic controls (26.6 vs. 1.9%). Similarly, in a multicenter case-control study, RSV was isolated from 36% of 1–11-month-old infants and 17% of 1–4 year-old children who were hospitalized with severe pneumonia compared with 3% of asymptomatic controls.[122]

Serology

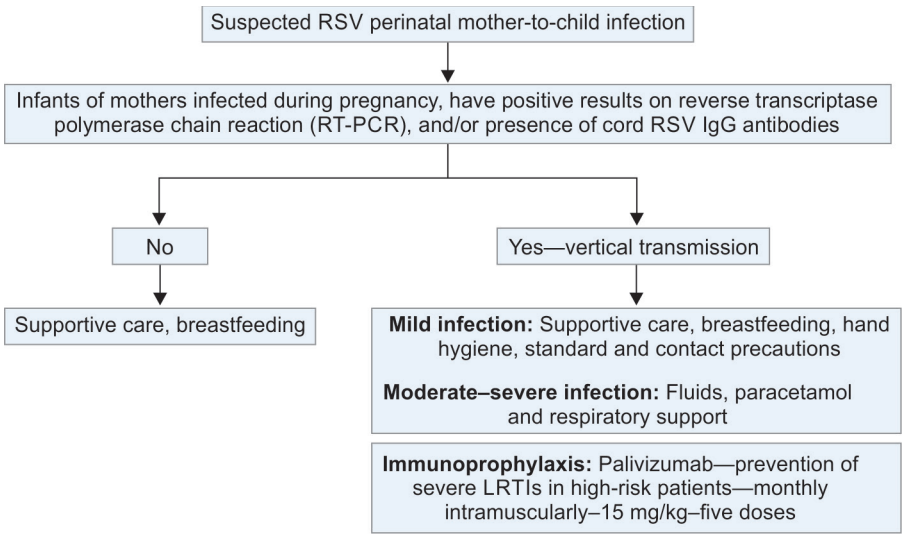
The cord RSV IgG antibody levels correlate with disease severity in the first 6 months. IgG antibodies transferred to the fetus during pregnancy decrease as time progresses reaching a nadir at the age of 2–3 months.

Serology has limitations as a diagnostic tool because seroconversion occurs in 2 weeks, and virus-specific antibodies cannot be detected in infants with RSV infections, and antibodies transmitted from the mother are also present. The direct fluorescence antibody test provides results in 2–3 hours with a sensitivity and specificity of about 95%, but it warrants expertise. Diagnostic serology is also not helpful in the evaluation and management of RSV infection because of maternal antibody in infants and a stable and sustained level of RSV-specific antibody in older children.[136]

Antigen Testing

Rapid antigen diagnostic tests provide results in the shortest time of less than 30 minutes. Sensitivity is 80% in children and specificity is 97%. Retesting may be required in patients with false-negative results.[132] The RADT can be used to screen and negative results can be confirmed with PCR.[137] It is less sensitive than PCR-based assays.[137] Palivizumab prophylaxis may interfere with RADT, leading

Flowchart 2: Management of perinatal RSV infections



to false-negative results.[131] In a meta-analysis of 71 studies, the sensitivity of RADT was 80% and the specificity was 97%.[132]

Viral Culture

Viral cell culture is gold-standard in the diagnosis of RSV but results take around 3–7 days. Rapid cell culture (shell-vial) yields result in 48 hours compared with classic cell culture. Definitive diagnosis can be made by viral isolation from human epithelial type 2 (HEp-2) cells demonstrating characteristic plaque morphology with syncytium formation.

Treatment

Therapy for RSV infection of the LRT is mainly supportive, and preventive measures like good hygiene and isolation are the mainstay of management (Flowchart 2).[138,139] Supportive care includes monitoring of clinical status; fluids, paracetamol, and respiratory support as required. Inhaled bronchodilators, hypertonic saline, inhaled and systemic steroids are not proven to be effective. Mechanical ventilation may be required in patients with severe respiratory symptoms or apnea due to RSV.

Ribavirin

Ribavirin is a synthetic nucleoside analog with good *in vitro* activity against RSV and is approved by the US Food and Drug Administration (FDA) for the treatment of RSV infection. But it is not routinely recommended for infants and children with RSV LRT infection because its efficacy has not been proven.[140,141] It is expensive and must be given early in the course to be effective with concerns about occupational exposure.[140] It is contraindicated in pregnant females because of teratogenic risk. Adverse effects include hemolytic anemia, leukopenia, cough, bronchospasm, rash, and conjunctival irritation.[142–145] Studies in rodents have shown teratogenicity although the risk in human pregnancy is uncertain.[146] It is also associated with bronchoconstriction and warrants caution in asthma or chronic obstructive pulmonary disease.[142] National Institute of Occupational Safety and Health has recommended to reduce the ambient air concentrations of ribavirin and limit occupational exposure to hospital personnel.[147]

Randomized controlled trials comparing ribavirin with placebo in children with RSV LRTI are inconclusive with some reporting decreased severity of illness; decreased duration of mechanical ventilation, oxygen therapy, and hospital stay; and decreased viral shedding,[148–151] whereas others have reported no benefit.[152–154] A 2004 systematic review comparing ribavirin with placebo in infants and children with RSV LRTI found that trials of ribavirin lack sufficient power to provide reliable estimates of the effects.[140]

The American Academy of Pediatrics recommends against the routine use of ribavirin because of long-term aerosol application and hospitalization, intoxication potential (bone marrow inhibition, carcinogenicity), teratogenicity and high cost.[129,155] Ribavirin should be reserved for immunosuppressed patients with severe RSV infection, with opinion of an infectious disease's specialist being required before its use.

Palivizumab

Palivizumab is an RSV-specific humanized IgG1 monoclonal antibody against an epitope in the A antigenic part of the RSV F-glycoprotein, which is highly conserved among various isolates. It prevents viral replication by inhibiting its adherence to the respiratory epithelium.[156] It is produced by recombinant DNA technology and was licensed in 1998 for the prevention of serious RSV LRT disease in high-risk children.[152] It is given intramuscularly at a dose of 15 mg/kg monthly for a total of five doses to maintain a serum concentration above 40 µg/mL in preterms with bronchopulmonary dysplasia (BPD).[157]

Palivizumab is administered intramuscularly and does not interfere with response to live virus vaccines.[153] Existing literature does not show any benefit of palivizumab in RSV bronchiolitis.[158, 159] Adverse reactions are manifested by fever, rash, and formation of antibodies. In a meta-analysis comparing palivizumab prophylaxis with placebo in BPD, preterm infants ≤35 weeks' gestation and congenital heart disease; palivizumab reduced RSV hospitalizations without increase in adverse events.[154] Palivizumab prophylaxis can be used for infants with BPD who are younger than 1 year of age at the start of RSV season,[143,160] or between the ages of 12–23 months in infants requiring medical management for BPD.[83,161] Recent AAP guidelines do not recommend pavlizumab prophylaxis for preterm infants born at 29–35 weeks without chronic lung disease, hemodynamically significant congenital heart disease

and coexisting conditions. But healthy preterms born at more than 32 gestational weeks may also have increased RSV-associated hospitalization.

RSV-IVIG

Intravenous immune globulin with a high neutralizing activity against RSV (RSV-IVIG) is a hyperimmune polyclonal immunoglobulin obtained from donors with high RSV neutralizing antibodies and prevents integration of F and G RSV surface glycoproteins with host.[156] It has five-fold greater efficiency in neutralizing RSV as compared with IVIG. It was approved by the FDA in 1996 for reduced hospitalizations in high-risk infants.[162] It is no longer available because RCTs showed no benefit.[163] Other disadvantages are necessity for hospitalization, long-term infusion, fluid loading because of high-volume doses, sudden cyanotic episodes and necessity to avoid live-attenuated vaccines for at least nine months after treatment with RSV-IVIG.[164] Other monoclonal antibodies against RSV are still under research.[165]

Nirsevimab

Nirsevimab is a monoclonal antibody with a long half-life, high neutralizing activity. It targets the prefusion-conformation of the RSV F-glycoprotein. In a multi-center, placebo-controlled RCTs in healthy infants born at ≥29 weeks' gestation, a single injection of nirsevimab effectively prevented RSV LRT infections and hospitalization for 150 days.[165,166] It was recently approved for clinical use.[167]

Breastfeeding

Exclusive breastfeeding reduces hospitalizations, risk of respiratory failure, and the need for oxygen treatment in neonatal RSV infection, attributed to high levels of interferon (IFN)-gamma, cytokines, lactoferrin, and T-cells in human milk and its microbiota.[168]

Outcomes

RSV can lead to long-term sequelae such as wheezing and asthma, associated with increased healthcare costs and reduced quality of life. Transplacental transmission of RSV leads to persistence of vertically transmitted virus in lungs postnatally, culminating in dysregulation of neurotrophic pathways and airway hyperreactivity.[85]

Prevention

Standard precautions, hand hygiene, breastfeeding, and contact isolation should be followed for RSV-infected newborns. The Centers for Disease Control and Prevention (CDC) recommends standard and contact precautions for the prevention of RSV.[169,170] Measures for healthcare providers include hand washing, appropriate use of gloves, surgical mask, eye protection, and disposable gowns.

In inpatient settings, infected patients should be isolated with standard and contact precautions in private rooms or cohorted in rooms with other RSV-infected patients.[169,171–173] During outbreaks, cohorting of healthcare personnels caring for RSV patients is also recommended. Healthcare personnel should have continued education about the symptoms, epidemiology, diagnosis, and transmission of RSV.

Vaccine Development

A new RSV vaccine, Arexvy, was recently approved in the US to prevent LRT disease caused by RSV in individuals 60 years of age and older.[174,175] Tests are needed in infants. Several other candidate vaccines are also being evaluated in clinical trials.[176] Live-attenuated vaccines, including molecular clones,[177–179] gene-based vector vaccines,[180] subunit vaccines,[181] or prefusion-conformations of RSV F-glycoproteins[182] are under evaluation. A variety of gene-based vector vaccines, nucleic acid vaccines, particle-based approaches, and novel adjuvants for candidate RSV vaccines are also in preclinical and early phase clinical development.[176] Challenges to development of an RSV vaccine for infants are immature immunity, suppression of immune response by maternal antibodies and antigenically divergent strains.[176,183,184]

Future Directions

We still need major, consolidated efforts to develop effective vaccines and monoclonal antibodies.

References

1. Chanock R, Roizman B, Myers R. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA). I. Isolation, properties and characterization. Am J Hyg 1957;66(3):281–290. DOI: 10.1093/oxfordjournals.aje.a119901.
2. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009;360(6):588–598. DOI: 10.1056/NEJMOA0804877.
3. Afonso CL, Amarasinghe GK, Bányai K, et al. Taxonomy of the order Mononegavirales: update 2016. Arch Virol 2016;161(8):2351–2360. DOI: 10.1007/S00705-016-2880-1/TABLES/1.
4. Johansson C. Respiratory syncytial virus infection: an innate perspective. F1000Res 2016;5:2898. DOI: 10.12688/F1000RESEARCH.9637.1.
5. White LJ, Waris M, Cane PA, et al. The transmission dynamics of groups A and B human respiratory syncytial virus (hRSV) in England & Wales and Finland: seasonality and cross-protection. Epidemiol Infect 2005;133(2):279–289. DOI: 10.1017/S0950268804003450.
6. Papadopoulos NG, Gourgiotis D, Javadyan A, et al. Does respiratory syncytial virus subtype influences the severity of acute bronchiolitis in hospitalized infants? Respir Med 2004;98(9):879–882. DOI: 10.1016/J.RMED.2004.01.009.
7. Gilca R, de Serres G, Tremblay M, et al. Distribution and clinical impact of human respiratory syncytial virus genotypes in hospitalized children over 2 winter seasons. J Infect Dis 2006;193(1):54–58. DOI: 10.1086/498526.
8. Walsh EE, McConnochie KM, Long CE, et al. Severity of respiratory syncytial virus infection is related to virus strain. J Infect Dis 1997;175(4):814–820. DOI:10.1086/513976.
9. McConnochie KM, Hall CB, Walsh EE, et al. Variation in severity of respiratory syncytial virus infections with subtype. J Pediatr 1990;117(1 Pt 1):52–62. DOI: 10.1016/S0022-3476(05)82443-6.
10. Hall CB, Walsh EE, Schnabel KC, et al. Occurrence of groups A and B of respiratory syncytial virus over 15 years: associated epidemiologic and clinical characteristics in hospitalized and ambulatory children. J Infect Dis 1990;162(6):1283–1290. DOI: 10.1093/INFDIS/162.6.1283.
11. Stein RT, Bont LJ, Zar H, et al. Respiratory syncytial virus hospitalization and mortality: systematic review and meta-analysis. Pediatr Pulmonol 2017;52(4):556–569. DOI: 10.1002/PPUL.23570.
12. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet 2017;390(10098):946–958. DOI: 10.1016/S0140-6736(17)30938-8.
13. Hall CB, Douglas RG, Geiman JM. Possible Transmission by Fomites of Respiratory Syncytial Virus. J Infect Dis 1980;141(1):98–102. DOI: 10.1093/INFDIS/141.1.98.
14. Rezaee F, Linfield DT, Harford TJ, et al. Ongoing developments in RSV prophylaxis: a clinician's analysis. Curr Opin Virol 2017;24:70–78. DOI: 10.1016/J.COVIRO.2017.03.015.

