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newborn

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In association with The Mozib Center for Neonatal Care
And The Carlo GNS Center for Saving Lives at Birth

And

GNS Down Syndrome Foundation 42
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Newborn Foundation of Azerbaijan
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The organization, Protecting Brains and Saving Futures, Brasil
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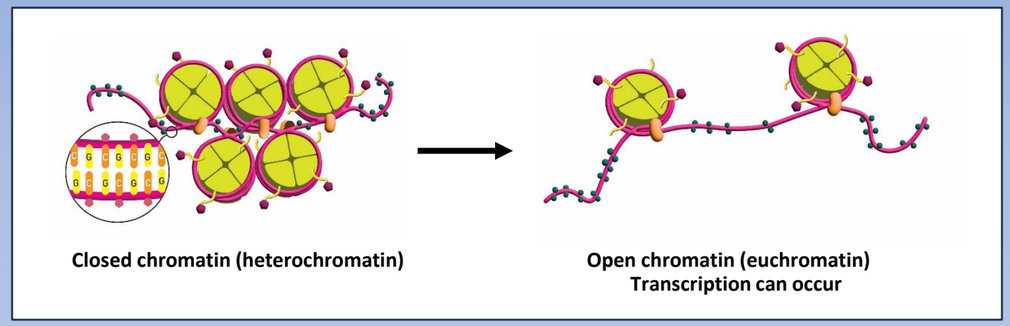
Friends Aid Africa, Bukedea, Uganda
Society of Bacteriophage Research and Therapy
GNS Center for Computational Scientific Methodology
GNS International Association of Neonatal POCUS
SABREE Enrichment Academy: Empowering Ability

Highlighted articles:



Epigenetic Regulation of Macrophage Polarization

Peri-operative Care of Infants after Surgical Correction of Congenital Heart Defects
Neonatal Small Colon Syndrome in an infant of a diabetic mother requiring early surgery: Is it always a transient condition?
Evaluation of Neonatal Infections in the Neonatal Intensive Care Unit over a 10-year period

Also available online at
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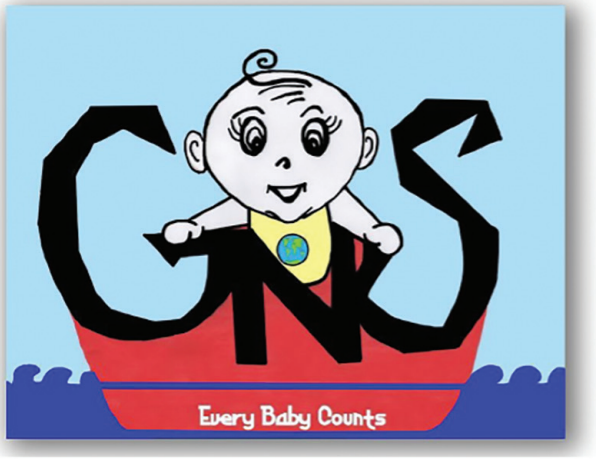

Global Newborn Society

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 eyelashes, 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, worldwide 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 cast 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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Contents

EDITORIAL 10.5005/newborn-4-1-iv

Are We Ready to View Artificial Intelligence Not as a Threat but as Supplementary and/or Supplemental Intelligence?

In 2025, the United Nations Educational, Scientific and Cultural Organization (UNESCO) dedicated January 24th, the International Day of Education, to celebrate artificial intelligence (AI).[1–3] In medicine, AI is still under evaluation until the possibilities of a negative impact on patient care can be confidently excluded; fears persist that biases and errors in clinical data could result in suboptimal algorithms with increased healthcare disparities, breaches in privacy of patient data, and decreased transparency in decision-making.[4–16] In the bigger picture, there are concerns that AI could lead to a partial/panoramic attrition in original thinking, creativity, ingenuity, and innovation.[16–19]

This issue needs serious thought. The use of electronic tools to augment functional efficiency is not entirely new—all of us have been using online search engines to polish/expand our ideas now for many years. Most of us have searched for synonyms, antonyms, sentence constructs, historical context, online articles, and blogs with opinions.[20] And does this ethical dilemma of "artificially" enhancing efficiency/productivity[21] not remind of the times when automobiles began to replace horse-carts? When typewriters replaced human calligraphers? Calculators for elementary mathematics? Basic computers for calculators? Using artistic fonts with these computers to replace calligraphers? Computing with databases has altered the life of chartered accountants. In medicine, electronic medical records have changed our way of storing details of a patient's medical history and hospital events.[22] This list could go on.

There are definitely some concerns. But AI has the potential to revolutionize many aspects of life—there can be a quantal impact on efficiency that would make it difficult to ignore it completely.[23] And all things considered, its advent and rapid progression in many areas of medicine so far is making it look unstoppable (**Fig. 1**).[24,25] Hence, we need to think—should we continue to consider it as "artificial", which has a negative connotation,[26] or accept it and call it "supplementary", or additional intelligence that augments human functionality.[27] In certain areas, it might even deserve further recognition to be called "supplemental", to acknowledge that many of these software programs can independently add to the efficiency of cognitive tasks.[28] We will definitely need to get together to evaluate AI for its merits and deficiencies for different tasks—no one solution will fit all.[29] In medicine, there are enormous possibilities in complex/high-volume data analysis, repetitive tasks, decision-making, personalized tailored therapy, and simulating human-like interaction.[30] It might also be useful in quality control and improvement; service automation, generation of creative content for personalized family education, monitoring of environmental factors by bringing in multisource expertise, and in development of accessible technology for infants with disabilities.[31–38] In research, the possibilities are even stronger, be it as one of the tools for literature search, for preliminary study design prior to expert review, additional training of personnel, and in integration of data—from *in vitro* studies of gene regulation to protein interaction to pathway analysis in neural networks or other methods, to evaluation/enhancement or even as an alternative to animal models, to development of chemical modulators/"drugs", and to human safety/efficacy studies.[39–47] There could be more.

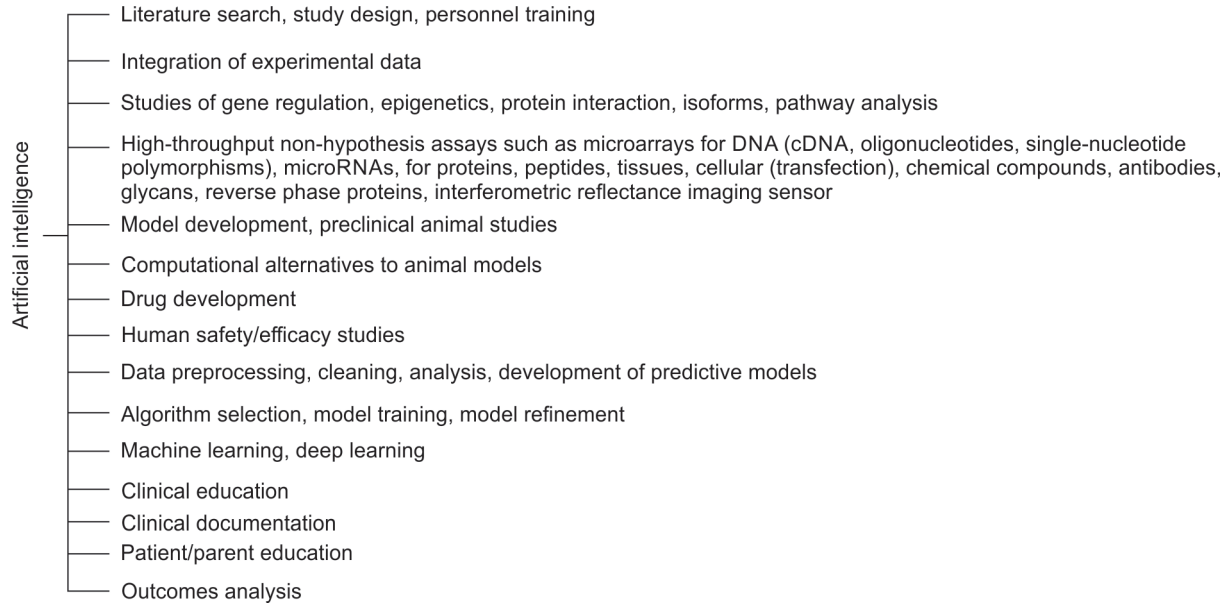

Fig. 1: Artificial intelligence is transforming medicine. When we look at the areas of impact in research and clinical medicine, the question is not about the likely areas of growth, but is more to identify the areas that would not benefit from correct application. Maybe we would be better off in getting involved to set priorities and prevent misuse. The cart is already in motion.

Moving from this line of discussion, we once again remind our readers and ourselves that the Global Newborn Society (GNS) aims to be a worldwide social movement for improving neonatal care. Recent commitments of financial support from the Mozib Center for Neonatal Care (Bangladesh) and the Carlo GNS Center for Saving Lives at Birth (USA) have added momentum. Since the last issue, 10 newly formed or existing organizations have joined the efforts; these include the Global Newborn Society Iran Chapter; National Federation of Neonatologists of Mexico; College of Neonatologists of the State of Jalisco, Mexico; The Skylar Project; American Society for Black Lives; Friends Aid Africa, Bukedea, Uganda; Society for Bacteriophage Research and Therapy; the GNS Center for Computational Scientific Methodology; the GNS International Association of Neonatal POCUS; and the SABREE Enrichment Academy: Empowering Ability. We are excited about the all the possibilities emerging in underserved geographic areas and populations, our understanding of the biological modifiers of bacterial pathogens, and novel monitoring systems of critically-ill/extremely premature infants. We have unfortunately lost the company of one organization, the GNS Cardiology Association of Iraq, because of their changed needs. Currently, our group is comprised of the GNS and 47 other organizations. We consult each other and share scientific data, viewpoints, and our experiences relevant for care of newborn infants in various parts of the world.

In each issue of this journal, our editorial team highlights the achievements of one of our partnering members. Here, we recollect the efforts of the neonatology team at the Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, to develop a human milk bank (HMB) compliant with Islamic religious practices **(Fig. 2)**.[48,49] There are more than 500 large HMBs in the world but only a few are functioning in Muslim countries.[50] Islamic laws do not allow infants to receive human milk from multiple unidentified donors.[51] To comply with these guidelines, milk from each donor has to be processed and stored separately, and can be provided to an infant only after counseling both the donor and recipient families about Islamic laws of prohibition of future marriages between milk siblings.[52] All relevant records need to be maintained for future reference. After extensive review of the proposals by the country's health services and Islamic foundations and community debates,[53] this HMB was developed with allocation of appropriate hospital space, investment in necessary equipment, and extensive training of personnel. The facility was finally inaugurated in December 2019.[54]

Our team would like to express our sincere gratitude to Professor Dr Robert D Christensen,[55,56] who is retiring from active academics after many decades of service. His contributions to neonatal hematology and large-cohort clinical research are known the world over. All of us hope and believe that he will resume his scholarly activities after a brief period of much-deserved rest. He has promised that he will remain available for guidance and solutions based on his experience. We need him.