15. Munywoki PK, Koech DC, Agoti CN, et al. Influence of age, severity of infection, and co-infection on the duration of respiratory syncytial virus (RSV) shedding. Epidemiol Infect 2015;143(4):804–812. DOI: 10.1017/S0950268814001393.
16. King JC, Burke AR, Clemens JD, et al. Respiratory syncytial virus illnesses in human immunodeficiency virus- and noninfected children. Pediatr Infect Dis J 1993;12(9):733–739. DOI: 10.1097/00006454-199309000-00006.
17. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. Pediatrics 2013;132(2). DOI:10.1542/PEDS.2013-0303.
18. Rose EB, Wheatley A, Langley G, et al. Respiratory syncytial virus seasonality – United States, 2014–2017. MMWR Morb Mortal Wkly Rep 2018;67(2):71–76. DOI: 10.15585/MMWR.MM6702A4.
19. Obando-Pacheco P, Justicia-Grande AJ, Rivero-Calle I, et al. Respiratory syncytial virus seasonality: a global overview. J Infect Dis 2018;217(9):1356–1364. DOI: 10.1093/INFDIS/JIY056.
20. Olsen SJ, Winn AK, Budd AP, et al. Changes in Influenza and Other Respiratory Virus Activity During the COVID-19 Pandemic – United States, 2020–2021. MMWR Morb Mortal Wkly Rep 2021;70(29): 1013–1019. DOI: 10.15585/MMWR.MM7029A1.
21. Haddadin Z, Schuster JE, Spieker AJ, et al. Acute Respiratory Illnesses in Children in the SARS-CoV-2 Pandemic: Prospective Multicenter Study. Pediatrics 2021;148(2): DOI: 10.1542/PEDS.2021-051462.
22. Nolen LD, Seeman S, Bruden D, et al. Impact of social distancing and travel restrictions on non-coronavirus disease 2019 (Non-COVID-19) respiratory hospital admissions in young children in rural Alaska. Clin Infect Dis 2021;72(12):2196–2198. DOI: 10.1093/CID/CIAA1328.
23. Friedrich F, Ongaratto R, Scotta MC, et al. Early impact of social distancing in response to coronavirus disease 2019 on hospitalizations for acute bronchiolitis in infants in Brazil. Clin Infect Dis 2021;72(12):2071–2075. DOI: 10.1093/CID/CIAA1458.
24. Yeoh DK, Foley DA, Minney-Smith CA, et al. Impact of coronavirus disease 2019 public health measures on detections of influenza and respiratory syncytial virus in children during the 2020 Australian winter. Clin Infect Dis 2021;72(12):2199–2202. DOI: 10.1093/CID/CIAA1475.
25. van Brusselen D, de Troeyer K, ter Haar E, et al. Bronchiolitis in COVID-19 times: a nearly absent disease? Eur J Pediatr 2021;180(6):1969–1973. DOI: 10.1007/S00431-021-03968-6.
26. Agha R, Avner JR. Delayed seasonal RSV surge observed during the COVID-19 pandemic. Pediatrics 2021;148(3):DOI: 10.1542/PEDS.2021-052089.
27. Perk Y, Özdil M. Respiratory syncytial virüs infections in neonates and infants. Turkish Archives of Pediatrics/Türk Pediatri Arşivi 2018;53(2):63. DOI: 10.5152/TURKPEDIATRIARS.2018.6939.
28. Boyce TG, Mellen BG, Mitchel EF, et al. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J Pediatr 2000;137(6):865–870. DOI: 10.1067/MPD.2000.110531.
29. Simoes EAF. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. J Pediatr 2003;143(5 SUPPL.). DOI: 10.1067/s0022-3476(03)00511-0.
30. Houben ML, Bont L, Wilbrink B, et al. Clinical prediction rule for RSV bronchiolitis in healthy newborns: prognostic birth cohort study. Pediatrics 2011;127(1):35–41. DOI: 10.1542/PEDS.2010-0581.
31. Munywoki PK, Koech DC, Agoti CN, et al. Frequent asymptomatic respiratory syncytial virus infections during an epidemic in a rural Kenyan household cohort. J Infect Dis 2015;212(11):1711–1718. DOI: 10.1093/INFDIS/JIV263.
32. Sheridan-Pereira M, Murphy J, Sloan J, et al. Respiratory syncytial virus preterm (32–36 completed weeks of gestation) risk estimation measure for RSV hospitalization in Ireland: a prospective study. Pediatr Infect Dis J 2016;35(1):19–24. DOI: 10.1097/INF.0000000000000918.
33. Mitchell I, Wong SK, Paes B, et al. Respiratory syncytial virus prophylaxis in cystic fibrosis: the Canadian registry of palivizumab data (2005–2016). Eur J Clin Microbiol Infect Dis 2018;37(7):1345–1352. DOI: 10.1007/S10096-018-3256-0.
34. Manzoni P, Figueras-Aloy J, Simões EAF, et al. Defining the incidence and associated morbidity and mortality of severe respiratory syncytial virus infection among children with chronic diseases. Infect Dis Ther 2017;6(3):383–411. DOI: 10.1007/S40121-017-0160-3.
35. Paes B, Fauroux B, Figueras-Aloy J, et al. Defining the risk and associated morbidity and mortality of severe respiratory syncytial virus infection among infants with chronic lung disease. Infect Dis Ther 2016;5(4):453–471. DOI: 10.1007/S40121-016-0137-7.
36. Wang EEL, Law BJ, Boucher FD, et al. Pediatric investigators collaborative network on infections in Canada (PICNIC) study of admission and management variation in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. J Pediatr 1996;129(3):390–395. DOI: 10.1016/S0022-3476(96)70071-9.
37. Gijtenbeek RGP, Kerstjens JM, Reijneveld SA, et al. RSV infection among children born moderately preterm in a community-based cohort. Eur J Pediatr 2015;174(4):435–442. DOI: 10.1007/S00431-014-2415-2.
38. Welliver RC, Checchia PA, Bauman JH, et al. Fatality rates in published reports of RSV hospitalizations among high-risk and otherwise healthy children. Curr Med Res Opin 2010;26(9):2175–2181. DOI: 10.1185/03007995.2010.505126.
39. Checchia PA, Paes B, Bont L, et al. Defining the risk and associated morbidity and mortality of severe respiratory syncytial virus infection among infants with congenital heart disease. Infect Dis Ther 2017;6(1):37–56. DOI: 10.1007/S40121-016-0142-X.
40. von Linstow ML, Høgh M, Nordbø SA, et al. A community study of clinical traits and risk factors for human metapneumovirus and respiratory syncytial virus infection during the first year of life. Eur J Pediatr 2008;167(10):1125–1133. DOI: 10.1007/S00431-007-0643-4.
41. Bradley JP, Bacharier LB, Bonfiglio JA, et al. Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy. Pediatrics 2005;115(1). DOI: 10.1542/PEDS.2004-0059.
42. Maedel C, Kainz K, Frischer T, et al. Increased severity of respiratory syncytial virus airway infection due to passive smoke exposure. Pediatr Pulmonol 2018;53(9):1299–1306. DOI: 10.1002/PPUL.24137.
43. Jallow S, Agosti Y, Kgagudi P, et al. Impaired transplacental transfer of respiratory syncytial virus-neutralizing antibodies in human immunodeficiency virus-infected versus -uninfected pregnant women. Clin Infect Dis 2019;69(1):151–154. DOI: 10.1093/CID/CIY1071.
44. Cohen C, Moyes J, Tempia S, et al. Epidemiology of acute lower respiratory tract infection in HIV-exposed uninfected infants. Pediatrics 2016;137(4). DOI: 10.1542/PEDS.2015-3272.
45. Weinberg A, Mussi-Pinhata MM, Yu Q, et al. Excess respiratory viral infections and low antibody responses among HIV-exposed, uninfected infants. AIDS 2017;31(5):669–679. DOI: 10.1097/QAD.0000000000001393.
46. Beckhaus AA, Castro-Rodriguez JA. Down syndrome and the risk of severe RSV infection: a meta-analysis. Pediatrics 2018;142(3): e20180225. DOI: 10.1542/PEDS.2018-0225.
47. Shi T, Balsells E, Wastnedge E, et al. Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: systematic review and meta-analysis. J Glob Health 2015;5(2): 020416. DOI: 10.7189/JOGH.05.020416.
48. Lanari M, Silvestri M, Rossi GA. Respiratory syncytial virus risk factors in late preterm infants. http://dx. DOI.org/101080/14767050903194438. 2009;22(SUPPL. 3):102–107. DOI: 10.1080/14767050903194438.
49. Choi EH, Lee HJ, Yoo T, Chanock SJ. A common haplotype of interleukin-4 gene IL4 is associated with severe respiratory syncytial virus disease in Korean children. J Infect Dis 2002;186(9):1207–1211. DOI: 10.1086/344310.
50. Hoebee B, Rietveld E, Bont L, et al. Association of severe respiratory syncytial virus bronchiolitis with interleukin-4 and interleukin-4 receptor alpha polymorphisms. J Infect Dis 2003;187(1):2–11. DOI: 10.1086/345859.
51. Goetghebuer T, Isles K, Moore C, et al. Genetic predisposition to wheeze following respiratory syncytial virus bronchiolitis. Clin Exp Allergy 2004;34(5):801–803. DOI: 10.1111/J.1365-2222.2004.1947.X.