This journal aims to cover fetal/neonatal problems that begin during pregnancy, at the time of birth, or during the first 1,000 days after birth.[57] As in our previous issues, we present 8 articles here **(Fig. 3)**. Hoyos et al.[58] have presented a new set of guidelines for adequate nutrition to promote growth for premature neonates. Although optimal postnatal growth should ideally replicate intrauterine rates, most premature infants lose weight for the first few days before resuming slow weight gains that are usually below intrauterine rates.[59] This extrauterine growth restriction (EUGR) can be seen at the time of discharge with lower weight Z-score medians than those

Figs 2A to F. Development of a human milk bank in Bangladesh. (A and B) The Special Care Neonatal Unit and Neonatal Intensive Care Unit at the Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, are respected for having saved countless newborn lives in the region; (C) In Islam, there are many important restrictions on sharing milk from one lactating mother between multiple infants. Considering the life-saving importance of human milk feeds, the Institute of Child Health at the BSMMU established a core medical group to discuss the possibilities for developing a socially accepted, religiously compliant human milk bank; (D and E) These potential solutions were reviewed by the National Health Services and Islamic Foundations, first together and then in smaller groups for in-depth discussions; (F) After much effort by medical and social leaders, a human milk bank was inaugurated in December 2019.

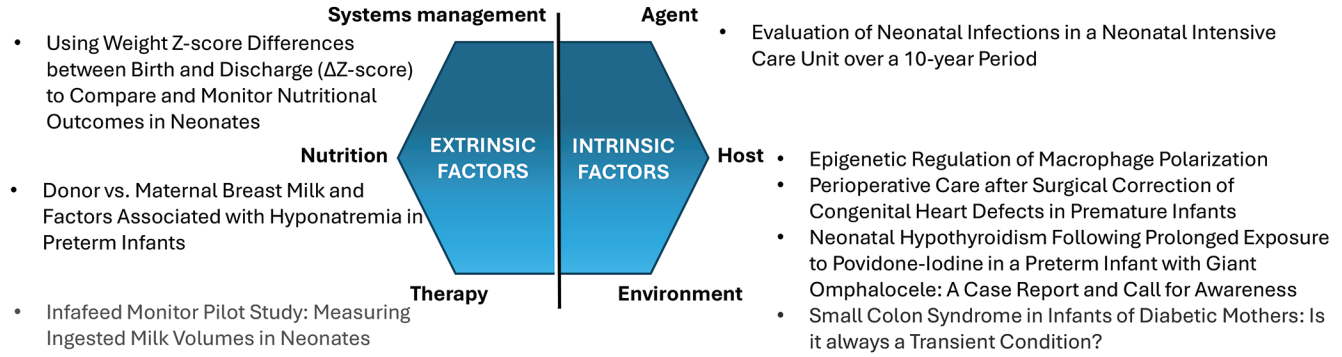

Fig. 3: Areas of focus in the *newborn*, Volume 4, Issue 1. We have expanded the traditional agent-host-environment trinodal disease model to a hexagonal system. The three additional foci represent extrinsic factors that can affect health—those originating in therapy, nutrition, and systems management are shown. This issue covers 5 nodes, with articles focused on agents, host factors, therapy/monitoring systems, nutrition, and systems management.

at birth.[60–62] The authors hypothesized that improved nutrition could reduce the incidence of EUGR in convalescing premature infants. They reviewed the clinical information of 480 infants born at ≤32 weeks' gestational age in EpicLatino units in the past 8 years. Even though the sample size was not large enough to establish causality, the authors noted that nutrition was not effective as the sole intervention. The risk of EUGR was higher in infants with higher severity of illness.

Bacterial infections are a leading cause of morbidity and mortality in premature and critically ill neonates.[63] In another quality-improvement (QI) study, Shah et al.[64] reviewed the spectrum of bacterial infections in their neonatal intensive care unit over a 10-year period. They identified 151 culture-positive bacterial sepsis events in 125 infants. The spectrum of bacterial isolates largely remained similar during the study period. Early-onset sepsis (EOS) was caused most frequently by *Escherichia coli* (*E. coli*) and group B *Streptococcus*, whereas the leading causes of late-onset sepsis (LOS) were coagulase-negative *Staphylococcus* (CoNS) and methicillin-sensitive *Staphylococcus aureus*. There was a trend for increasing *Klebsiella* isolates since 2015. Overall, there was no significant shift in organisms causing neonatal infections in this hospital during the last decade. This study is an important template; these bacterial isolates need to be monitored in all centers, all over the world.

Gomez Pomar et al.[65] compared the clinical profile of premature infants who developed hyponatremia, defined as plasma sodium (Na) <135 mEq/L, during their clinical course. Existing studies have suggested that infants who receive donor human milk may be at higher risk of having low serum Na levels.[66,67] In this cohort, 60 infants were noted to have developed hyponatremia at some point, including 32 who received supplemental Na and 28 who did not. These were compared with 29 controls. Contrary to assumptions, most infants with hyponatremia received more mothers' own, not donor, milk. They might have had a higher severity of illness. Sodium chloride supplementation did not always correct serum Na levels or improve the growth parameters at discharge. Further studies are needed.

Boyd et al.[68] have studied the technical feasibility of a novel noninvasive prototype instrument for measuring ingested milk volumes in 24 neonates. A monitor recorded feeding sounds via a microphone placed on the infant's neck, and a secondary microphone captured background noise for cancellation. This modality could help in serial monitoring of milk intake in breast-fed infants without disrupting the natural nursing process because test-weighing during the feeding session is not necessary. Power spectral density analysis[69] was performed to differentiate swallow and non-swallow events, and a linear regression model[70] was then used to estimate feed volumes based on 20 recordings. More studies are needed in larger cohorts.

Al-Ethawi et al.[71] reviewed existing information on factors that might affect outcomes of premature infants with congenital heart defects following corrective surgical interventions. Many pathophysiological changes related to surgery-related tissue disruption and cardiopulmonary bypass include Na/water overload, systemic inflammatory response syndrome (SIRS), and ischemia/reperfusion in the heart and other major organs are seen during this period.[72] Focused intensive care is needed with close monitoring of cardiac function, tissue oxygenation, hemostasis, pain control, and sedation.[73] There are also some center-specific needs; all care-providers need to reach a consensus on evidence-based protocols for initiation, maintenance, and weaning from assisted ventilation, which can facilitate earlier extubation and prevent ventilation-related complications.[74,75] Finally, a clearly defined discharge protocol can enhance safety.[76]

Singh and Maheshwari[77] have reviewed the presence and mechanisms of innate immune memory of prior stimuli in macrophages in infants. This memory is rooted in epigenetic regulation of lineage- and tissue-specific transcription that may enhance/suppress immune responses to repeated exposures to a stimulus.[78,79] In this article, they have specifically focused on lineage-determining changes such as those in the erythroblast transformation-specific gene purine-rich sequence binding protein 1 (PU.1) and histone methylation, and have also outlined the role of several other newly discovered regulators.[80–82] These changes promote macrophage differentiation into several phenotypes essential for host defense or tissue homeostasis in response to environmental stimuli.[83] Maladaptive changes in macrophages can disrupt the normal sequence of immune/inflammatory responses and predispose to disease states.[84]

Raghavendra et al.[85] have described a 36-week-gestation infant of a diabetic mother with an unusually severe and persistent neonatal small colon syndrome (NSCS).[86] She manifested signs of intestinal obstruction at about 6 hours after birth and a contrast enema showed a small caliber distal small intestine and colon. There was no clinical improvement over the next 2 weeks and so an exploratory laparotomy was performed after much discussion. Intra-operatively, the surgeons noted viscous meconium with pellets in

the involved bowel and later histopathological examination showed normal bowel histoarchitecture with an appropriate morphology/number of ganglion cells.[87] A double barrel enterostomy was created and the distal gastrointestinal tract was regularly flushed. She then showed good improvement and was discharged home. The authors want to remind that NSCS may not always show prompt, spontaneous resolution and should be considered in the differential diagnosis of a newborn infant with unusually prolonged signs of intestinal obstruction.[88] Some of these infants may require surgical management with ostomy formation.[89]

Finally, Ben Ayad et al.[90] call for caution about the risk of secondary hypothyroidism in infants with large omphaloceles who are managed conservatively with topical iodine on polymeric carriers. There are two well-accepted strategies for management of giant omphaloceles (GOs): (a) surgical closure after initial stabilization;[91] or (b) a more conservative "paint and wait" strategy without graft closure.[92] In this second protocol, the sac is maintained with topical medications such as silver sulfadiazine or combinations of polyvinylpyrrolidone (povidone), iodine, and, sometimes, with added topical antibiotics. This repeated exposure to iodine is usually tolerated well[93] but there is a need for cautious monitoring as some infants have been noted to develop thyroid dysfunction.[94] The authors present one such case; the goal is to sensitize the medical care-providers to these adverse effects.

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ORIGINAL RESEARCH

Using Weight Z-score Differences between Birth and Discharge to Compare and Monitor Nutritional Outcomes in Neonatal Units: Variables Associated with Poor Growth

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Abstract

Introduction: There is a need for clear guidelines to support adequate nutrition and growth for premature neonates. Unfortunately, we do not have a consensus on the ideal parameters and timing for assessment of growth in these infants. Even though optimal postnatal growth should ideally replicate intrauterine rates, after the initial physiological normal drop, many premature infants follow gains below intrauterine rates. This extrauterine growth restriction (EUGR) can be quantified as lower weight Z-score medians at discharge than those at birth, indicated by a negative difference between birth and discharge (Δ Z-score) below 1 SD. We hypothesized that improved nutrition could reduce the incidence of EUGR in convalescing premature infants.

Materials and methods: We reviewed the clinical information from all EpicLatino units in the past 8 years (2015–2022); all infants who were born at ≤32 weeks' gestational age (GA) and discharged home at ≥34 weeks' corrected age were included. Statistical comparisons were performed to analyze growth parameters and potential causes of poor nutrition. The weight Δ Z-score from birth to discharge was used as a surrogate for adequacy of nutrition. Birth weight medians and interquartile ranges were correlated with weight Δ Z-score, GA, and head circumference (HC) at discharge.

Results: We reviewed 480 cases that met the established criteria. Gestational age at birth, necrotizing enterocolitis, unit of origin, rupture of membranes >24 hours, temperature at admission, and intraventricular hemorrhage were significantly different. There was a negative correlation between the Δ Z-score and corrected GA at discharge. Head circumference at discharge also correlated with weight Δ Z-score.

Conclusion: The frequency of EUGR varied between units. There were some clinical associations, but our sample size was not large enough to establish causality. The risk of EUGR may increase with severity of illness or could be higher in some specific populations. Quality improvement programs to optimize nutrition policies and practices may help.

Keywords: Difference between birth and discharge (Δ Z-score), EpicLatino neonatal database, Extrauterine growth restriction, Head circumference at discharge, Latin America, Newborns, Risk factors for poor growth.