52. Hoebee B, Bont L, Rietveld E, et al. Influence of promoter variants of interleukin-10, interleukin-9, and tumor necrosis factor-alpha genes on respiratory syncytial virus bronchiolitis. J Infect Dis 2004;189(2):239–247. DOI: 10.1086/380908.
53. Hull J, Rowlands K, Lockhart E, et al. Variants of the chemokine receptor CCR5 are associated with severe bronchiolitis caused by respiratory syncytial virus. J Infect Dis 2003;188(6):904–907. DOI: 10.1086/377587.
54. Puthothu B, Krueger M, Forster J, et al. Association between severe respiratory syncytial virus infection and IL13/IL4 haplotypes. J Infect Dis 2006;193(3):438–441. DOI: 10.1086/499316.
55. Löfgren J, Rämet M, Renko M, et al. Association between surfactant protein A gene locus and severe respiratory syncytial virus infection in infants. J Infect Dis 2002;185(3):283–289. DOI: 10.1086/338473.
56. Lahti M, Löfgren J, Marttila R, et al. Surfactant protein D gene polymorphism associated with severe respiratory syncytial virus infection. Pediatr Res 2002;51(6):696–699. DOI: 10.1203/00006450-200206000-00006.
57. Tal G, Mandelberg A, Dalal I, et al. Association between common Toll-like receptor 4 mutations and severe respiratory syncytial virus disease. J Infect Dis 2004;189(11):2057–2063. DOI: 10.1086/420830.
58. Amanatidou V, Sourvinos G, Apostolakis S, et al. T280M variation of the CX3C receptor gene is associated with increased risk for severe respiratory syncytial virus bronchiolitis. Pediatr Infect Dis J 2006;25(5):410–414. DOI: 10.1097/01.INF.0000214998.16248.B7.
59. El Saleeby CM, Li R, Somes GW, et al. Surfactant protein A2 polymorphisms and disease severity in a respiratory syncytial virus-infected population. J Pediatr 2010;156(3): 409–414. DOI: 10.1016/J.JPEDS.2009.09.043.
60. López EL, Ferolla FM, Toledano A, et al. Genetic Susceptibility to life-threatening respiratory syncytial virus infection in previously healthy infants. Pediatr Infect Dis J 2020;39(11):1057–1061. DOI: 10.1097/INF.0000000000002827.
61. Battles MB, McLellan JS. Respiratory syncytial virus entry and how to block it. Nature Rev Microbiol 2019;17(4):233–245. DOI: 10.1038/s41579-019-0149-x.
62. Mohapatra SS, Lockey RF. Respiratory syncytial virus infection: from biology to therapy a perspective. World Allergy Organ J 2008;1(2):21. DOI: 10.1097/WOX.0B013E31816549A2.
63. McLellan JS, Ray WC, Peeples ME. Structure and function of RSV surface glycoproteins. Curr Top Microbiol Immunol 2013;372:83. DOI: 10.1007/978-3-642-38919-1_4.
64. Johnson SM, McNally BA, Ioannidis I, et al. Respiratory Syncytial Virus Uses CX3CR1 as a Receptor on Primary Human Airway Epithelial Cultures. PLoS Pathog 2015;11(12):e1005318. DOI: 10.1371/JOURNAL.PPAT.1005318.
65. Fleming EH, Kolokoltsov AA, Davey RA, et al. Respiratory Syncytial Virus F Envelope protein associates with lipid rafts without a requirement for other virus proteins. J Virol 2006;80(24):12160–12170. DOI: 10.1128/JVI.00643-06.
66. Guo X, Liu T, Shi H, et al. Respiratory syncytial virus infection upregulates NLRC5 and major histocompatibility complex class I expression through RIG-I induction in airway epithelial cells. J Virol 2015;89(15):7636–7645. DOI: 10.1128/JVI.00349-15.
67. Schlender J, Zimmer G, Herrler G, et al. Respiratory syncytial virus (RSV) fusion protein subunit F2, not attachment protein G, determines the specificity of RSV infection. J Virol 2003;77(8):4609. DOI: 10.1128/JVI.77.8.4609-4616.2003.
68. Tiwari PM, Eroglu E, Boyoglu-Barnum S, et al. Atomic force microscopic investigation of respiratory syncytial virus infection in HEp-2 cells. J Microsc 2014;253(1):31. DOI: 10.1111/JMI.12095.
69. Efstathiou C, Abidi SH, Harker J, et al. Revisiting respiratory syncytial virus's interaction with host immunity, towards novel therapeutics. Cell Mol Life Sci 2020;77(24):5045. DOI: 10.1007/S00018-020-03557-0.
70. Zhao X, Singh M, Malashkevich VN, et al. Structural characterization of the human respiratory syncytial virus fusion protein core. Proc Natl Acad Sci U S A 2000;97(26):14172. DOI: 10.1073/PNAS.260499197.
71. Shahriari S, Wei KJ, Ghildyal R. Respiratory syncytial virus matrix (M) protein interacts with actin in vitro and in cell culture. Viruses 2018;10(10). DOI: 10.3390/V10100535.
72. Cao D, Gao Y, Liang B. Structural insights into the respiratory syncytial virus RNA synthesis complexes. Viruses 2021;13(5). DOI: 10.3390/V13050834.
73. Sutto-Ortiz P, Tcherniuk S, Ysebaert N, et al. The methyltransferase domain of the respiratory syncytial virus L protein catalyzes cap N7 and 2'-O-methylation. PLoS Pathog 2021;17(5):e1009562. DOI: 10.1371/JOURNAL.PPAT.1009562.
74. Cervantes-Ortiz SL, Cuervo NZ, Grandvaux N. Respiratory syncytial virus and cellular stress responses: impact on replication and physiopathology. Viruses 2016;8(5): 124. DOI:10.3390/V8050124.
75. Whelan SPJ, Barr JN, Wertz GW. Transcription and replication of nonsegmented negative-strand RNA viruses. Curr Top Microbiol Immunol 2004;283:61–119. DOI: 10.1007/978-3-662-06099-5_3.
76. Paes B, Fullarton JR, Rodgers-Gray BS, et al. Adoption in Canada of an international risk scoring tool to predict respiratory syncytial virus hospitalization in moderate-to-late preterm infants. Curr Med Res Opin 2021;37(7):1149–1153. DOI: 10.1080/03007995.2021.1911974.
77. Ák ZS, Saliba E, Kosma P, et al. Predictors of RSV LRTI Hospitalization in Infants Born at 33 to 35 weeks gestational age: a large multinational study (PONI). PLoS One 2016;11(6): e0157446. DOI: 10.1371/JOURNAL.PONE.0157446.
78. Figueras-Aloy J, Carbonell-Estrany X, Quero-Jiménez J, et al. FLIP-2 Study: risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born in Spain at a gestational age of 32 to 35 weeks. Pediatr Infect Dis J 2008;27(9):788–793. DOI: 10.1097/INF.0B013E3181710990.
79. Ambrose CS, Anderson EJ, Simões EAF, et al. Respiratory syncytial virus disease in preterm infants in the U.S. born at 32–35 weeks gestation not receiving immunoprophylaxis. Pediatr Infect Dis J 2014;33(6):576–582. DOI: 10.1097/INF.0000000000000219.
80. Waycaster G, Vo P, Deaton R, et al. Respiratory syncytial virus-related hospitalization in premature infants without bronchopulmonary dysplasia: subgroup efficacy analysis of the IMpact-RSV trial by gestational age group. Pediatric Health Med Ther. Published online May 2014:43. DOI: 10.2147/PHMT.S59572.
81. Anderson EJ, Carbonell-Estrany X, Blanken M, et al. Burden of severe respiratory syncytial virus disease among 33–35 weeks' gestational age infants born during multiple respiratory syncytial virus seasons. Pediatr Infect Dis J 2017;36(2):160–167. DOI: 10.1097/INF.0000000000001377.
82. Blanken MO, Paes B, Anderson EJ, et al. Risk scoring tool to predict respiratory syncytial virus hospitalisation in premature infants. Pediatr Pulmonol 2018;53(5):605–612. DOI: 10.1002/PPUL.23960.
83. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. Pediatrics 1998;102(3 Pt 1):531–537. PMID: 9738173.
84. Simoes EA, Groothuis JR. Respiratory syncytial virus prophylaxis--the story so far. Respir Med 2002;96 Suppl B:S15–S24. DOI: 10.1016/S0954-6111(02)90066-1.
85. Piedimonte G, Walton C, Samsell L. Vertical transmission of respiratory syncytial virus modulates pre- and postnatal innervation and reactivity of rat airways. PLoS One 2013;8(4):e61309. DOI: 10.1371/journal.pone.0061309.
86. Piedimonte G, Harford TJ. Effects of maternal-fetal transmission of viruses and other environmental agents on lung development. Pediatr Res 2020;87(2):420–426. DOI: 10.1038/S41390-019-0657-4.
87. Rezaee F, Gibson LF, Piktel D, et al. Respiratory syncytial virus infection in human bone marrow stromal cells. Am J Respir Cell Mol Biol 2011;45(2):277–286. DOI: 10.1165/RCMB.2010-0121OC.
88. Scuri M, Samsell L, Piedimonte G. The role of neurotrophins in inflammation and allergy. Inflamm Allergy Drug Targets 2010;9(3):173–180. DOI: 10.2174/187152810792231913.

89. Lindsay RM, Harmar AJ. Nerve growth factor regulates expression of neuropeptide genes in adult sensory neurons. Nature 1989;337(6205):362–364. DOI: 10.1038/337362A0.
90. Bonini S, Lambiase A, Bonini S, et al. Circulating nerve growth factor levels are increased in humans with allergic diseases and asthma. Proc Natl Acad Sci U S A 1996;93(20):10955–10960. DOI: 10.1073/PNAS.93.20.10955.
91. Braun A, Lommatzsch M, Lewin GR, et al. Neurotrophins: a link between airway inflammation and airway smooth muscle contractility in asthma? Int Arch Allergy Immunol 1999;118(2–4): 163–165. DOI: 10.1159/000024056.
92. Othumpangat S, Gibson LF, Samsell L, et al. NGF is an essential survival factor for bronchial epithelial cells during respiratory syncytial virus infection. PLoS One 2009;4(7). DOI: 10.1371/JOURNAL.PONE.0006444.
93. Lambert L, Sagfors AM, Openshaw PJM, et al. Immunity to RSV in early-life. Front Immunol 2014;5(SEP). DOI: 10.3389/FIMMU.2014.00466.
94. Russell CD, Unger SA, Walton M, et al. The human immune response to respiratory syncytial virus infection. Clin Microbiol Rev 2017;30(2):481–502. DOI: 10.1128/CMR.00090-16.
95. Hall CB, Walsh EE, Long CE, et al. Immunity to and frequency of reinfection with respiratory syncytial virus. J Infect Dis 1991;163(4):693–698. DOI: 10.1093/INFDIS/163.4.693.
96. Henderson FW, Collier AM, Clyde WA, et al. Respiratory-syncytial-virus infections, reinfections and immunity. A prospective, longitudinal study in young children. N Engl J Med 1979;300(10):530–534. DOI: 10.1056/NEJM197903083001004.
97. Glezen WP, Paredes A, Allison JE, et al. Risk of respiratory syncytial virus infection for infants from low-income families in relationship to age, sex, ethnic group, and maternal antibody level. J Pediatr 1981;98(5):708–715. DOI: 10.1016/S0022-3476(81)80829-3.
98. Stensballe LG, Ravn H, Kristensen K, et al. Seasonal variation of maternally derived respiratory syncytial virus antibodies and association with infant hospitalizations for respiratory syncytial virus. J Pediatr 2009;154(2). DOI:10.1016/J.JPEDS.2008.07.053.
99. Hoffman SJ, Laham FR, Polack FP. Mechanisms of illness during respiratory syncytial virus infection: The lungs, the virus and the immune response. Microbes Infect 2004;6(8):767–772. DOI: 10.1016/j.micinf.2004.03.010.
100. Johnson JE, Gonzales RA, Olson SJ, et al. The histopathology of fatal untreated human respiratory syncytial virus infection. Mod Pathol 2007;20(1):108–119. DOI: 10.1038/MODPATHOL.3800725.
101. Aherne W, Bird T, Court SD, et al Pathological changes in virus infections of the lower respiratory tract in children. J Clin Pathol 1970;23(1):7–18. DOI: 10.1136/JCP.23.1.7.
102. Everard ML, Swarbrick A, Wrightham M, et al. Analysis of cells obtained by bronchial lavage of infants with respiratory syncytial virus infection. Arch Dis Child 1994;71(5):428–432. DOI: 10.1136/ADC.71.5.428.
103. Nadal D, Wunderli W, Meurmann O, et al. Isolation of respiratory syncytial virus from liver tissue and extrahepatic biliary atresia material. Scand J Infect Dis 1990;22(1):91–93. DOI: 10.3109/00365549009023125.
104. Zlateva KT, van Ranst M. Detection of subgroup B respiratory syncytial virus in the cerebrospinal fluid of a patient with respiratory syncytial virus pneumonia. Pediatr Infect Dis J 2004;23(11):1065–1066. DOI: 10.1097/01.INF.0000143654.12493.C9.
105. Fishaut M, Tubergen D, McIntosh K. Cellular response to respiratory viruses with particular reference to children with disorders of cell-mediated immunity. J Pediatr 1980;96(2):179–186. DOI: 10.1016/S0022-3476(80)80799-2.
106. Noah TL, Henderson FW, Wortman IA, et al. Nasal cytokine production in viral acute upper respiratory infection of childhood. J Infect Dis 1995;171(3):584–592. DOI: 10.1093/INFDIS/171.3.584.
107. Matsuda K, Tsutsumi H, Okamoto Y, et al. Development of interleukin 6 and tumor necrosis factor alpha activity in nasopharyngeal secretions of infants and children during infection with respiratory syncytial virus. Clin Diagn Lab Immunol 1995;2(3):322–324. DOI: 10.1128/CDLI.2.3.322-324.1995.
108. Smyth RL, Fletcher JN, Thomas HM, et al. Immunological responses to respiratory syncytial virus infection in infancy. Arch Dis Child 1997;76(3):210–214. DOI: 10.1136/ADC.76.3.210.
109. Garofalo RP, Patti J, Hintz KA, et al. Macrophage inflammatory protein-1alpha (not T helper type 2 cytokines) is associated with severe forms of respiratory syncytial virus bronchiolitis. J Infect Dis 2001;184(4):393–399. DOI: 10.1086/322788.
110. Welliver RC, Garofalo RP, Ogra PL. Beta-chemokines, but neither T helper type 1 nor T helper type 2 cytokines, correlate with severity of illness during respiratory syncytial virus infection. Pediatr Infect Dis J 2002;21(5):457–461. DOI: 10.1097/00006454-200205000-00033.
111. Garofalo RP, Hintz KH, Hill V, et al. A comparison of epidemiologic and immunologic features of bronchiolitis caused by influenza virus and respiratory syncytial virus. J Med Virol 2005;75(2):282–289. DOI: 10.1002/JMV.20268.
112. Tregoning JS, Schwarze J. Respiratory viral infections in infants: causes, clinical symptoms, virology, and immunology. Clin Microbiol Rev 2010;23(1):74–98. DOI: 10.1128/CMR.00032-09.
113. Ralston S, Hill V. Incidence of apnea in infants hospitalized with respiratory syncytial virus bronchiolitis: a systematic review. J Pediatr 2009;155(5): 728–733. DOI:10.1016/J.JPEDS.2009.04.063.
114. Leo Arms J, Ortega H, Reid S. Chronological and clinical characteristics of apnea associated with respiratory syncytial virus infection: a retrospective case series. Clin Pediatr (Phila) 2008;47(9):953–958. DOI: 10.1177/0009922808320699.
115. Hall CB, Hall WJ, Speers DM. Clinical and physiological manifestations of bronchiolitis and pneumonia. Outcome of respiratory syncytial virus. Am J Dis Child 1979;133(8):798–802. DOI: 10.1001/ARCHPEDI.1979.02130080038006.
116. Church NR, Anas NG, Hall CB, et al. Respiratory syncytial virus-related apnea in infants. Demographics and outcome. Am J Dis Child 1984;138(3):247–250. DOI: 10.1001/ARCHPEDI.1984.02140410027010.
117. Bruhn FW, Mokrohisky ST, McIntosh K. Apnea associated with respiratory syncytial virus infection in young infants. J Pediatr 1977;90(3):382–386. DOI: 10.1016/S0022-3476(77)80697-5.
118. Anas N, Boettrich C, Hall CB, et al. The association of apnea and respiratory syncytial virus infection in infants. J Pediatr 1982;101(1):65–69. DOI: 10.1016/S0022-3476(82)80184-4.
119. Lindgren C, Jing L, Graham B, et al. Respiratory syncytial virus infection reinforces reflex apnea in young lambs. Pediatr Res 1992;31(4 Pt 1):381–385. DOI: 10.1203/00006450-199204000-00015.
120. Murray J, Bottle A, Sharland M, et al. Risk factors for hospital admission with RSV bronchiolitis in England: a population-based birth cohort study. PLoS One 2014;9(2). DOI: 10.1371/JOURNAL.PONE.0089186.
121. Hervás D, Reina J, Yañez A, et al. Epidemiology of hospitalization for acute bronchiolitis in children: differences between RSV and non-RSV bronchiolitis. Eur J Clin Microbiol Infect Dis 2012;31(8):1975–1981. DOI: 10.1007/S10096-011-1529-Y
122. O'Brien KL, Baggett HC, Brooks WA, et al. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet 2019;394(10200):757–779. DOI: 10.1016/S0140-6736(19)30721-4.
123. Glezen WP, Taber LH, Frank AL, et al. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986;140(6):543–546. DOI: 10.1001/ARCHPEDI.1986.02140200053026.
124. Hall CB, Long CE, Schnabel KC. Respiratory syncytial virus infections in previously healthy working adults. Clin Infect Dis 2001;33(6):792–796. DOI: 10.1086/322657.
125. Rady MY, Johnson DJ, Patel B, et al. Extrapulmonary manifestations of severe respiratory syncytial virus infection – a systematic review. Crit Care 2006;10(4):R107. DOI: 10.1186/CC4984.
126. Hanna S, Tibby SM, Durward A, et al. Incidence of hyponatraemia and hyponatraemic seizures in severe respiratory syncytial virus bronchiolitis. Acta Paediatr 2003;92(4):430–434. DOI: 10.1111/J.1651-2227.2003.TB00573.X.
127. van Steensel-Moll HA, Hazelzet JA, van der Voort E, et al. Excessive secretion of antidiuretic hormone in infections with respiratory

syncytial virus. Arch Dis Child 1990;65(11):1237–1239. DOI: 10.1136/ADC.65.11.1237.
128. Berry CE, Billheimer D, Jenkins IC, et al. A Distinct low lung function trajectory from childhood to the fourth decade of life. Am J Respir Crit Care Med 2016;194(5):607–612. DOI: 10.1164/RCCM.201604-0753OC.
129. Overview: Bronchiolitis in children: diagnosis and management. Guidance NICE.
130. Ginocchio CC, McAdam AJ. Current best practices for respiratory virus testing. J Clin Microbiol 2011;49(9 Suppl):S44. DOI: 10.1128/JCM.00698-11.
131. Deming DJ, Patel N, McCarthy MP, et al. Potential for palivizumab interference with commercially available antibody-antigen based respiratory syncytial virus diagnostic assays. Pediatr Infect Dis J 2013;32(10):1144–1146. DOI: 10.1097/INF.0B013E31829561DD.
132. Chartrand C, Tremblay N, Renaud C, et al. Diagnostic Accuracy of Rapid Antigen Detection Tests for Respiratory Syncytial Virus Infection: Systematic Review and Meta-analysis. J Clin Microbiol 2015;53(12):3738–3749. DOI: 10.1128/JCM.01816-15.
133. Somerville LK, Mala Ratnamohan V, Dwyer DE, et al. Molecular diagnosis of respiratory viruses. Pathology 2015;47(3):243. DOI: 10.1097/PAT.0000000000000240.
134. Puppe W, Weigl JAI, Aron G, et al. Evaluation of a multiplex reverse transcriptase PCR ELISA for the detection of nine respiratory tract pathogens. J Clin Virol 2004;30(2):165–174. DOI: 10.1016/j.jcv.2003.10.003.
135. Vos LM, Bruning AHL, Reitsma JB, et al. Rapid molecular tests for influenza, respiratory syncytial virus, and other respiratory viruses: a systematic review of diagnostic accuracy and clinical impact studies. Clin Infect Dis 2019;69(7):1243–1253. DOI: 10.1093/CID/CIZ056.
136. Miller JM, Binnicker MJ, Campbell S, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis 2018;67(6):e1–e94. DOI: 10.1093/CID/CIY381.
137. Allen KE, Chommanard C, Haynes AKet al. Respiratory syncytial virus testing capabilities and practices among National Respiratory and Enteric Virus Surveillance System Laboratories, United States, 2016. J Clin Virol 2018;107:48–51. DOI: 10.1016/J.JCV.2018.08.009.
138. Jorquera PA, Tripp RA. Respiratory syncytial virus: prospects for new and emerging therapeutics. Expert Rev Respir Med 2017;11(8):609–615. DOI: 10.1080/17476348.2017.1338567.
139. Kodama F, Nace DA, Jump RLP. Respiratory syncytial virus and other noninfluenza respiratory viruses in older adults. Infect Dis Clin North Am 2017;31(4):767–790. DOI: 10.1016/J.IDC.2017.07.006.
140. Ventre K, Randolph A. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. Cochrane Database Syst Rev 2004;(4). DOI: 10.1002/14651858.CD000181.PUB2.
141. Ottolini MG, Hemming VG. Prevention and treatment recommendations for respiratory syncytial virus infection. Background and clinical experience 40 years after discovery. Drugs 1997;54(6):867–884. DOI: 10.2165/00003495-199754060-00006.
142. Shah JN, Chemaly RF. Management of RSV infections in adult recipients of hematopoietic stem cell transplantation. Blood 2011;117(10):2755–2763. DOI: 10.1182/BLOOD-2010-08-263400.
143. Hirsch HH, Martino R, Ward KN, et al. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. Clin Infect Dis 2013;56(2):258–266. DOI: 10.1093/CID/CIS844.
144. Krilov LR. Safety issues related to the administration of ribavirin. Pediatr Infect Dis J 2002;21(5):479–481. DOI: 10.1097/00006454-200205000-00037.
145. Manuel O, Estabrook M. RNA respiratory viral infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33(9). DOI: 10.1111/CTR.13511.
146. Roberts SS, Miller RK, Jones JK, et al. The Ribavirin Pregnancy Registry: Findings after 5 years of enrollment, 2003–2009. Birth Defects Res A Clin Mol Teratol 2010;88(7):551–559. DOI: 10.1002/BDRA.20682.
147. OSHA Technical Manual (OTM) – Section VI: Chapter 1: Occupational Safety and Health Administration. Accessed January 15, 2023.
148. Hall CB, McBride JT, Walsh EE, et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. A randomized double-blind study. N Engl J Med 1983;308(24):1443–1447. DOI: 10.1056/NEJM198306163082403.
149. Rodriguez WJ, Kim HW, Brandt CD, et al. Aerosolized ribavirin in the treatment of patients with respiratory syncytial virus disease. Pediatr Infect Dis J 1987;6(2):159–163. DOI: 10.1097/00006454-198702000-00004.
150. Smith DW, Frankel LR, Mathers LH, et al. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. N Engl J Med 1991;325(1):24–29. DOI: 10.1056/NEJM199107043250105.
151. Taber LH, Knight V, Gilbert BE, et al. Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants. Pediatrics 1983;72(5):613–618.
152. Meert KL, Sarnaik AP, Gelmini MJ, et al. Aerosolized ribavirin in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease: a prospective, double-blind, randomized trial. Crit Care Med 1994;22(4):566–572. DOI: 10.1097/00003246-199404000-00010.
153. Moler FW, Steinhart CM, Ohmit SE, et al. Effectiveness of ribavirin in otherwise well infants with respiratory syncytial virus-associated respiratory failure. Pediatric Critical Study Group. J Pediatr 1996;128(3):422–428. DOI: 10.1016/S0022-3476(96)70294-9.
154. Guerguerian AM, Gauthier M, Lebel MH, et al. Ribavirin in ventilated respiratory syncytial virus bronchiolitis. A randomized, placebo-controlled trial. Am J Respir Crit Care Med 1999;160(3):829–834. DOI: 10.1164/AJRCCM.160.3.9810013.
155. American Academy of Pediatrics. Respiratory Syncytial Virus. In: Red Book: 2021–2024 Report of the Committee on Infectious Diseases. 32nd ed. (Kimberlin DW BELRSM, ed.). American Academy of Pediatrics; 2021.
156. Huang K, Wu H. Prevention of respiratory syncytial virus infection: from vaccine to antibody. Microbiol Spectr 2014;2(4). DOI: 10.1128/MICROBIOLSPEC.AID-0014-2014.
157. Johnson S, Oliver C, Prince GA, et al. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. J Infect Dis 1997;176(5):1215–1224. DOI: 10.1086/514115.
158. Sáez-Llorens X, Moreno MT, Ramilo O, et al. Safety and pharmacokinetics of palivizumab therapy in children hospitalized with respiratory syncytial virus infection. Pediatr Infect Dis J 2004;23(8):707–712. DOI: 10.1097/01.INF.0000133165.85909.08.
159. Alansari K, Toaimah FH, Almatar DH, et al. Monoclonal antibody treatment of rsv bronchiolitis in young infants: a randomized trial. Pediatrics 2019;143(3). DOI: 10.1542/PEDS.2018-2308.
160. Beaird OE, Freifeld A, Ison MG, et al. Current practices for treatment of respiratory syncytial virus and other non-influenza respiratory viruses in high-risk patient populations: a survey of institutions in the Midwestern Respiratory Virus Collaborative. Transpl Infect Dis 2016;18(2):210–215. DOI: 10.1111/TID.12510.
161. Andabaka T, Nickerson JW, Rojas-Reyes MX, et al. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Cochrane Database Syst Rev 2013;2013(4). DOI: 10.1002/14651858.CD006602.PUB4.
162. Connor E. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. The PREVENT Study Group. Pediatrics 1997;99(1):93–99. DOI: 10.1542/PEDS.99.1.93.