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Key Points

- Some premature infants, after the initial drop in weight after birth considered physiological, may follow a resumption at levels below those seen *in utero*. The drop in weight Z-score medians from birth to discharge (computed as negative Δ Z-scores) if it drops below 1 SD is sometime called extrauterine growth restriction (EUGR).
- We noted that the incidence of EUGR at discharge differed between different units of origin and correlated with various other clinical variables.
- A review of nutrition policies and practices suggests that focused quality improvement programs could possibly reduce EUGR in our organization.
- Discussions with colleagues all over the world suggest that this is a global issue, and there is a need for larger, well-designed randomized studies to clarify this problem.

Introduction

There is a need for clear guidelines to support adequate nutrition and growth for premature neonates. Even though optimal postnatal

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Table 1: Units belonging to the EpicLatino network

Units	*City/Country*
Centenario H. de Esp. Miguel Hidalgo	Aguascalientes, Mexico
Clínica Dávila	Santiago, Chile
Clínica de Santa María de Santiago	Santiago, Chile
Clínica del Country	Bogotá, Colombia
Clínica la Colina	Bogotá, Colombia
Clínica Materno Infantil San Luis	Bucaramanga, Colombia
Clínica San Felipe	Lima, Perú
Clínica Santa Bárbara	Quito, Ecuador
Clínica Somer	Rio Negro, Colombia
Clínica Universitaria Colombia	Bogotá, Colombia
Clínica Vespucio	Santiago, Chile
Colsanitas – Clínica Pediátrica UCI Neonatal	Bogotá, Colombia
Curaçao Medical Center	Willemstad, Curaçao
H Regional DR Rafael Pascacio Gamboa	Tuxtla Gutiérrez, México
Hospital Central Dr. Ignacio Morones Prieto	San Luis Potosí, México
Hospital Civil de Ipiales E.S.E	Ipiales, Colombia
Hospital de los Valles	Quito, Ecuador
Hospital Departamental San Vicente de Paul	Garzón, Huila, Colombia
Hospital Dr. Florencio Escardó	Tigre, Argentina
Hospital Español de Mendoza	Mendoza, Argentina
Hospital General EISS de Manta	Manta, Ecuador
Hospital Italiano de La Plata	La Plata, Argentina
Hospital Luis Lagomaggiore	Mendoza, Argentina
Hospital Metropolitano	Quito, Ecuador
Hospital Militar Central	Bogotá, Colombia
Hospital Regional Universitario de Colima	Colima, México
Hospital San Francisco de Quito	Quito, Ecuador
Hospital San José	Bogotá, Colombia
Hospital Santísima Trinidad	Asunción, Paraguay
Los Cobos Medical Center	Bogotá, Colombia
Maternidad Nuestra Sra. de las Mercedes	Tucumán, Argentina
S.E.S. Hospital de Caldas	Manizales, Colombia

growth should ideally replicate intrauterine rates, many premature infants show an initial drop in weight after birth (physiological) followed by gains below intrauterine rates.[1] In this article, we share our experience in EpicLatino, a network of 32 Neonatal Intensive Care Units (NICUs) in Latin America and the Caribbean islands (Table 1).[2] This EUGR can be quantified as lower weight Z-score medians at discharge than those at birth, indicated by a negative difference between birth and discharge (Δ Z-score) below 1 SD. For the past 9 years, we have been using the difference in weight Δ Z-score medians between birth and discharge to assess the nutritional outcomes.[1] With the normal postnatal contraction of the extracellular fluid compartment in the body, the difference between birth and discharge weights is often negative.[3–5]

After birth, preterm infants show a more pronounced initial drop in weight than their term counterparts; their weights can decrease by a 0.5–1 weight Z-score point on postnatal curves. Many clinicians have begun to accept growth patterns with a progressive gain in anthropometric parameters that are below intrauterine rates but are measurable, and the infant remains healthy and safe. Many recent studies have recognized this EUGR in preterm infants and have discussed possible steps to curtail these changes.[6] There is still no consensus about the best timing for assessment, the ideal growth monitoring tool(s), and therapeutic interventions. An ongoing debate persists even for the appropriate terminology to equate intrauterine and postnatal growth patterns. Consequently, we have not been able to accept uniform nutritional interventions. Early fortification of human milk soon after birth may promote gain in length but does not seem to increase fat-free mass accretion at 36 weeks' post-menstrual age; the head circumference (HC) may still show attrition.[7]

Extrauterine growth restriction can be defined in cross-sectional and longitudinal perspectives. Additionally, several growth charts are available to track postnatal growth, each yielding varying outcomes. According to a reviewed study, the prevalence of EUGR differs across growth charts.[8] The Italian neonatal study (INeS) reports 40.9%, Intergrowth-21 23.8%, and the Fenton shows 33.5%. When assessed longitudinally (defined as a loss of 1 SD), the rates were 20.4% for INeS, 4% for Intergrowth-21, and 15% for Fenton ($p < 0.001$). Cross-sectional EUGR, based on a discharge weight below the 10th percentile, showed similar variability: 22.8%, 28.2%, and 22.4%, respectively ($p = 0.27$).

Materials and Methods

We analyzed data from the past 8 years (2015–2022) in surviving homes to at least 34 weeks corrected age infants with ≤32 weeks gestational age (GA) at birth. To identify the variables that need to be controlled to measure the risk of poor nutrition unrelated to outdated or unvalidated unit policies, we conducted a series of statistical comparisons with variables that have been mentioned as potential causes of poor nutrition in the literature, if available in our database.[9,10] We used the weight Δ Z-score from birth to discharge as a surrogate for nutrition. The first risk variable is GA. We also included necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and the time (before/during-after 2020, pandemic). We added small for gestational age (SGA), temperature at admission, sex, presentation, inborn/outborn, oxygen at 36 weeks post-menstrual age, delivery type, antenatal corticosteroids, premature rupture of membranes (PROM) more than 24 hours, suspected chorioamnionitis, and the unit of origin. Only inborn surviving patients who were discharged home beyond 34 weeks corrected GA were included. We also obtained the weight Δ Z-score median and interquartile range (IQR) from all the EpicLatino units. We performed a nonparametric median logistic regression adjusted for the mentioned variables and included the different units of origin as well. We also calculated the correlation between weight Δ Z-score and GA and HC at discharge to see if change in weight z-score affects the GA at discharge or the HC also at discharge and calculated a regression analysis corrected by GA, unit of origin, and SGA. We used Stata 18, StataCorp LLC, Texas, USA.

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Results

There were 480 cases that met the established criteria. The statistical significance of the different variables used in the nonparametric median regression model is shown in Table 2. Gestational age at birth, NEC, unit of origin, PROM >24 hours, temperature at admission, and IVH were significant.

The box plot results from the different units of origin (median and IQR) are presented in Figure 1. There was a negative correlation between weight Δ Z-score and corrected GA at discharge of −0.38, $p < 0.0001$ (Fig. 2). The regression analysis of weight Δ Z-score versus GA at discharge was significant when adjusted by GA and unit of origin but not with SGA. Head circumference at discharge also correlated with weight Δ Z-score; Spearman's rho = −0.2657, $p < 0.001$ also adjusted by the same variables (Fig. 3).

Discussion

There was considerable variability in the different units of origin. Regarding risk factors, as shown in Table 2, GA, NEC, unit of origin, PROM, temperature at admission, and IVH were significant. When looking for risk factors, we confirmed that the characteristics of the study population are determinant to EUGR at discharge. The degree of longitudinal EUGR is influenced by the birth weight Z-score: the lower the birth weight centile, the lower the

Table 2: Variables, their impact (percent of normal), and the results of the nonparametric median logistic regression results

Variable	*% Normal or mean*	*p*
GA	29.6 ± 2.3 weeks	**<0.0000**
No NEC	93%	**<0.0000**
Unit of origin	32 units	**<0.0000**
No ROM >24 hours	87%	**0.0190**
Temperature at admission	36.0°C ± 1	**0.0350**
No IVH pathology	71%	**0.0350**
Sex M	55%	0.056
Presentation (cephalic)	71%	0.072
Inborn	89%	0.091
No oxygen at 36 weeks	79%	0.095
Vaginal delivery	22%	0.146
Receive antenatal corticosteroids	72%	0.218
AGA	89%	0.234
No suspected chorioamnionitis	91%	0.346
Period (before/after 2020)	45%	0.636

AGA, appropriate for gestational age; IVH, intraventricular hemorrhage; M, masculine; NEC, necrotizing enterocolitis; ROM, premature rupture of membranes. Statistically significant in bold

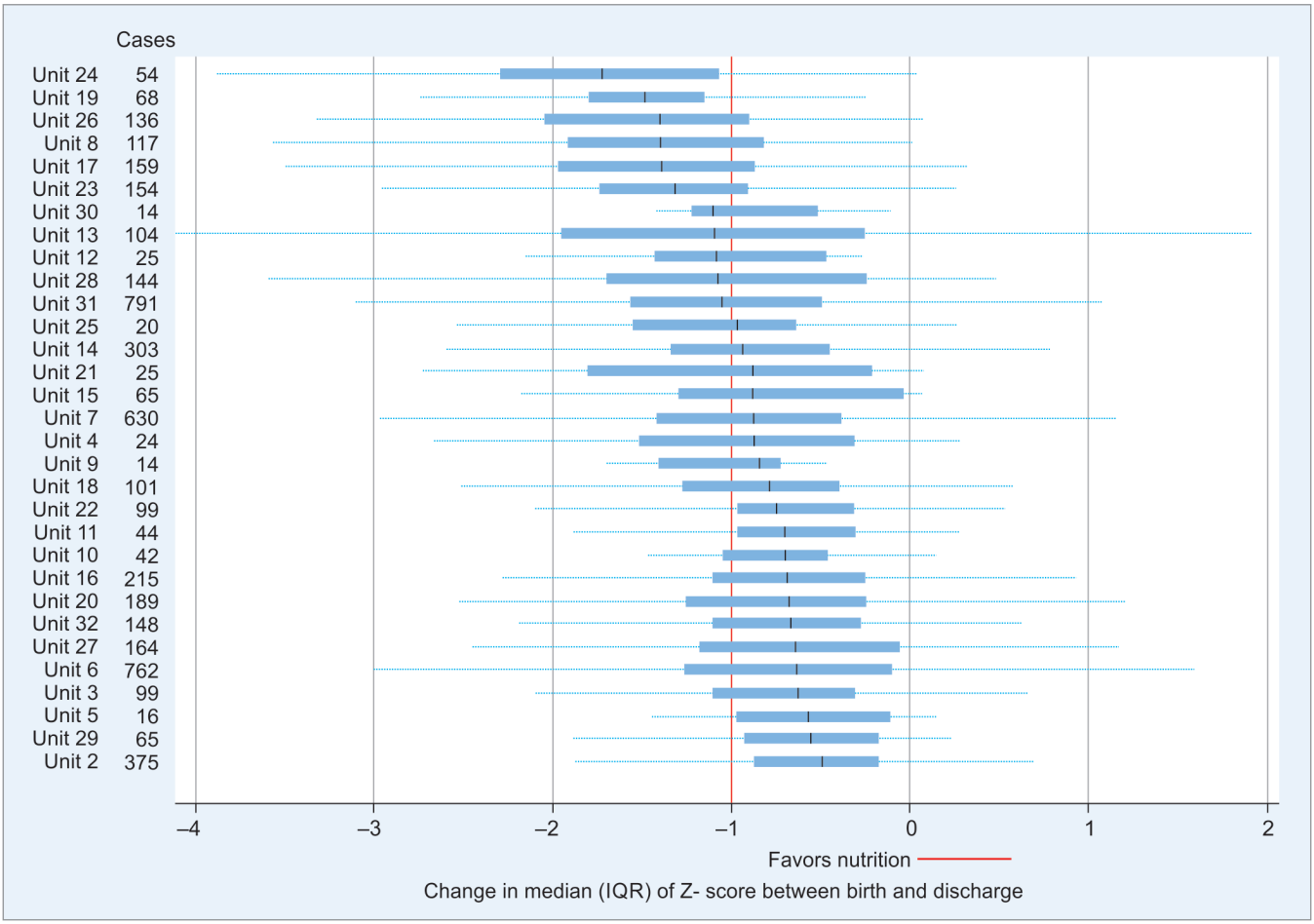

Fig. 1: Changes of median and interquartile range (IQR) of Z-score change between birth and discharge of the units in EpicLatino network arranged in ascending order. Unit 1 excluded for only one case. In second column number of cases in each unit