163. Hemming VG, Rodriguez W, Kim HW, et al. Intravenous immunoglobulin treatment of respiratory syncytial virus infections in infants and young children. Antimicrob Agents Chemother 1987; 31(12):1882–1886. DOI: 10.1128/AAC.31.12.1882.
164. Ruckwardt TJ, Morabito KM, Graham BS. Determinants of early life immune responses to RSV infection. Curr Opin Virol 2016;16:151–157. DOI: 10.1016/J.COVIRO.2016.01.003.
165. Griffin MP, Yuan Y, Takas T, et al. Single-dose Nirsevimab for prevention of RSV in preterm infants. N Engl J Med 2020;383(5):415–425. DOI: 10.1056/NEJMOA1913556.
166. Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for Prevention of RSV in healthy late-preterm and term infants. N Engl J Med 2022;386(9): 837–846. DOI: 10.1056/NEJMOA2110275.
167. FDA Approves New Drug to Prevent RSV in Babies and Toddlers/FDA. Accessed on: 31 August 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-prevent-rsv-babies-and-toddlers.
168. Dixon DL. The role of human milk immunomodulators in protecting against viral bronchiolitis and development of chronic wheezing illness. Children (Basel) 2015;2(3):289–304. DOI: 10.3390/CHILDREN2030289.
169. Isolation Precautions: Guidelines Library. Infection Control. CDC. Accessed January 15, 2023.
170. Guide to Infection Prevention for Outpatient Settings: Minimum Expectations for Safe Care. HAI CDC. Accessed January 15, 2023.
171. Hertz MI, Englund JA, Snover D, et al. Respiratory syncytial virus-induced acute lung injury in adult patients with bone marrow transplants: a clinical approach and review of the literature. Medicine 1989;68(5):269–281. DOI: 10.1097/00005792-198909000-00002.
172. Krasinski K, LaCouture R, Holzman RS, et al. Screening for respiratory syncytial virus and assignment to a cohort at admission to reduce nosocomial transmission. J Pediatr 1990;116(6):894–898. DOI: 10.1016/S0022-3476(05)80646-8.
173. Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health-care--associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep 2004;53(RR-3):1–36.
174. NIH Celebrates FDA Approval of RSV Vaccine for People 60 Years of Age and Older NIH: National Institute of Allergy and Infectious Diseases. Accessed August 5, 2023.
175. FDA Approves First Respiratory Syncytial Virus (RSV) Vaccine. FDA. Accessed August 5, 2023.
176. Mazur NI, Higgins D, Nunes MC, et al. The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates. Lancet Infect Dis 2018;18(10):e295-e311. DOI: 10.1016/S1473-3099(18)30292-5.
177. Karron RA, Wright PF, Belshe RB, et al. Identification of a recombinant live attenuated respiratory syncytial virus vaccine candidate that is highly attenuated in infants. J Infect Dis 2005;191(7):1093–1104. DOI: 10.1086/427813.
178. Karron RA, Luongo C, Thumar B, et al. A gene deletion that up-regulates viral gene expression yields an attenuated RSV vaccine with improved antibody responses in children. Sci Transl Med 2015;7(312). DOI:10.1126/SCITRANSLMED.AAC8463.
179. Karron RA, Luongo C, Mateo JS, et al. Safety and Immunogenicity of the Respiratory Syncytial Virus Vaccine RSV/ΔNS2/Δ1313/I1314L in RSV-Seronegative Children. J Infect Dis 2020;222(1): 82–91. DOI:10.1093/INFDIS/JIZ408.
180. Cicconi P, Jones C, Sarkar E, et al. First-in-Human Randomized Study to Assess the Safety and Immunogenicity of an Investigational Respiratory Syncytial Virus (RSV) Vaccine Based on Chimpanzee-Adenovirus-155 Viral Vector-Expressing RSV Fusion, Nucleocapsid, and Antitermination Viral Proteins in Healthy Adults. Clin Infect Dis 2020;70(10):2073–2081. DOI: 10.1093/CID/CIZ653.
181. Madhi SA, Polack FP, Piedra PA, et al. Respiratory Syncytial virus vaccination during pregnancy and effects in infants. N Engl J Med 2020;383(5):426–439. DOI: 10.1056/NEJMOA1908380.
182. Crank MC, Ruckwardt TJ, Chen M, et al. A proof of concept for structure-based vaccine design targeting RSV in humans. Science 2019;365(6452):505–509. DOI: 10.1126/SCIENCE.AAV9033.
183. Polack FP, Teng MN, Collins PL, et al. A role for immune complexes in enhanced respiratory syncytial virus disease. J Exp Med 2002;196(6):859–865. DOI: 10.1084/JEM.20020781.
184. Graham BS, Henderson GS, Tang YW, et al. Priming immunization determines T helper cytokine mRNA expression patterns in lungs of mice challenged with respiratory syncytial virus. J Immunol 1993;151(4):2032–2040.

REVIEW ARTICLE

Digital Stethoscope Use in Neonates: A Systematic Review

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Abstract

Aim: To assess the evidence for the use of digital stethoscopes in neonates and evaluate whether they are effective, appropriate, and advantageous for neonatal auscultation.

Methods: A systematic review and narrative synthesis of studies published between January 1, 1990 and May 29, 2023 was conducted following searches of MEDLINE, Embase, PubMed, Scopus, and Google Scholar databases, as well as trial registries.

Results: Of 3,852 records identified, a total of 41 papers were eligible and included in the narrative synthesis. Thirteen records were non-full-text articles, either in the form of journal letters or conference abstracts, and these were included separately for completion purposes but may be unreliable. Twenty eight papers were full-text articles and were included in a full qualitative analysis. Digital stethoscopes have been studied in neonatology across various clinical areas, including 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 paper discusses the potential utility of digital stethoscope technology for the interpretation of neonatal sounds for both humans and artificial intelligence. The limitations of current devices are also assessed.

Conclusions: The utilization of digital stethoscopes in neonatology is an emerging field with a wide range of potential applications, which has the capacity to advance neonatal auscultation. Artificial intelligence and digital stethoscope technology offer novel objective avenues for automatic pathological sound detection. Further, digital stethoscopes may improve our scientific understanding of normal neonatal physiology and can be employed in telemedicine to facilitate remote medical access. Digital stethoscopes can also provide phonocardiograms, enabling enhanced interpretation of neonatal cardiac sounds. However, current digital stethoscopes necessitate refinement as they consistently produce low-quality sounds when used on neonates.

Keywords: Artificial Intelligence, Auscultation, Computer-assisted auscultation, Infant, Machine learning, Murmur detection, Newborn, Phonocardiography, Respiratory distress, Telemedicine.

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Introduction

The stethoscope has been a crucial component of patient examination since its invention in 1816 by French physician, Laennec.[1] Over the past 200 years, it has undergone significant transformations and upgrades, with the standard device used by clinicians today being the dual-sided acoustic stethoscope.[1–3] However, there are several drawbacks of the acoustic stethoscope: interpretation is subjective and dependent on clinician expertise and hearing ability.[4–8] Furthermore, in neonates, even infant-sized acoustic stethoscopes can be unreliable and produce poor-quality sounds due to neonatal factors such as their small size, fast heart and respiratory rates, irregular breathing patterns, and noise interference (e.g., crying and respiratory support noise).[9–13] This can hinder accurate clinician analysis and may lead to delayed diagnosis and management of neonatal conditions (Fig. 1).

Technological advancements have led to the development of a digital (or electronic) stethoscope (DS), which offers solutions to the limitations seen in acoustic stethoscopes. Digital stethoscopes can amplify sounds, filter out unnecessary noises, and separate desired sounds. This improves sound focus and reduces reliance on hearing ability.[14,15] They also allow for the recording, playback, and sharing of sounds with other doctors for secondary opinions.[1,14,15] Furthermore, the integration of artificial intelligence (AI) into DS technology enables a more objective interpretation of auscultatory sounds.[16] For example, Eko Health's AI mobile application connects to DSs via Bluetooth, providing AI features such as heart rate estimation and murmur analysis (88% sensitivity and specificity for murmur detection).[17,18]

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Commercially available DSs designed for children and adults exist, but there is currently no specific DS designed for neonates.[19–24] A systematic review by Ramanathan et al. in 2018 concluded that further research was required to determine the advantages and disadvantages of current DSs for use in pediatrics.[25] Since then, several studies have assessed DSs exclusively in neonates, yet the suitability of DSs for use in this population remains uncertain. This systematic review aimed to evaluate the current evidence on DS use in neonates. Specifically, we assessed their utility, suitability, and limitations in neonatal areas such as the cardiovascular, respiratory, and gastrointestinal systems. Additionally, this review investigated the integration of DSs with AI for neonatal care.

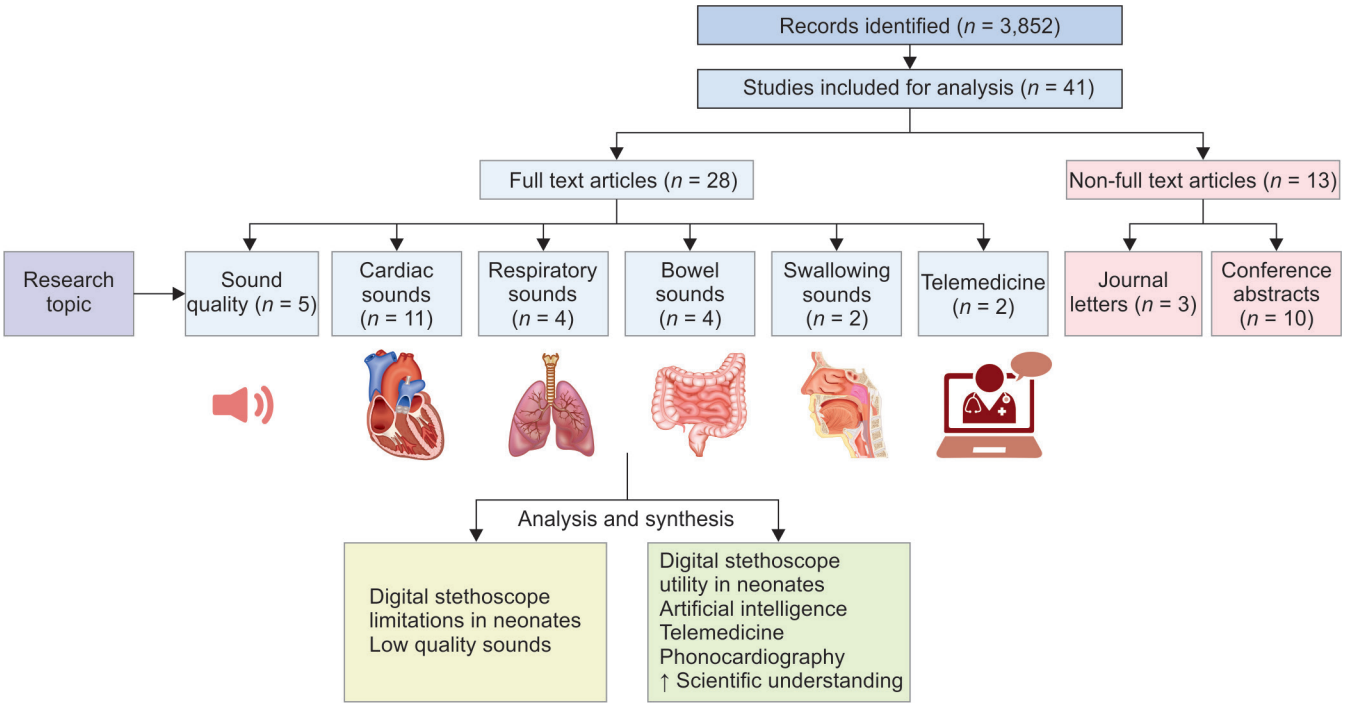

Fig. 1: Graphical abstract
Created with BioRender.com

Methods

A systematic review was performed to assess the utility of DSs in neonates. Digital stethoscopes were defined as any device that can record internal sounds via skin contact.

Inclusion criteria consisted of (1) involved neonates, (2) DS involvement, and (3) human studies. Exclusion criteria included (1) no subgroup analysis of neonatal population in studies with broader age range, (2) no DS involvement, (3) animal studies, (4) review articles or systematic reviews, and (5) non-English-accessible papers.

The databases searched included MEDLINE, Embase, PubMed, Scopus, and Google Scholar. Gray literature was searched for on clinical trial registries (WHO ICTRP, Clinicaltrials.gov, ANZCTR) and conference papers on Google Scholar. Relevant articles underwent backward and forward citation searching. The latest search was conducted on 29/05/2023.

The search strategy is provided in Table 1 of Supplementary File. MeSH, keywords, Boolean operators, synonyms, and truncations were used. The search was limited to English language articles published from January 1st, 1990 to present (DSs first discussed in 1990s).

Papers identified were uploaded onto the Covidence Systematic Review Software, which was used for screening and reviewing full-text papers for inclusion by two independent reviewers (MR and OS).[26] Duplicates were automatically removed, and conflicts were resolved by a third reviewer (AM).

Papers meeting inclusion criteria were included in a narrative synthesis. A narrative synthesis was deemed to be the most suitable approach to comprehensively synthesize findings due to the absence of randomized controlled trials and heterogeneity of studies, making a meta-analysis inappropriate. One author (MR) collected and synthesized the data, and two authors (AM and FM) reviewed it. Information sought from papers included: author, year, aim, number of participants, participant characteristics, DS device used, and main findings. Studies were categorized into six groups based on their study focus: AI for sound quality assessment and chest sound separation, cardiac sounds, respiratory sounds, bowel sounds, swallowing sounds, and telemedicine.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist for this systematic review is provided in Table 2 of Supplementary File.[27]

Results

A total of 3,852 records were identified through the search strategy, 41 records fulfilled the inclusion criteria. Figure 2 illustrates the PRISMA flow diagram for the systematic review.[27]

Twenty-eight full-text papers on DSs in neonates were identified, focusing on six clinical domains: AI for sound quality assessment and chest sound separation ($n = 5$), cardiac sounds ($n = 11$), respiratory sounds ($n = 4$), bowel sounds ($n = 4$), swallowing sounds ($n = 2$), and DS use in telemedicine ($n = 2$). Studies utilized DS devices originally designed for different age groups: adults ($n = 11$), children ($n = 8$), neonatal bowel sounds ($n = 1$), and unspecified ($n = 8$). Table 1 presents the full-text papers, and the evidence regarding DS use in the neonatal domains is discussed below.

Thirteen non-full-text papers, including journal letters ($n = 3$) and conference abstracts ($n = 10$), were identified. However, these papers may be unreliable due to incomplete reporting, publication bias, and some results may be preliminary findings. See Table 3 in Supplementary File for the non-full-text records.

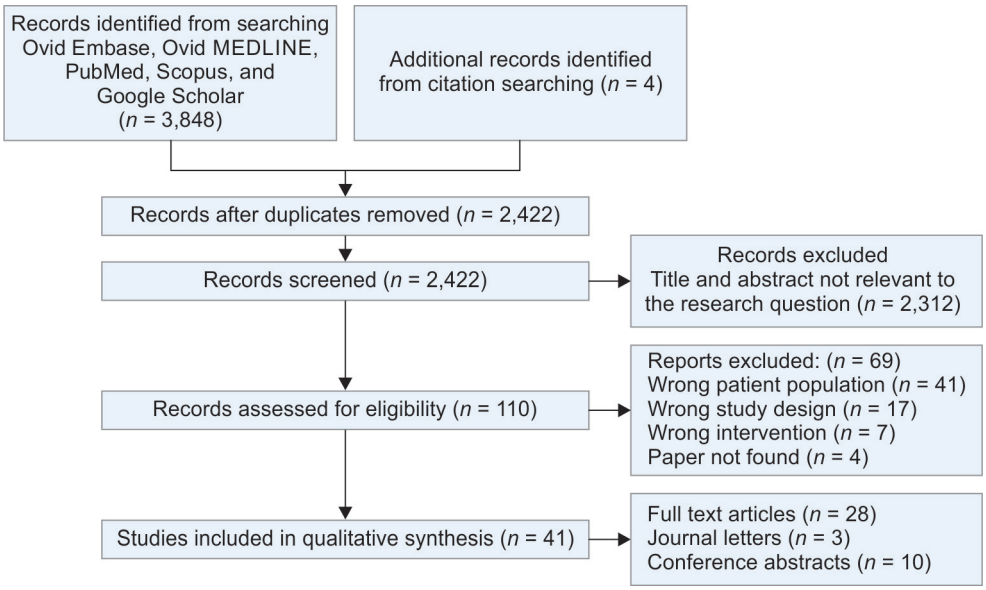

Fig. 2: PRISMA flow diagram for the systematic review of digital stethoscopes use in neonates. Adapted from the "The PRISMA 2020 statement: An updated guideline for reporting systematic reviews"[27]

Table 1: Full-text published studies on digital stethoscope use in neonates

Author (year)	*Principal aim*	*Participant characteristics*	*Device used*	*Main findings*
AI for sound quality assessment and chest sound separation				
Grooby et al. (2021)[9]	Heart and lung sound quality assessment	Preterm/term neonates (2–48 hours old) *n* = 76	CliniCloud DS	The algorithm differentiated between high- and low-quality heart and lung sounds. Improved signal quality correlated with improved vital sign estimation.
Grooby et al. (2021)[28]	NMCF chest sound separation	Preterm/term neonates (2–48 hours old) *n* = 60	CliniCloud DS	NMCF algorithm outperformed existing methods in separating chest sounds.
Grooby et al. (2022)[10]	Real-time, multilevel heart and lung sound quality assessment	Preterm/term neonates (2–48 hours old) *n* = 119	CliniCloud DS	The method achieved real-time quality assessment of heart and lung sounds on a scale of 1–5.
Fattahi et al. (2022)[11]	SCBSS chest sound separation	Preterm/term neonates (24–48 hours old) *n* = 91	CliniCloud DS	SCBSS produced better-quality recordings and more accurate vital sign estimation compared with seven existing chest sound separation methods.
Grooby et al. (2023)[12]	NMCF and NMF chest sound separation	Extremely preterm-to-term neonates (2 hours–60 days old) *n* = 213	CliniCloud DS	NMCF and NMF systems outperformed the best existing methods in separating chest sounds.
Cardiac sounds				
Yang and Zeng (2010)[29]	PCG to evaluate cardiac reserve	Preterm/term neonates (unspecified age) *n* = 385	PCG sensor	PCG cardiac indicators were higher in term neonates than preterm neonates, correlating with increased cardiac reserve.

(Contd...)

Table 1: *(Contd....)*

Author (year)	*Principal aim*	*Participant characteristics*	*Device used*	*Main findings*
Balogh and Kovács (2011)[30]	AI neonatal PCG PDA closure classification	Preterm neonates (average age of 6 days) *n* = 25	Self-made DS (electret microphone capsule)	Characteristic heart sound calculation method showed favorable results for the identification of PDAs.
Sung et al. (2013)[31]	Temporal correlogram method to analyze PDA murmur before and after transcatheter closure	PDA neonates (unspecified age) *n* = 2	3M Littmann 3200 DS	Cochlear spectrogram and temporal correlogram show distinct differences in neonatal heart sounds following PDA transcatheter closure.
Amiri et al. (2017)[32]	AI neonatal PCG murmur classification	Neonates with/without heart murmurs (1–20 days old) *n* = 116	DS (unspecified)	Classified PCG heart recordings as normal or pathological with an AUC of 0.98.
Shelevytska and Mavropulo (2018)[33]	PCG analysis of hemodynamic disorders in preterm neonates	Preterm NICU neonates with/without PDA (median day 5 of life) *n* = 45	ThinkLabs ds32a	Differences observed in computer analyzed PCG recordings between hemodynamically stable and unstable preterm neonates.
Grgic-Mustafic et al. (2019)[34]	AI neonatal PCG murmur classification	NICU neonates, both preterm and term, with or without heart murmurs (1–5 days old) *n* = 36	3M Littmann 3200 DS	Developed PCG classification demonstrated higher sensitivity and comparable specificity to pediatrician auscultation in distinguishing between normal and pathological heart sounds.
Bobillo-Perez et al. (2021)[35]	Comparison of devices for HR estimation at birth	Healthy-term newborns (at birth) *n* = 50	3M Littmann 3200 DS	Ultrasound detected HR fastest, followed by DS, ECG, and pulse oximetry.
Gómez-Quintana et al. (2021)[36]	AI neonatal PCG segmentation	Healthy, PDA, and CHD neonates (0–6 days old) *n* = 265	ThinkLabs ds32a and ThinkLabs One DS	Developed PCG segmentation method outperformed previously designed adult-based version.
Gómez-Quintana et al. (2021)[37]	AI neonatal PCG PDA detection	Healthy, PDA and CHD neonates (0–6 days old) *n* = 265	ThinkLabs ds32a and ThinkLabs One DS	Developed method reached an AUC of 77% and 78% for the detection of PDA and CHD, respectively, outperforming human listeners.
Takahashi et al. (2021)[38]	Piezoelectric sensor vs. electronic stethoscope in neonatal heart murmur detection	Neonates with/without systolic heart murmurs caused by CHD (1–26 days old) *n* = 18	3M Littmann 3200 DS and self-made piezoelectric sensor	Piezoelectric sensor performed marginally lower than the DS in detecting systolic murmurs.
Amiri et al. (2022)[39]	AI neonatal PCG heart disease classification	Neonates with/without heart murmurs (1–20 days old) *n* = 120	DS (unspecified)	Detected heart disease with 96.15% sensitivity and 91.67% specificity.
Respiratory sounds				
Blowes et al. (1995)[40]	Neonatal lung sound interpretation with and without added dead space	Term neonates (12 hours–6 days old) *n* = 16	Small piezoelectric accelerometer	Added dead space increased lung sound intensity but had no uniform influence on lung sound frequency.