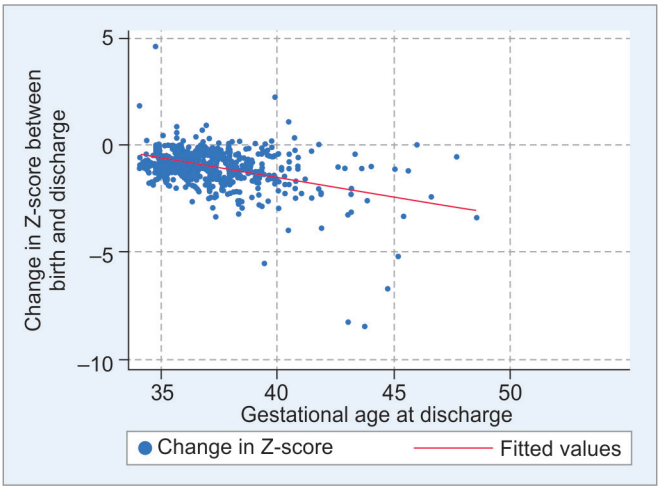

Fig. 2: Changes of median Δ Z-score between birth and discharge (*y-axis*) in cases discharged home at ≥34 weeks corrected GA in babies born at ≤32 weeks, correlation with corrected GA at discharge. 8 years (2015–2022)

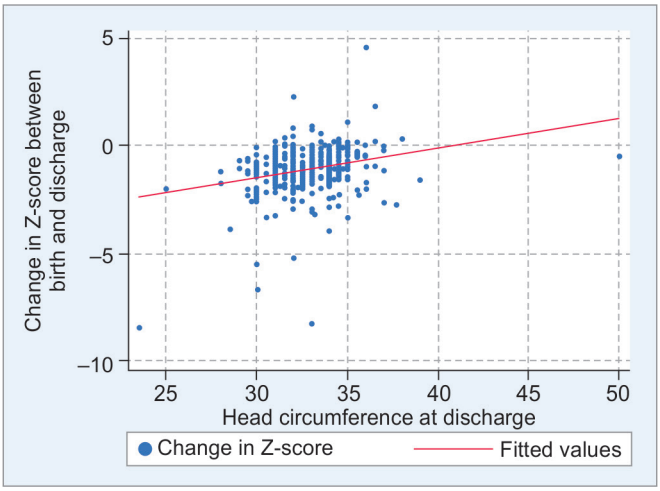

Fig. 3: Changes of median Δ Z-score between birth and discharge (*y-axis*) in cases discharged home at ≥34 weeks corrected GA in babies born at ≤32 weeks, correlation with HC at discharge. 8 years (2015–2022)

probability of losing 1 or 2 SDs.[11] As known, these associations do not establish causality. Some of these variables may identify the challenge of nourishing a sick or very small preterm infant, but the unit of origin variability identifies nutrition policies and practices that can be modified through a quality improvement program; the wide variability of results in Figure 1 confirms these observations.

The correlation between changes in weight Z-score and corrected age at discharge suggested that babies with less drop in weight Z-score were able to go home with lower GA; the length of hospital stay was also shorter at various GAs. The correlation of less drop in weight Z-score with HC size in Figure 3 confirmed that better growth with a larger overall size of the infant was likely better for earlier discharge.[12,13] Previous studies have shown that larger HC at discharge has been associated with better neurodevelopment, especially in preterm infants.[12,14–17]

Limitations of our study are inherent to the retrospective observational nature of the study and the use of database cases. Another limitation may lie in the choice of discharge as a time point for assessing EUGR, as there is a wide range of time of evaluation, and a long time passes between birth and discharge.

Our study was done because knowing and monitoring the prevalence of EUGR in our units, is considered to be a quality measure of care for preterm infants.[11] There are no management guidelines that can precisely determine which parameters should be maintained in the units, but aiming to prevent a weight Δ Z-score drop beyond -1 could be a reasonable goal.

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ORIGINAL RESEARCH

Evaluation of Neonatal Infections in the NICU over a 10-year Period

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Abstract

Background: Bacterial infections are a leading cause of morbidity and mortality in premature and critically ill neonates. In this quality-improvement (QI) study, we sought to characterize the bacterial infections in our neonatal intensive care unit (NICU).

Aim: Our aim was to determine whether the spectrum of bacteria causing neonatal sepsis and their antibiotic susceptibility was changing over time. This information is essential for optimizing the empirical antibiotic treatment protocols needed for treating suspected sepsis prior to identification of the bacterial isolates.

Materials and methods: We retrospectively reviewed the medical records of all infants treated for culture-positive sepsis in our NICU over the last 10 years.

Results: We identified 151 culture-positive bacterial sepsis events in 125 infants. The organisms isolated each year largely remained similar throughout the study. Early-onset sepsis (EOS) was caused most frequently by *Escherichia coli* (*E. coli*) and group B *Streptococcus*, whereas the leading causes of late-onset sepsis (LOS) were coagulase-negative *Staphylococcus* (CoNS) and methicillin-sensitive *Staphylococcus aureus*. We are also seeing a trend for increasing *Klebsiella* isolates since 2015.

Conclusion: There was no significant shift in organisms causing neonatal infections during the last 10-years. We need to carefully follow the number of *Klebsiella* spp. isolates and also record the antibiotic sensitivity profiles of *E. coli* over time.

Clinical significance: In our NICU, the bacterial isolates and antibiotic susceptibility patterns have not shown major changes in recent years. Hence, the empirical antibiotic protocols for suspected sepsis do not need to be revised right now. We do need to monitor the number and antibiotic sensitivity of certain Gram-negative bacterial isolates. Our antibiotic protocols will need fine adjustment to cover the most frequently isolated bacteria for good outcomes, but also to avoid overuse and secondary resistance.

Keywords: Antibiotic use practices, Infection, Neonate, Neonatal intensive care unit, Newborn, Organism susceptibility.

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Key Points

- Neonatal sepsis continues to be a leading cause of neonatal morbidity and mortality.
- This study was a retrospective review of 151 bacterial infections in neonates admitted to the neonatal intensive care unit (NICU) over a 10-year study period.
- The most common organisms causing sepsis in premature and critically ill newborn infants remained similar throughout the study period. In early-onset sepsis (EOS), *Escherichia coli* and group B *Streptococcus* were the leading agents. Late-onset sepsis (LOS) was caused most often by coagulase-negative Staphylococci and methicillin-sensitive *Staphylococcus aureus*. There has been a recent rise in the number of *Klebsiella* isolates that has not reached statistical significance yet.
- Close surveillance of bacterial isolates and antibiotic sensitivity profiles is needed in all NICUs; these data can help optimize the empirical therapy of suspected neonatal sepsis before the diagnosis is confirmed and the isolated bacteria are fully characterized.

Introduction

Infections can become a life-threatening emergency in premature and critically ill neonates in NICUs. Despite major advancements in the management of neonatal sepsis, infections still continue to be

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a leading cause of neonatal morbidity and mortality. The Global Burden of Disease study in 2016–2017 identified a worldwide annual incidence of 1.3 million cases of neonatal sepsis.[1]

Neonatal sepsis is divided into early-onset infections occurring within the first 3 days after birth, and the late-onset infections that are seen there after.[2,3] Early diagnosis and appropriate empiric antibiotic treatment can minimize morbidity and mortality resulting from these infections. Early onset sepsis is most commonly caused by group B *Streptococcus* (GBS) and *Escherichia coli* (*E. coli*) and recommended empiric antimicrobial therapy is typically ampicillin and gentamicin.[3] Late-onset sepsis organisms vary based on patient-specific risk factors and differ between NICUs; however, coagulase-negative *Staphylococcus* (CoNS), *Staphylococcus aureus*, and Gram-negative bacteria are still the leading causes.[4] Monitoring the epidemiology and resistance patterns in neonatal sepsis over time are important as it would determine the choice and efficacy of empirical antibiotic therapy. For instance, GBS has been viewed as the most frequently-seen organism for EOS. Maternal antibiotic prophylaxis was introduced in 1996 in the United States to minimize GBS vertical transmission, and the incidence of early-onset GBS sepsis decreased from 1.3 to 1.7 per 1000 in the early 1990's to 0.3–0.6 per 1000, even though there has been some increase in the rates of *E. coli* sepsis during this period.[2,5] Intravenous penicillin is the agent of choice for intrapartum prophylaxis, with intravenous ampicillin as an acceptable alternative. First-generation cephalosporins and clindamycin are considered in women with a risk of allergy.[6] There are some regional differences in the organisms responsible for neonatal sepsis; further studies are needed to design prophylactic strategies to reduce neonatal sepsis.[7]

This is a retrospective observational study of all neonates with culture-positive sepsis in a single NICU cohort to identify any major shifts in organisms over a 10-year-period (2011–2020). We listed the most frequently-identified organisms to determine whether currently-accepted treatment guidelines and our unit protocols for EOS and LOS will likely be effective.[8,9] We also sought to identify the host and or clinical factors that would increase the risk of infections with certain organisms or more resistant pathogens. The risk of infection can increase, particularly in preterm infants, due to an immature immune system, prolonged hospitalization and frequent use of invasive devices.[10] Identification of these risk factors could help develop/improve the treatment regimens currently used to treat neonates with suspected infections.

Materials and Methods

This retrospective cohort study included neonates admitted to a single regional perinatal center level IIIB NICU with 40 licensed beds located in New Jersey, US between January 1, 2011, to December 31, 2020. We have an average of 896 admissions per year and approximately 5% of patients are out born. The cohort has a high case mix index.[11] The study was approved by the institutional review board and informed consent was waived.

During the study period, we did not have a formalized antimicrobial stewardship program in the NICU. We retrieved patient information from a central, electronic data repository. Demographic data included gestational and postnatal age at time of infection, birth-weight, and sex. Patient specific risk factors for infection included mode of delivery, need for mechanical ventilation and presence of a central line. Comorbid conditions present at the time of infection, such as necrotizing enterocolitis (NEC) and bacterial meningitis were also included.

Information about positive cultures [blood, urine, respiratory or cerebrospinal fluid (CSF)] over the 10-year time period was evaluated. If a neonate had more than 1 infection at different times during the hospitalization, those were recorded as separate events as these were not always caused by the same organism. Neonates whose cultures were identified as contaminants by the treatment team and not treated for infection, and those who had only positive respiratory cultures were excluded from the study. Fungal cultures were not included.

The primary endpoint in this study was to identify the prevalence of organisms causing neonatal infections and evaluate the susceptibility patterns of the most common organisms throughout the study period. For EOS, our primary empiric protocol included ampicillin and gentamicin. Late-onset sepsis was typically treated with vancomycin and gentamicin.

Secondary endpoints included evaluating potential risk factors for resistant organisms including time onset of sepsis (early vs late), gestational age (very preterm (≤30 weeks), preterm (31–36 weeks), and term infants (≥37 weeks), mode of delivery, presence of central line or mechanical ventilation and diseases including meningitis or NEC . Resistant organisms for our study were defined as strains of *E. coli* resistant to gentamicin, any organisms with detectable AmpC beta-lactamase production or extended spectrum beta-lactamases or *Staphylococcus aureus* strains resistant to methicillin. Results were categorized by EOS (onset within the first 3 days of life) or LOS (occurring after 3 days of life). In addition, we evaluated the correlation of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal screens with systemic infection MRSA.

Summary statistics were used for descriptive purposes. Depending on variable type and underlying distribution, these included mean with standard deviation, median with interquartile range, or counts with associated percentages. Longitudinal plots, heat maps and bar charts were used to visualize relationships between infection, antibiotic usage and time. Generalized linear regression models were used to explore significant associations between infection type and central line or mechanical ventilation, with a significance threshold of 0.05. Only primary infections were considered to preserve the independent assumption of the model for patients that had more than 1 infection for secondary endpoints. All statistical analyses were performed using JMP®, Version 17.2. SAS Institute Inc., Cary, NC, 1989–2023.

Results

During the 10-year study period, we had an average of 896 admissions per year, where about 5% were out born. There were 151 recorded bacterial infection events in 125 infants. As mentioned above, we have a high case mix index.[12] During the study period, we did not have a formalized antimicrobial stewardship program in our NICU.[13]

There were 131 cases of isolated bacteremia, 7 cases of meningitis, 9 isolated urinary tract infections (UTI), and 4 cases of bacteremia with UTI. Four cases had positive cultures for two separate organisms. Complete baseline demographics are provided in Table 1. In our cohort, 69 (55%) were male. The gestational age was median (range) 26.6 (24.9–32.3) weeks and the birth weight was 0.9 (0.7–1.5) kg. Most [92 (72%)] were delivered via cesarean sections and singletons (87.2%).

We did not find any significant changes in the occurrence of infections over time. The rate of infections ranged from 0.4 to 1.7% during the 10-year study period, but there were no obvious trends.

The highest number of neonatal infections were noted in the years 2012, 2015, and 2019 (n = 16 each year), and the lowest number of infections (n = 4) was seen in 2013 (Fig. 1). Of the total 151 infection events, 32 were EOS and 119 were LOS. The most common organisms responsible for EOS were *E. coli* (n = 14) and GBS (n = 6). In infants with LOS, CoNS (n = 42) and methicillin-sensitive *Staphylococcus aureus* (MSSA; n = 22; Table 2). Figure 2 shows the yearly frequencies of *gram-positive* and *gram-negative* pathogens over the study period.

Table 1: Demographics

	Total (n = 125)			
Characteristics	*Count*	*Percentage (%)*	*Median*	*IQR*
Repeated infections				
Yes	16	12.8		
Delivery				
C-section	90	72.0		
Gestation				
Multiple	16	12.8		
Gender				
Male	69	55.2		
Race*				
African American	13	15.3		
Asian	16	18.8		
White	55	64.7		
Ethnicity**				
Hispanic	32	34.8		
Nonhispanic	60	65.2		
Gestational age (weeks)			26.6	24.9–32.3
Birthweight (kg)			0.9	0.7–1.5

Table 1 depicts the demographics for all the patients who had an infection in the NICU. Summary statistics include the count, percentage, median and interquartile range (IQR); *Total number of patients is 84; **Total number of patients is 92

Gram-positive Infections

The majority of the infections were caused by gram-positive organisms (99, 65.5%) with CoNS as the most common cause (n = 45). Coagulase-negative *Staphylococcus* infections were noted in the entire study period; the largest number was seen in 2015 (n = 11). Eleven percent of the CoNS isolates were susceptible to

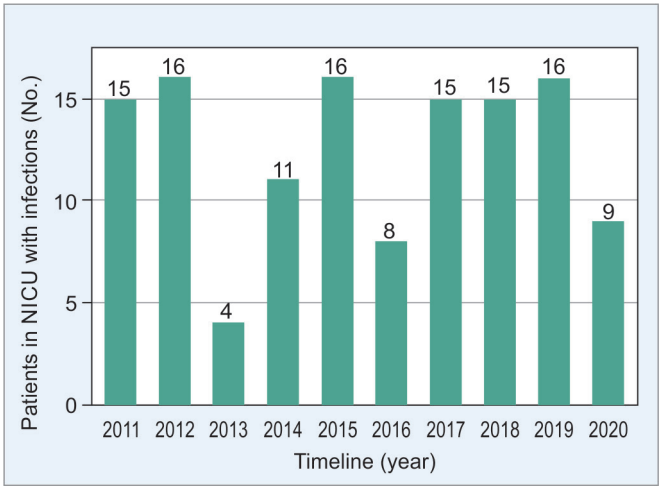
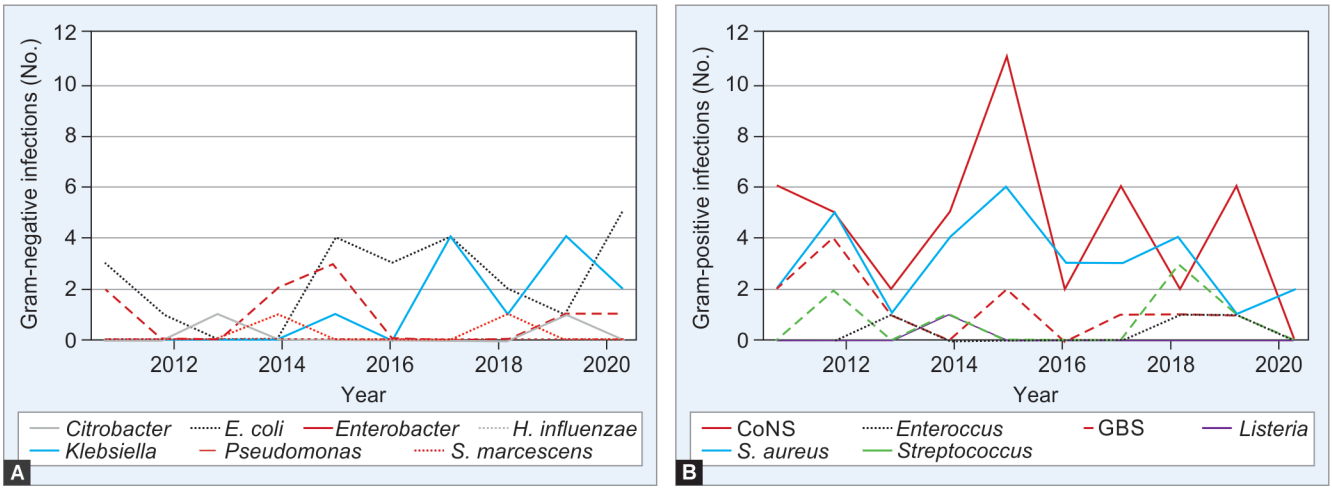


Fig. 1: Patients in the NICU with infections from 2011 to 2020
Bar chart depicts the number of patients admitted to the NICU with infections over a 10-year span. Counts are displayed for each year.

Table 2: Organisms isolated in early onset sepsis and late onset sepsis

	EOS (n = 32)		LOS (n = 119)		Total (n = 151)	
Isolated cultures	*Count*	*Percentage (%)*	*Count*	*Percentage (%)*	*Count*	*Percentage (%)*
Gram-negative						
E. coli	14	43.8	9	7.6	23	15.2
Klebsiella	1	3.1	11	9.2	12	7.9
Pseudomonas	0	0.0	9	7.6	9	6.0
Enterobacter	1	3.1	6	5.0	7	4.6
Citrobacter	1	3.1	1	0.8	2	1.3
Haemophilus influenzae	1	3.1	0	0.0	1	0.7
Serratia marcescens	0	0.0	1	0.8	1	0.7
Gram-positive						
CoNS	3	9.4	42	35.3	45	29.8
MSSA	1	3.1	21	17.6	22	14.6
GBS	6	18.8	8	6.7	14	9.3
Nonhemolytic *Streptococcus*	4	12.5	3	2.5	7	4.6
MRSA	0	0.0	8	6.7	8	5.3
Enterococcus	0	0.0	3	2.5	3	2.0
Listeria	1	3.1	0	0.0	1	0.7

The EOS, LOS and totals reflect infection events. Some infections may include co-infections resulting in more organisms than infection events



Figs 2A and B: Number of infections by organism per year
Above figure illustrates the trends of infection over a 10-year timespan (2011–2020). The graph on the left is gram-negative trends and the graph on the right is gram-positive trends. Organisms depicted in grey scale and patterned according to each respective legend.

penicillin and resistance did not show any change over the 10-year study period (Fig. 3). The number of MSSA infections declined over the 10-year period with the highest numbers of yearly cases (4 per year) in 2012 and 2015. We recorded only 0–2 MRSA infections per year. A few GBS cases (1–2 per year) were seen every year and all isolates were susceptible to penicillin. There were no obvious trends of change in the susceptibility patterns of the most-frequently seen Gram-positive organisms throughout the study period (Fig. 3).

Gram-negative Infections

E.coli was the most frequently-seen gram-negative bacterial isolate; isolated in 23 total cases, where the highest number occurred in 2020 ($n = 5$). Table 2 shows the susceptibility patterns of most prevalent *Gram-positive* infections, with no obvious trends over the 10-year study period. Ten of these *E.coli* isolates (43%) were susceptible to ampicillin and gentamicin. One extended spectrum β-lactamase *E. coli* isolate was identified in 2019 and another that was resistant to gentamicin was seen in 2020.[14] The remaining 11 isolates were susceptible to both gentamicin and 1st generation cephalosporins. *Klebsiella* spp. emerged as a pathogen in our NICU with cases occurring almost every year since 2015; all isolates showed susceptibility to gentamicin and 1st generation cephalosporins. All patients with Klebsiella sepsis were premature, with a gestational age >30 weeks. We noted a total of 8 *Pseudomonas aeruginosa* infections during the study period; all were susceptible to cefepime and ceftazidime. There were 7 *Enterobacter* infections, where all isolates were susceptible to carbapenems.