Ramanathan et al. (2020)[41]	Lung sound changes in transitioning newborns	Term neonates (at 1 minute and 2 hours of life) $n = 61$	CliniCloud DS	Lung sound frequencies decreased over the first 2 hours of life; neonates who developed RD had higher frequencies at birth.
Zhou et al. (2020)[42]	Lung sound characteristics in preterm and term neonates	Preterm/term neonates without respiratory support (24–48 hours old) $n = 52$	CliniCloud DS	Preterm and term newborns had different lung sound features.
Grooby et al. (2022)[43]	AI to predict the development of RD at birth before symptom onset	Term neonates, 9 later developed RD (at 1 minute of life, clinical condition tracked for the first few hours) $n = 51$	CliniCloud DS	Algorithm predicted neonatal RD with a 66.7% sensitivity and 85% specificity in combined chest recordings.
Bowel sounds				
Song et al. (2021)[44]	AI bowel sound detection and classification	NICU neonates (unspecified age) $n = 113$	BoSS (microelectronic stethoscope)	Classified bowel sounds into short (91% sensitivity, 71% specificity) and long bursts (97% sensitivity, 72% specificity).
Sitaula et al. (2022)[45]	AI bowel sound detection	NICU neonates (unspecified age) $n = 49$	3M Littmann 3200 DS	Identified bowel sounds with an AUC 83.96%, outperforming the next-best method by 3%.
Burne et al. (2022)[46]	AI bowel sound detection	NICU neonates (unspecified age) $n = 49$	3M Littmann 3200 DS	Identified bowel sounds with an AUC 85.6%.
Zhou et al. (2022)[47]	Feasibility of long continuous bowel sound recordings and AI analysis	Stable term neonates with/without mild–moderate hyperbilirubinemia (4.51 ± 5.34 days old) $n = 82$	MEMS sensor	Recordings made for 20 hours. AI analysis measured five bowel sound characteristics that were unaffected by hyperbilirubinemia but influenced by intake of mother's breast milk.
Swallowing sounds				
Da Nobrega et al. (2004)[48]	Assessing swallowing pattern for feeding maturation in newborns	Preterm neonates (37.8 ± 1.5 weeks postmenstrual age) $n = 23$	Small microphone	Swallowing time and bursts increased during transition from tube bottle feeding to bottle feeding.
Ince et al. (2014)[49]	Assessing feeding maturation in newborns	Preterm/term neonates (regular follow-up until 40 weeks postmenstrual age) $n = 94$	ThinkLabs ds32a	Volume of milk ingested and number of rhymical swallows increased with gestational age.
Telemedicine				
Garingo et al. (2012)[50]	NICU robotic telemedicine compared with in-person consults	Preterm/term NICU neonates (3–112 days old) $n = 46$	DS (unspecified)	NICU telemedicine is feasible. Disagreements between in-person acoustic stethoscope and telemedicine DS interpretation.
Umoren et al. (2020)[51]	Feasibility of in-hospital telemedicine for infection control	NICU neonates in strict isolation due to infection (unspecified age) $n = 3$	3M Littmann 3200 DS	Threefold reduction in potential exposures between neonates and healthcare workers using in-hospital telemedicine.

AI, artificial intelligence; AUC, area under curve; BoSS, bowel sounds sensor; CHD, congenital heart disease; DS, digital stethoscope; ECG, electrocardiogram; HR, heart rate; MEMS sensor, microelectromechanical system sensor; NICU, neonatal intensive care unit; NMCF, non-negative matrix co-factorization; NMF, non-negative matrix factorization; PDA, patent ductus arteriosus; PCG, phonocardiogram; RD, respiratory distress; RR, respiratory rate; SCBSS, single-channel blind source separation

AI for Sound Quality Assessment and Chest Sound Separation

Robust AI sound analysis software requires reliable algorithms trained on large datasets, with high-quality data that correspond with future input requirements.[52,53] Five papers in this review focused on developing AI methods to enhance overall sound quality and improve the accuracy of future AI classification systems.[9–12,28]

Two papers developed algorithms to distinguish between low- and high-quality recordings.[9,10] High-quality recordings yielded significantly more accurate estimations of heart and breathing rates compared with low-quality recordings.[9] In their 2021 software, Grooby et al. achieved 82% accuracy (69% sensitivity and 86% specificity) in differentiating low- and high-quality lung sounds and 93% accuracy (81% sensitivity and 86% specificity) for heart sounds.[9] Furthermore, Grooby et al.'s 2022 paper introduced multilevel and real-time quality features.[10] Incorporating this software into DS technology could provide real-time quality assessment during auscultation, eliminating the need for retrospective analysis of recordings. However, further refinement is necessary as the algorithm's accuracy was relatively low, possibly due to annotator disagreement when scoring recordings on a scale of 1–5 rather than categorizing them as low- or high-quality.[10]

Auscultation in newborns is challenging for both humans and AI due to the presence of a mixture of different sounds (e.g., cardiac, respiratory, gastrointestinal, crying, and environment noises). Three papers developed chest sound separation programs to isolate cardiac, respiratory, and other sounds.[11,12,28] These papers examined three sound separation methods: non-negative matrix co-factorization, non-negative matrix factorization, and single-channel blind source separation. Using the aforementioned sound quality assessment tools, they evaluated the quality of cardiac and respiratory sounds after separation and all three papers demonstrated improved signal quality compared with previous approaches.[11,12,28] However, complete separation of chest sounds remained challenging, particularly in neonates on respiratory support. This was due to overlapping frequencies between sounds of interest and the impurity of training mixtures.[11,12,28] Using higher-quality recordings for software training could potentially address this issue.[11,12,28]

These algorithms improve the overall quality, focus, and clarity of DS-recorded neonatal sounds.[9–12,28] This software can be integrated into DS technology to enhance human interpretation and the accuracy of future AI programs.

Cardiac Sounds

Eight cardiac studies utilized the phonocardiogram (PCG) component of DS technology to analyze neonatal heart sounds, revealing additional features beyond auscultation alone. Phonocardiograms can enhance neonatal heart sound interpretation by detecting decreased cardiac reserve, hemodynamic disorders, and with the assistance of AI, heart sounds can be segmented, and murmurs automatically detected.[29,30,32–34,37,39]

Artificial intelligence murmur detection programs can indicate the presence of neonatal murmurs and classify them as either innocent or pathological.[30,32,34,37,39] Additionally, specific PCG features have been identified for murmurs related to patent ductus arteriosus, leading to the development of AI detection program specifically for this common neonatal condition.[30,37] Eventually, this software could be widely used to screen newborns for the early detection of cardiac murmurs. However, software refinement is needed due to limitations in accuracy arising from small datasets and low-quality recordings.[30,32,34,36,37,39]

Respiratory Sounds

Digital stethoscope recorded breath sound analysis reveals differences in lung sound characteristics between preterm and term newborns.[42] Power spectra analysis demonstrates that term newborns exhibit higher power in the middle- and high-frequency range, while preterm newborns have higher power in the very-high-frequency range.[42] These differences may be attributed to the smaller size and underdeveloped lungs of preterm newborns. Further research is needed to explore the clinical implications of these findings, including their potential impact on AI detection methods.[42]

During the newborn transition period, DS technology observes a decrease in lung sound frequency over the first 2 hours of life.[41] Newborns who develop respiratory distress (RD) show higher frequencies from birth, suggesting a correlation with decreased fluid clearance.[41] Grooby et al. developed an AI program based on these findings to predict RD at birth before symptom onset.[43] When combining anterior and posterior recordings and utilizing both heart and lung sounds, the program achieved an overall accuracy of 81.8% (66.7% sensitivity and 85% specificity) for predicting RD, thus demonstrating the potential of DS AI for early detection and management of neonatal conditions.[43]

However, these studies are limited by low-quality recordings and small datasets.

Bowel Sounds

AI models, including Hidden Semi-Markov and Convolutional Neural Network models, have been used to detect and locate neonatal bowel sounds (including peristalsis) in DS recordings that contain mixtures of sounds.[45,46] These studies detected bowel sounds with an area under the curve of 83.96% and 85.6%, respectively, outperforming previous AI methods. The detection and localization of bowel sounds may improve clinician interpretation and the accuracy of AI-based bowel sound characterization and classification methods.[45,46]

Artificial intelligence has enabled the successful extraction of bowel sound characteristics, providing additional parameters beyond what can be measured with an acoustic stethoscope.[44,47] However, further research is necessary to determine the clinical significance of these characteristics in normal and pathological neonatal bowel activity before these programs can be utilized in a clinical setting.[44,47]

Overall, integrating bowel sound detection and characterization methods into future classification models holds promise in enhancing the timely diagnosis of neonatal bowel conditions. Nonetheless, these studies are limited by low-quality recordings, which may impact AI accuracy.[44–47]

Swallowing Sounds

Feeding difficulties in premature neonates pose challenges in timing the advancement of feeding methods.[48,49] Digital stethoscope studies indicate that feeding maturation is associated with increased swallowing features, which correlate with gestational age.[48,49] Accordingly, DS technology can assess swallowing sounds and guide feeding strategies for neonates experiencing swallowing difficulties.

Telemedicine

Digital stethoscopes in neonatal telemedicine have been studied for infection control within neonatal intensive care units.[50,51] Garingo et al. observed the differences between telemedicine DS and in-person acoustic stethoscope findings, as well as variations in the results among multiple neonatologists using the acoustic stethoscope on the same newborn.[50] This suggests observer interpretation variability rather than DS error, and raises the concern of stethoscope interpretation subjectivity that can affect clinical decision-making.[4,50] Additionally, neonatal intensive care unit telemedicine can reduce infection exposure by threefold, aiding in infection control and minimizing the use of personal protective equipment in resource-limited settings.[51]

Neonatal telemedicine should be explored further and may also facilitate remote access in areas with pediatric specialist shortages and promote collaboration between specialists.[50,51]

Discussion

Digital stethoscopes show promise in enhancing the analysis of neonatal cardiac, respiratory, and gastrointestinal sounds. A key advantage lies in the integration of AI within DS technology, enabling the improved acquisition of clear neonatal sounds and the automatic detection, characterization, and classification of neonatal sounds.[9–12,28,30,32,34,36,37,39,43–47] This surpasses the capabilities of traditional acoustic stethoscopes and eliminates listener subjectivity. In the reviewed studies, DS AI was used to improve sound quality, isolate sounds of interest, estimate vital signs, segment PCG heart sounds, and detect indicators of pathological conditions (e.g., murmurs, RD).[9–12,28,30,32,34,36,37,39,43–47] These findings lay the groundwork for a plethora of possible AI tools and opportunities that could be developed to further advance automatic neonatal sound analysis. Such advancements have the potential to improve the timeliness of diagnosis and management for various neonatal medical conditions. Digital stethoscopes offer other benefits, including their application in neonatal telemedicine for infection control, their potential to enhance our scientific understanding of neonatal physiology, and the utilization of PCGs to capture additional cardiac features.[29,30,32–34,36,37,39,41,42,48–51]

Several limitations in the literature impacted the accuracy and reliability of findings, thereby hindering the clinical application of DSs in neonates. Major limitations included small sample sizes, findings with an unclear clinical relevance, and low-quality recordings. Small sample sizes have limited the reliability and generalizability of results. Furthermore, the clinical utility of these findings is hindered by a knowledge gap concerning the correlation between sound characteristics and different neonatal conditions, as well as factors such as gestational age, postnatal age, and size. Bridging these gaps through novel studies is required to facilitate the translation of these findings into clinical practice and to advance AI classification programs. Additionally, a consistent issue identified throughout the reviewed articles was the production of low-quality DS sounds, which reduced human and AI sound interpretation accuracy. This was a particular issue in AI-focused studies; low-quality sounds were either used to train AI algorithms, reducing overall data quality, or they were removed, reducing data quantity. Both options decreased the accuracy of the developed AI methods, thereby reducing program reliability.

Low-quality DS sounds raise concerns about the suitability of current DSs for neonatal use, as they may not adequately account for neonatal factors, and this can be detrimental to accurate clinician and AI analysis. It is worth noting that many devices used in the reviewed studies were devices originally designed for children ($n = 8$), adults ($n = 11$), or unspecified $n = 8$), rather than specifically for neonates.[9–12,28–43,45–51] While sound quality assessment and sound separation AI programs can help isolate high-quality sounds, they have limitations and do not address the issue of having low-quality sounds in the first place.[9–12,28] Alternatively, a DS specifically designed for neonates could be a viable solution to improve the device's capacity in producing high-quality neonatal sounds. Ultimately, a device capable of capturing high-quality neonatal sounds has the potential to enhance clinician interpretation and AI accuracy and capability for the improved diagnosis and management of neonatal medical conditions.

Regarding the limitations of this systematic review, although efforts were made to ensure a comprehensive search strategy, it is possible that not every relevant paper was identified, introducing potential selection bias. Additionally, the included studies exhibited heterogeneity, making it challenging to draw definitive conclusions regarding the suitability of DSs in neonates. Finally, the non-full-text articles in supplementary file may be lower quality and subject to publication and reporting bias.

Conclusions

Digital stethoscopes show promise in improving neonatal cardiovascular, respiratory, and gastrointestinal auscultation. The integration of DS technology with AI may facilitate the early diagnosis and management of neonatal conditions. However, current DS devices do not appear to be appropriate for neonates due to the production of low-quality sounds.

Supplementary Materials

All the Supplementary Tables are available online on the website of https://www.newbornjournal.org/.