Patient Factors

A total of 23 (15.3%) infection-events occurred in patients with NEC. The most frequently seen organisms in these patients were CoNS ($n = 8$), *E. coli* ($n = 4$), and *S. aureus* ($n = 6$; 3 MSSA, 3 MRSA). A total of 19 (12.6%) infection events were treated for meningitis, although only 7 had documented positive CSF cultures. Group B *Streptococcus* ($n = 5$), *E.coli* ($n = 3$) and MSSA ($n = 3$) were identified most frequently with meningitis.

In preterm infants, the top 3 infections were CoNS ($n = 39$), MSSA ($n = 22$) and *E.coli* ($n = 17$). These babies were also more likely to have drug-resistant infections such as MRSA ($n = 7$), *Pseudomonas* spp. ($n = 5$) and *Enterobacter* spp. ($n = 6$). In patients with central lines ($n = 81$, 58.9%), 60 (39.7%) isolates were gram-positive bacteria. However, the presence of a central line was not a significant factor for having a gram-positive infection ($p = 0.7$). Seventy infection-events (46.4%) occurred in patients who required mechanical ventilation; 46 (65.7%) bacterial isolates were Gram positive. There was no significant difference in the odds of Gram-positive or Gram-negative primary infections between patients on ventilatory support (OR = 0.80, 95% CI: 0.37–1.74) vs those who were not (OR = 1.28, 95% CI: 0.59–2.78). Nasal screens were evaluated for MRSA colonization to determine whether a positive result could predict later invasive MRSA infections. A negative MRSA screen almost excluded a later MRSA infection with a negative predictive value (NPV) of 97.8%. A positive MRSA screen had a sensitivity = 62.5%.

Discussion

This study examined the clinical factors and bacterial genera associated with neonatal sepsis in our center over a 10-year period. *E. coli,* GBS and *S. aureus* were identified most frequently but remained similar year-to-year throughout the study period. Considering that some *Klebsiella* isolates are now being identified, we need to carefully monitor these numbers to determine whether there could be a need for modifications in antibiotic management of suspected sepsis before the culture reports become available.[15]

In EOS, our frequent identification of GBS and *E.coli* is consistent with existing literature.[3] We need to continuously monitor maternal and neonatal information at all centers to validate the protocols for perinatal prophylaxis and treatment of suspected neonatal sepsis.[16] Currently, the antibiotic susceptibility patterns of bacteria isolated in our NICU are reassuring for continued empiric use of ampicillin and gentamicin for suspected EOS before culture results become available, as recommended by the American Academy of Pediatrics (AAP).[8,9] However, if *E. coli* or *Klebsiella* species emerge as important causes of EOS, the antibiotic protocols may need to be updated.[10,11] The concerns about ampicillin resistance in our *E. coli* isolates call for continuous monitoring.[17] Our current regimen of vancomycin and gentamicin for LOS is effective effective as most *E. coli* strains are susceptible to gentamicin.[18] However, the clinical utility and long-term safety of gentamicin monotherapy when secondary

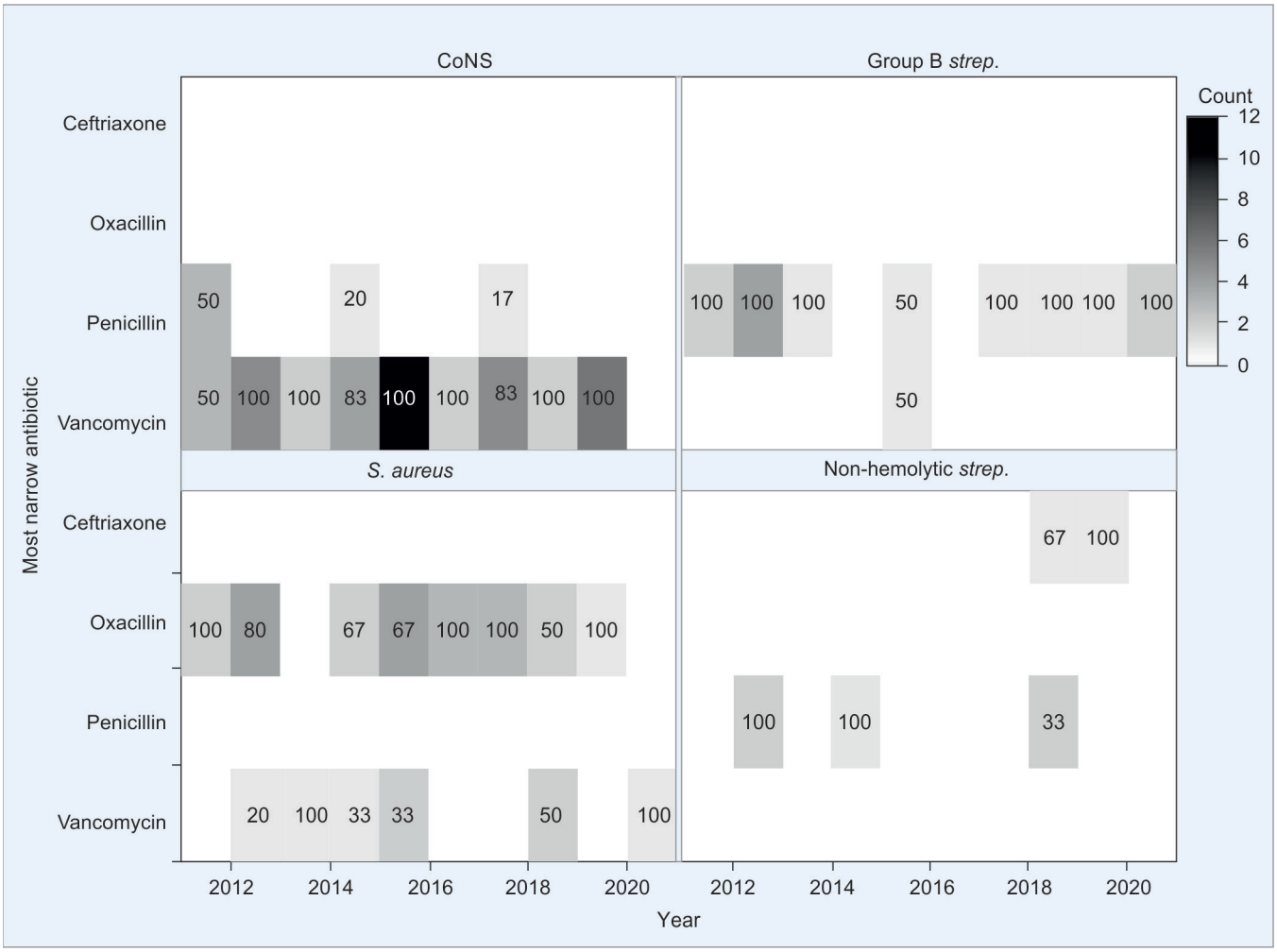


Fig. 3: Susceptibility patterns of most prevalent gram-positive organisms
Above figure shows a heatmap of the antibiotic susceptibility of the most common gram-positive organisms (CoNS, Group B *Streptococcus*, *Staphylococus aureus* and non-hemolytic *Streptococcus*) by year. Color intensity corresponds to the number of infections treated by each antibiotic for each organism. Antibiotic susceptibility percentage is shown within each cell.

resistance is considered, remains controversial.[19,20] We may need to consider revising our empiric antibiotic panels for use prior to the availability of culture/sensitivity results if Gram-negative organisms or ampicillin resistance is seen more frequently.[21]

In patients presenting with LOS, Gram-positive organisms such as CoNS and *S. aureus* were seen frequently during the entire study period. These data resemble those from the entire United States.[2,22,23] Most of our *S. aureus* isolates show oxacillin susceptibility, with resistance in about 25% of the strains. Studies show MRSA rates varying between <1 and 23% between centers.[2] Currently, our empiric regimen covers for MRSA with vancomycin, although some recent studies have found oxacillin to be effective for LOS Gram-positive coverage.[24] These steps are attractive for less adverse effects and limiting bacterial resistance due to overuse of broad spectrum antibiotics.[25] In our patients, a negative MRSA nasal screen showed a strong NPV in identifying patients who would be less likely to develop MRSA infections and hence, the need for using vancomycin. On the other hand, infants who have central lines and are started on empiric oxacillin for suspected sepsis should be switched to vancomycin once the blood cultures are confirmed as positive for CoNS.[26] Finally, many recent studies have noted an increasing frequency of *Klebsiella* spp. in neonatal sepsis.[22,23] Hence, many centers have either actively considered or included a first-generation cephalosporin to broaden empiric antibiotic therapy in a decompensating patient.[15]

Infection prevention is key to minimizing infections and preventing antibiotic resistance. One strength of our study is that every single patient who qualified by the inclusion criteria was included.[27] We acknowledge that there have been changes in our practice over the 10-year period of the study. There are some steps that we have applied very stringently in our NICU and could affect the number of infants who have tested positive and hence, included in the study.[28] We perform weekly MRSA nasal screens in all NICU patients, and those who test positive are immediately placed on contact precautions.[29] Procedures such as central line insertion, initiation of fluid administration, or obtaining blood cultures are performed after sequentially wiping the site with alcohol and povidone-iodine or lately with chlorhexidine.[30–32] Each step is performed only after the site has dried after the previous step.[33,34] Irrespective of the disinfection protocol, we have included every patient who were treated for a positive culture infection related to EOS or LOS. These practices could have altered the spectrum

of organisms isolated in cultures as compared to other NICUs. Our practices could also have minimized the overlap between bacteria isolated in EOS vs LOS.[23]

There are limitations to our study. It is a single center retrospective study with a limited number of subjects and therefore may not be generalizable to other NICUs.[35] However, in discussions in the Global Newborn Society, such small unit-specific studies will very likely be needed in NICUs all over the world.[36] In large consortia of NICUs, even though the number of enrolled infants is larger, there is considered center-to-center variability.[37] Differences in host genetic susceptibility, bacterial flora, environmental factors, previously-administered and ongoing drugs, nutrition, and systems management all likely vary in different parts of the world thus making generalizable studies challenging. Furthermore, due to our evaluation of only patients with positive cultures, we were unable to clearly identify the patients who would be at risk for infection and risk factors for resistant organisms in the overall NICU population. Shortly after this study was concluded, the change in skin disinfectants in our NICU could shift the microflora in our unit.[38] During this time, we also did not have antibiotic guidelines for late-onset neonatal infections. This could have led to unrecognized but possibly suboptimal overuse of broad-spectrum antibiotics leading to emergence of resistant pathogens.[39] The overuse of antibiotics in NICUs is a topic of concern due to the increased risk of antimicrobial resistance in addition to associations with alternations in the gut microbiome. We have been very cautious in our empiric antibiotic use for EOS by using risk-of-sepsis calculators to minimize unnecessary antibiotics.[40,41] We still need strong risk-assessment tools for LOS.