References

1. Permin H, Norn S. Stethoscope – Over 200 years. J Pulmonol Respir Res 2019;3:001–008. DOI: 10.29328/journal.jprr.1001010.
2. Harbison J. 'The old guessing tube': 200 years of the stethoscope. QJM: An Int J Med 2017;110(1):9–10. DOI: 10.1093/qjmed/hcw108.
3. 3M Littmann. 3M Littmann Classic II Infant Stethoscope [cited 2023 March 28]. Available from: https://www.littmann.com.au/3M/en_AU/littmann-stethoscopes-au/products/~/3M-Littmann-Classic-II-Infant-Stethoscope/?N=5932256+8711017+3290700351+3294857444&rt=rud.
4. Hafke-Dys H, Bręborowicz A, Kleka P, et al. The accuracy of lung auscultation in the practice of physicians and medical students. PLoS One 2019;14(8):e0220606. DOI: 10.1371/journal.pone.0220606.
5. Bank I, Vliegen HW, Bruschke AV. The 200th anniversary of the stethoscope: Can this low-tech device survive in the high-tech 21st century? Eur Heart J 2016;37(47):3536–3543. DOI: 10.1093/eurheartj/ehw034.
6. Richardson TR, Moody JM. Bedside cardiac examination: Constancy in a sea of change. Curr Probl Cardiol 2000;25(11):783–825. DOI: 10.1067/mcd.2000.109835.
7. Zun LS, Downey L. The effect of noise in the emergency department. Acad Emerg Med 2005;12(7):663–666. DOI: 10.1197/j.aem.2005.03.533.
8. Arts L, Lim EHT, van de Ven PM, et al. The diagnostic accuracy of lung auscultation in adult patients with acute pulmonary pathologies: A meta-analysis. Sci Rep 2020;10(1):7347. DOI: 10.1038/s41598-020-64405-6.
9. Grooby E, He J, Kiewsky J, et al. Neonatal heart and lung sound quality assessment for robust heart and breathing rate estimation

for telehealth applications. IEEE J Biomed Health Inform 2021;25(12): 4255–4266. DOI: 10.1109/JBHI.2020.3047602.
10. Grooby E, Sitaula C, Fattahi D, et al. Real-time multi-level neonatal heart and lung sound quality assessment for telehealth applications. IEEE Access 2022;10:10934–10948. DOI: 10.1109/ACCESS.2022.3144355.
11. Fattahi D, Sameni R, Grooby E, et al. A blind filtering framework for noisy neonatal chest sounds. IEEE Access 2022;10:50715–50727. DOI: 10.1109/ACCESS.2022.3170052.
12. Grooby E, Sitaula C, Fattahi D, et al. Noisy neonatal chest sound separation for high-quality heart and lung sounds. IEEE J Biomed Health Inform 2023;27(6):2635–2646. DOI: 10.1109/JBHI.2022.3215995.
13. Elphick HE, Lancaster GA, Solis A, et al. Validity and reliability of acoustic analysis of respiratory sounds in infants. Arch Dis Child 2004;89(11):1059–1063. DOI: 10.1136/adc.2003.046458.
14. Swarup S, Makaryus AN. Digital stethoscope: Technology update. Med Devices (Auckl) 2018;11:29–36. DOI: 10.2147/MDER.S135882.
15. Tavel ME. Cardiac auscultation: A glorious past--and it does have a future! Circulation 2006;113(9):1255–1259. DOI: 10.1161/CIRCULATIONAHA.105.591149.
16. Ghanayim T, Lupu L, Naveh S, et al. Artificial intelligence-based stethoscope for the diagnosis of aortic stenosis. Am J Med 2022;135(9):1124–1133. DOI: 10.1016/j.amjmed.2022.04.032.
17. Eko Health Inc. Eko AI Validation White Paper; 2020 [cited 2023 March 29]. Available from: https://uploads-ssl.webflow.com/5fca50c07c4b1314fe246a86/6247c228d81d9f7823c752c1_Eko%20AI%20White%20Paper%20-%20LBL105B.pdf.
18. Eko Health Inc. Eko App [cited 2023 March 29]. Available from: https://www.ekohealth.com/pages/smart-stethoscope-app.
19. 3M Littmann. 3M Littmann CORE Digital Stethoscope [cited 2023 March 29]. Available from: https://www.littmann.com/3M/en_US/littmann-stethoscopes/advantages/core-digital-stethoscope/.
20. 3M Littmann. 3M Littmann Electronic Stethoscope Model 3200 [cited 2023 March 29]. Available from: https://www.littmann.com.au/3M/en_AU/littmann-stethoscopes-au/products/~/3M-Littmann-Electronic-Stethoscope-Model-3200/?N=5142935+8711017+3290263838+3294857444&preselect=5002684+3293786499&rt=rud.
21. Design and Industry. CliniCloud Digital Stethoscope [cited 2023 March 29]. Available from: https://www.design-industry.com.au/clinicloud.
22. Eko Health Inc. Eko DUO ECG + Digital Stethoscope [cited 2023 March 29]. Available from: https://www.ekohealth.com/products/duo-ecg-digital-stethoscope?variant=39350415655008.
23. Eko Health Inc. Eko CORE Digital Attachment [cited 2023 March 29]. Available from: https://www.ekohealth.com/products/core-digital-attachment?variant=32764121251936.
24. Thinklabs. Thinklabs One Digital Stethoscope [cited 2023 March 29]. Available from: https://www.thinklabs.com/.
25. Ramanathan A, Zhou L, Marzbanrad F, et al. Digital stethoscopes in paediatric medicine. Acta Paediatr 2019;108(5):814–822. DOI: 10.1111/apa.14686.
26. Covidence Systematic Review Software. Veritas Health Innovation, Melbourne, Australia. Available from: www.covidence.org.
27. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. DOI: 10.1136/bmj.n71.
28. Grooby E, He J, Fattahi D, et al. A new non-negative matrix co-factorisation approach for noisy neonatal chest sound separation. Annu Int Conf IEEE Eng Med Biol Soc 2021:5668–5673. DOI: 10.1109/EMBC46164.2021.9630256.
29. Yang X, Zeng W. A relative value method for measuring and evaluating neonatal cardiac reserve. Indian J Pediatr 2010;77(6):661–664. DOI: 10.1007/s12098-010-0058-5.
30. Balogh ÁTK, Kovács F. Application of phonocardiography on preterm infants with patent ductus arteriosus. Biomed Sign Process Control 2011;6(4):337–345. DOI: 10.1016/j.bspc.2011.05.009.
31. Sung P-H, Wang J-N, Chen B-W, et al. Auditory-inspired heart sound temporal analysis for patent ductus arteriosus. In: 2013 1st International Conference on Orange Technologies (ICOT) 2013. pp. 231–234.
32. Amiri AM, Abtahi M, Constant N, et al. Mobile phonocardiogram diagnosis in newborns using support vector machine. Healthcare (Basel) 2017;5(1):16. DOI: 10.3390/healthcare5010016.
33. Shelevytska VA, Mavropulo TK. Computer-aided auscultation of hemodynamic disorders in preterm neonates. S WorldJournal 2018:22–27. DOI: 10.30888/2663-5712.2020-06-02-052.
34. Grgic-Mustafic R, Baik-Schneditz N, Schwaberger B, et al. Novel algorithm to screen for heart murmurs using computer-aided auscultation in neonates: A prospective single center pilot observational study. Minerva Pediatr 2019;71(3):221–228. DOI: 10.23736/S0026-4946.18.04974-5.
35. Bobillo-Perez S, Balaguer M, Jordan I, et al. Delivery room ultrasound study to assess heart rate in newborns: DELIROUS study. Eur J Pediatr 2021;180(3):783–790. DOI: 10.1007/s00431-020-03776-4.
36. Gomez-Quintana S, Shelevytsky I, Shelevytska V, et al. Automatic segmentation for neonatal phonocardiogram. Annu Int Conf IEEE Eng Med Biol Soc 2021:135–138. DOI: 10.1109/EMBC46164.2021.9630574.
37. Gómez-Quintana S, Schwarz CE, Shelevytsky I, et al. A Framework for AI-assisted detection of patent ductus arteriosus from neonatal phonocardiogram. Healthcare (Basel) 2021;9(2):169. DOI: 10.3390/healthcare9020169.
38. Takahashi K, Ono K, Arai H, et al. Detection of pathologic heart murmurs using a piezoelectric sensor. Sensors (Basel) 2021;21(4):1376. DOI: 10.3390/s21041376.
39. Amiri A, Armano G, Ghasemi S. Neonatal heart disease screening using an ensemble of decision trees. Int J Biomed Eng Technol 2022;39(2):107–130. DOI: 10.1504/IJBET.2022.124014.
40. Blowes RW, Yiallouros P, Milner AD. Lung sounds in neonates with and without an added dead space. Pediatr Pulmonol 1995;19(6):348–354. DOI: 10.1002/ppul.1950190607.
41. Ramanathan A, Marzbanrad F, Tan K, et al. Assessment of breath sounds at birth using digital stethoscope technology. Eur J Pediatr 2020;179(5):781–789. DOI: 10.1007/s00431-019-03565-8.
42. Zhou L, Marzbanrad F, Ramanathan A, et al. Acoustic analysis of neonatal breath sounds using digital stethoscope technology. Pediatr Pulmonol 2020;55(3):624–630. DOI: 10.1002/ppul.24633.
43. Grooby E, Sitaula C, Tan K, et al. Prediction of neonatal respiratory distress in term babies at birth from digital stethoscope recorded chest sounds. Annu Int Conf IEEE Eng Med Biol Soc 2022;2022:4996–4999. DOI: 10.1109/EMBC48229.2022.9871449.
44. Song I, Huang Y, Koh THHG, et al. Pervasive monitoring of gastro-intestinal health of newborn babies. In: Pham DN, Theeramunkong T, Governatori G, eds. PRICAI 2021: Trends in Artificial Intelligence. Springer, Cham; 2021, vol. 13031. pp. 359–369.
45. Sitaula C, He J, Priyadarshi A, et al. Neonatal bowel sound detection using convolutional neural network and laplace hidden semi-Markov model. IEEE/ACM Trans Audio, Speech, Lang Process 2022;30:1853–1864. DOI: 10.1109/TASLP.2022.3178225.
46. Burne L, Sitaula C, Priyadarshi A, et al. Ensemble approach on deep and handcrafted features for neonatal bowel sound detection. IEEE J Biomed Health Inform 2022;27(6):2603–2613. DOI: 10.1109/JBHI.2022.3217559.
47. Zhou P, Lu M, Chen P, et al. Feasibility and basic acoustic characteristics of intelligent long-term bowel sound analysis in term neonates. Front Pediatr 2022;10:1000395. DOI: 10.3389/fped.2022.1000395.
48. Da Nobrega L, Boiron M, Henrot A, et al. Acoustic study of swallowing behaviour in premature infants during tube-bottle feeding and bottle feeding period. Early Hum Dev 2004;78(1):53–60. DOI: 10.1016/j.earlhumdev.2004.03.008.
49. Ince DA, Ecevit A, Acar BO, et al. Noninvasive evaluation of swallowing sound is an effective way of diagnosing feeding maturation in newborn infants. Acta Paediatr 2014;103(8):e340–e348. DOI: 10.1111/apa.12686.
50. Garingo A, Friedlich P, Tesoriero L, et al. The use of mobile robotic telemedicine technology in the neonatal intensive care unit. J Perinatol 2012;32(1):55–63. DOI: 10.1038/jp.2011.72.

51. Umoren RA, Gray MM, Handley S, et al. In-hospital telehealth supports care for neonatal patients in strict isolation. Am J Perinatol 2020;37(8):857–860. DOI: 10.1055/s-0040-1709687.
52. Stowell D. Computational bioacoustics with deep learning: A review and roadmap. PeerJ 2022;10:e13152. DOI: 10.7717/peerj.13152.
53. Xu Y, Liu X, Cao X, et al. Artificial intelligence: A powerful paradigm for scientific research. Innovation (Camb) 2021;2(4):100179. DOI: 10.1016/j.xinn.2021.100179.