Conclusion

In our retrospective review, the spectrum of bacteria causing neonatal sepsis did not change significantly over the 10-year study period. Although no significant trends were observed in the frequency of susceptibility patterns, the NICU staff expressed a concern about the need to monitor for drug resistance in Gram-negative pathogens such as *E. coli* and the total number of *Klebsiella* infections requiring cephalosporin therapy. At this time, we do not have strong evidence for an immediate need for a change in antibiotic protocols, but we are continuing with QI efforts to monitor the spectrum of bacterial isolates. The development of a Global Newborn Society-wide patient database with records of infections and a standardized antimicrobial stewardship program could help but considering the heterogeneity in different parts of the world, we might still need advanced prediction-focused statistical tools.[42] If the heterogeneity precludes the derivation of major conclusions, alternative methods such as systemic reviews/meta-analysis of small, comparable studies could help.[43] To facilitate this idea, performing a well-considered single-center study could provide a template for multiple, similarly-structured small studies all over the world to improve precision.[44,45]

Ethical Approval

This study was approved by the Hackensack Meridian Health IRB. The protocol number for approval is Pro2021-0879. This study was conducted in accordance with the Declaration of Helsinki.

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ORIGINAL RESEARCH

Infafeed Monitor Pilot Study: Measuring Ingested Milk Volumes in Neonates

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Abstract

Aim: This study evaluates the technical feasibility of Infafeed, a novel noninvasive prototype for measuring ingested milk volumes in neonates, offering an objective assessment to support breastfeeding.

Materials and methods: A single-center pilot study was conducted. Twenty-four newborn infants (mean gestational age: 37 ± 1 weeks, birth weight: 2.88 ± 0.63 kg) receiving bottle or syringe feeds were recruited. Two cases were excluded due to data-saving errors, and two more were removed due to excessive noise. The Infafeed monitor recorded feeding sounds via a microphone placed on the infant's neck, while a secondary microphone captured background noise for cancellation. Power spectral density analysis was performed to differentiate swallow and nonswallow events, and a linear regression model was used to estimate feed volumes based on 20 recordings.

Results: Spectral analysis revealed a significant difference in swallow vs nonswallow spectral power in bottle-fed infants. Total power in the 400–600 Hz frequency band showed the strongest correlation with milk volume per swallow ($r = 0.94$). The linear regression model achieved a mean absolute error of 6.44 mL for estimated feed volumes.

Conclusion: The Infafeed monitor demonstrated feasibility for neonatal feeding assessment. The observed acoustic differences between swallow and nonswallow periods provide a foundation for automated swallow detection, which can enhance milk volume estimation. Further studies with a larger cohort are required to improve accuracy and evaluate the technical and clinical applicability.

Clinical significance: Maternal concern about insufficient milk supply is a leading cause of premature cessation of exclusive breastfeeding. The Infafeed monitor has the potential to provide a noninvasive, objective tool for assessing neonatal milk intake, reducing unnecessary supplementation, enabling early identification of feeding problems, and supporting breastfeeding continuation. If validated in larger studies, this device could enhance breastfeeding support strategies in both clinical and home settings.

Keywords: Breastfeeding, Infant, Monitor, Neonatal, Nutrition, Swallow.

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Introduction

The benefits of breastfeeding infants are well documented, and the World Health Organization recommends exclusive breastfeeding for the first 6 months of life.[1] Despite this, globally, fewer than 50% of infants are exclusively breastfed until 6 months of age, with significantly lower rates in higher-income countries.[2,3]

One of the most common reasons for earlier-than-planned cessation of breastfeeding is self-reported maternal concerns around inadequate milk supply and their ability to provide adequate nutrition to their baby through breastfeeding alone.[4–7] This perception of insufficient milk supply is common among women who stop exclusive breastfeeding early; however, primary insufficiency of milk production has been found to affect only 5% of women.[8,9] Many women who report insufficient breastmilk describe infant satiety cues, such as crying as their primary indication of milk supply, despite these having been proven as an unreliable indication of actual milk supply, rather than proven clinical indicators of adequate milk supply, including infant weight gain and growth and urine and stool output.[8,10–12] While weight gain is the primary clinical indicator of adequate milk intake, it does not provide real-time feedback on individual feeding sessions. In cases where feeding adequacy is uncertain—such as

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in preterm infants transitioning to breastfeeding, neonates with poor weight gain, or infants at risk of dehydration—objective feeding assessments may be beneficial.

Additionally, studies have shown that a perception of insufficient milk by a mother does not commonly correlate with an actual insufficiency of milk production, highlighting a need for an objective way to measure breast milk volumes to improve maternal confidence in their ability to feed their infant without requiring supplementary formula.[9,11]

A number of modalities can be used to assess breastfeeds and swallowing. Breastfeeding scoring systems are frequently used, as they are noninvasive and simple to use.[13] However, these are not accurate methods for quantifying feed volumes.[14] Imaging modalities have been studied to visualize swallowing in breast-fed infants, including ultrasound, fiberoptic endoscopic evaluation of swallowing (FEES), and magnetic resonance imaging. These modalities have been shown to be able to visualize milk ingestion and may be able to estimate feed volumes; however, as with breastfeeding scoring systems, they require trained staff, appropriate equipment, and, in the case of FEES, are an invasive procedure.[15–18] They are useful for the evaluation of dysphagia or concerns for aspiration, but are unlikely to be feasible for parents as a tool to evaluate the volume of milk taken by an infant repeatedly over several breastfeeds.[15,17,18] Test weights, which involve weighing a baby before and after a breastfeed, are currently the most accurate noninvasive tool for estimating feed volumes.[11] Test weights have been shown to be effective, but again require staff available to weigh the infant before and after the feed, and have been reported to be perceived negatively by some mothers as it interrupts bonding time and medicalizes breastfeeding.[11,19]

There are currently no commercially available products which have been scientifically proven to accurately provide estimates of ingested breastmilk by an infant. Given that concerns around lack of adequate milk supply is one of the most frequently cited reasons for cessation of exclusive breastfeeding in the first 6 months and the lack of a noninvasive, accurate and easy-to-use bedside method of evaluating milk ingestion from breastfed infants, our goal was to develop a monitor which could easily and noninvasively measure the volume of milk taken by an infant while breastfeeding. The ultimate goal of this device is to improve infant nutrition and breastfeeding rates. Developing this technology requires multiple steps: first, enabling automatic detection and measurement of milk swallows; second, providing real-time feedback to users; and finally, the design must be simple and user friendly, so that it can be used quickly and easily by clinicians and parents without interfering with the infants feeding.

As the first clinical study in the development of this technology, the aim of this project was to assess the technical feasibility of the Infafeed Smart Feeding Monitor, a noninvasive feeding monitoring device. Specifically, this study evaluated the prototype's ability to differentiate acoustic characteristics between swallow and nonswallow periods and to estimate milk intake automatically. It is worth noting that this technology is designed as a noninvasive, supportive tool for specific cases where feeding adequacy is uncertain, such as neonates with poor weight gain, rather than for routine use in all breastfeeding infants. This device aims to complement existing clinical assessments by providing real-time, objective measurements of milk intake, which may be particularly valuable in settings where early identification of feeding difficulties can help guide interventions.

Materials and Methods

Study Design and Data Collection

This was a prospective, single-center, pilot study conducted on the postnatal wards of Monash Medical Center, Melbourne, Australia (a tertiary multispecialty public hospital) and was approved by the Monash Health Human Research Ethics Committee (HREC/89481/MonH-2022-345330). The study population comprised term or late-preterm infants (gestational age: 35–42 weeks) receiving bottle or syringe feeds of expressed breast milk (EBM) or infant formula. Infants were excluded from the study if they were born less than 35 weeks gestation, required nasogastric feeds, had a known major congenital abnormality or genetic condition, or whose parents were unable to give informed consent. Recruitment occurred by informed consent from the parent(s) of infants who had already been born and were admitted to the postnatal ward. All infants recruited were already having a bottle or syringe feed as part of their feeding plan prior to being recruited.

Syringe-fed infants were included to evaluate the feasibility of using the Infafeed monitor in detecting swallows and estimating milk intake at very low volumes. This is particularly relevant as newborns typically consume small quantities of milk in the early stages of breastfeeding. Since the study required a known measure of actual milk intake, only bottle- and syringe-fed infants were included, ensuring accurate volume estimation. The inclusion of syringe-fed infants allowed us to examine the device's performance in detecting swallows at the lowest intake levels.

The Infafeed monitor (first prototype, not yet commercialized) is being developed as a wearable device for accurate feed volume measurement. It uses two microphones: one placed on the infant's neck to record swallowing sounds, and another within the main unit to capture background noise.

After informed consent was obtained, a recording of the feed from a bottle or syringe was made. The Infafeed sensor was placed on the right or left lateral neck surface of the infant and adhered to the skin using a small amount of DuoDerm (Convatec Inc., Victoria, Australia) adhesive dressing (Fig. 1). A note of the volume taken by the baby during the feed was made at the end of the feed, and during any interruptions to the feed. To identify swallow events, a noise was made by the investigator each time the baby swallowed; for the initial 12 recordings, this was done using verbal cues each time the baby swallowed and picked up

Fig. 1: Infafeed sensor applied to lateral neck of infant mannequin

by the background microphone in the Infafeed sensor head. To improve swallow recognition, from the 13th recording onward, a clicking noise was made by the investigator using a click noise on their phone; this clicking was recorded separately and saved, to synchronize with the audio recorded by the Infafeed microphone. The clicker was pressed every time the investigator saw the use of swallowing muscles in the infant's neck. This clicker was introduced as a reference to assist in locating swallow events for spectral analysis. However, the clicker data was not used in the automated volume estimation process, ensuring that the estimation model does not depend on any manual cues.

The medical records were accessed for each infant to document demographic data, including gestational age, chronological age, birth weight, sex, mode of delivery, the type of milk being fed, and the total volume of milk taken by the infant during the feed. Infant characteristics were assessed for normality and the mean and standard deviation (SD) or median and interquartile range (IQR) were calculated for each domain.

Preprocessing

Following the collection of all data, the sensor data was processed. This included noise removal and spectral analysis of milk swallows. To obtain power spectral density (PSD) plots, primary and background microphones were sampled at 5,000 Hz. Background noise cancellation was achieved by spectral oversubtraction of the secondary background microphone, which picks up background noise, from the primary microphone, as described by Emmanouilidou et al.[20]

Spectral Analysis

Primary microphone data was broken up into swallow and nonswallow periods. Swallow periods were defined as the entire region in which feeding associated with swallows occurred. Power spectral density was then calculated. The difference between swallow and nonswallow periods was also calculated for different power bands from 0 to 2,500 Hz and the total power. Significance testing was performed using two-sided paired Wilcoxon signed rank test.

Milk Intake Volume Estimation

A linear regression model was trained with feed volume as the target variable and total power of the sound, age, and delivery mode as independent variables. The model was trained iteratively on subsets of the dataset, with one infant's recording reserved for testing in each iteration, while the remaining data was used for training. This iterative leave-one (infant)-out validation process ensures a reliable and unbiased evaluation of the model's ability to generalize across different infants.

Results

Infant Recruitment

The parents of 24 infants receiving bottle or syringe feeds provided consent for their participation in this study. One recording of a bottle or syringe feed was made for each infant. None of the infants in the study received feeds from a cup or other alternative feeding methods. Of the 24 recordings, two were excluded from the analysis due to errors in saving the data (in one case, the device was turned off before the recording was saved, and in the second, the device was not turned on to record correctly). Two further recordings were significantly corrupted by noise and were excluded. Final analysis was performed on the remaining 20 recordings. Recordings took place over a 6-month period from December 2022 to May 2023.

Table 1: Demographic data

Demographic variables	*Infants (n = 24)*
Gestational age (week), mean (SD)	37 (1)
Birth weight (kg), mean (SD)	2.88 (0.63)
Female	13 (54%)
Male	11 (46%)
Mode of delivery	
Vaginal	10 (42%)
Cesarean section	14 (58%)
Type of feed	
Bottle	17 (71%)
Syringe	7 (29%)
Milk type	
EBM	12 (50%)
Formula	12 (50%)
Feed volume (mL), median (IQR)	
Bottle	20 (15)
Syringe	2.5 (0.5)

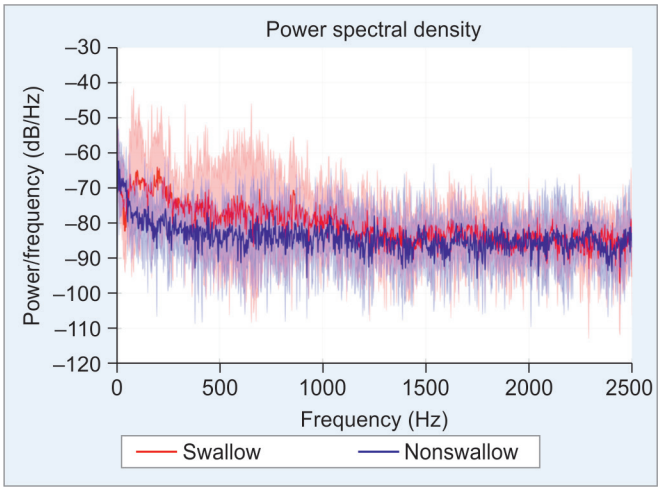

Fig. 2: Overall PSD plot for bottle feeds. Solid lines represent median value and shaded regions represent first quartile to third quartile values

Demographic Information

The infants had a mean (SD) gestational age of 37 (1) completed weeks. The mean (SD) birth weight was 2.88 (0.63) kg, and 13 (54%) of the infants were female. The feed volume taken by bottle [median (IQR)] was 20 (15) mL, and volume taken by syringe [median (IQR)] was 2.5 (0.5) mL; 12 (50%) of the infants took EBM, and 17 (71%) took their feed from a bottle. Demographic data is shown in Table 1.

Spectral Analysis Results

Power spectral density plots were created for seven sample recordings of bottle feeds, which were of the highest quality. The overall PSD is shown in Figure 2. There was a significant difference in power between the swallow and nonswallow periods in the total

Table 2: Difference in power between swallow and nonswallow events for bottle feeds and correlation coefficient of power band with feed volume per swallow

Power band (Hz)	*Median difference (dB/Hz)*	*p-value*	*Correlation coefficient*
Total power	2.51	0.02	0.8508
Power 0–200 Hz	1.42	0.02	0.6793
Power 200–400 Hz	6.90	0.08	0.4315
Power 400–600 Hz	10.46	0.22	0.9360
Power 600–800 Hz	6.17	0.16	0.6182
Power 800–1000 Hz	6.80	0.11	0.6374
Power 1000–1200 Hz	1.32	0.58	0.5949
Power 1200–1400 Hz	0.93	0.38	0.5138
Power 1400–1600 Hz	1.78	0.38	0.2153
Power 1600–1800 Hz	2.10	0.22	0.7640
Power 1800–2000 Hz	0.37	1	0.7191
Power 2000–2500 Hz	1.62	0.02	0.4240

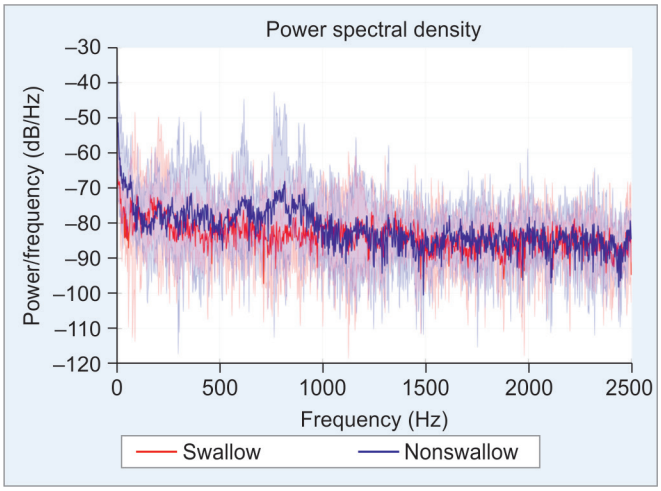

Fig. 3: Overall PSD chart for syringe feeds. Solid lines represent median value and shaded regions represent first quartile to third quartile values

power, and in the range of 0–200 Hz (Table 2). A high correlation was seen with the feed volume per swallow in the 400–600 Hz range and in the total power, with a correlation coefficient of 0.94 and 0.85, respectively (Table 2).

Recordings of syringe feeds were analyzed separately. Of the seven recordings of syringe feeds, four with the highest quality were used for analysis. The overall PSD chart for syringe feeds is shown in Figure 3. Unlike bottle-fed infants, there was not a noticeable dominant power peak for milk swallows taken from a syringe (Table 3).

Milk Intake Volume Estimation Results

Figure 4 shows the line of best fit for the actual and estimated swallow volumes for all 20 recordings of bottle and syringe feeds. The overall root mean squared error was 6.44 mL and overall mean absolute error was also 6.44 mL.

Table 3: Difference in power between swallow and nonswallow events for syringe feeds

Power band (Hz)	*Median difference (dB/Hz)*	*p-value*
Total power	−0.96	0.13
Power 0–200 Hz	0.17	0.88
Power 200–400 Hz	−7.93	0.63
Power 400–600 Hz	−5.80	0.38
Power 600–800 Hz	−12.92	0.25
Power 800–1000 Hz	−9.25	0.38
Power 1000–1200 Hz	−0.84	1
Power 1200–1400 Hz	−0.99	1
Power 1400–1600 Hz	1.20	0.63
Power 1600–1800 Hz	−1.46	0.63
Power 1800–2000 Hz	−0.35	0.88
Power 2000–2500 Hz	0.48	0.25

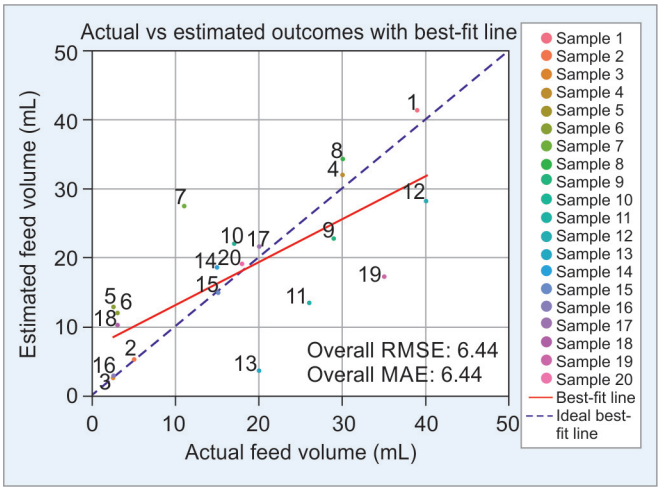

Fig. 4: Line of best fit for actual vs estimated swallow volumes from the linear regression model

Discussion

This is the first study of the use of a feeding monitor to assess feed volumes in bottle- or syringe-fed newborn infants. The Infafeed Smart Feeding Monitor is being developed as an automated technology to assist in determining milk volumes taken by breastfeeding infants to improve breastfeeding rates and long-term nutrition. This first step in its development aimed to test the monitor's ability to estimate the volume of milk intake, with the goal for the software to automatically measure milk intake for each swallow in real time when correctly placed on the infant's neck. This was the first study of this device conducted on infants and utilized an initial prototype model of the sensor. Use of the monitor was feasible, did not interfere with feeding, and parents were generally accepting of the device.

This study represents an initial step toward developing a noninvasive, user-friendly device for assessing neonatal milk intake. While the current prototype requires manual placement and monitoring, the ultimate goal is a small, lightweight, and wearable device that seamlessly integrates into breastfeeding

without requiring continuous supervision. This final design is intended for specific cases where parents or healthcare providers are concerned about feeding adequacy, such as dehydrated infants, those with poor weight gain, or preterm infants transitioning to breastfeeding. At this early stage, our focus is on validating the technology's ability to differentiate swallows and estimate milk intake, with future studies addressing usability, placement, and potential impact on bonding.

We observed significant differences in the power spectrum between swallow and nonswallow regions in bottle feed recordings. This information can inform future models for automatic swallow detection. There was a strong correlation with the total power, especially in the 400–600 Hz band range and the quantity of milk per swallow, which may be helpful in future to improve the milk intake quantification. In this study, we identified total power as the most effective feature for estimating milk intake volume. Previous studies of cervical auscultation in adults have shown differences in the peak frequency recorded based on the swallowed volume, though this was not consistent across males and females, and the effect size was small in both studies.[21,22] It is difficult to know how these results would translate to the neonatal swallow, though highlights the need for further assessment on a larger number of infants. The four recordings of feeds taken by a syringe did not show a statistically significant difference in the power peak. This may be due to the smaller volume taken being a lot quieter and not being picked up as easily on this prototype, with limited denoising and amplification; however, recordings of these smaller volumes will be important in future studies of the device.

Few studies have characterized cervical auscultation for infant swallowing analysis, primarily focusing on dysphagia evaluation rather than feed volume measurement or automated swallow detection.[23,24] As the first study of this unique monitor in infants, we were able to identify differences in the acoustic characteristics of swallow and nonswallow periods, which may be a key to further develop this as an automated technology to detect swallowing. Difficulties encountered in the use of this prototype device during the study were mostly related to the design of the sensor head, which was large and heavy, meaning that the researcher had to hold the sensor in place and affected its ability to have contact with the skin at all times. A new flexible probe is currently being designed as our second prototype, which has a lower profile and would allow more constant contact with the skin.

There were also difficulties in identifying swallows for spectral analysis. This was initially done by the investigator making a noise to be picked up by the background microphone in the sensor head. In subsequent recordings, a clicker noise was used and recorded separately, requiring the recording from the Infafeed device to be synchronized with the recording of clicking for each swallow. Due to challenges in capturing and synchronizing verbal cues for each swallow on the background microphone, some recordings were excluded from the spectral analysis. However, since the milk intake measurement did not rely on the number or timing of swallows, all 20 recordings were included for this analysis. To allow for better swallow detection, the next prototype will include an inbuilt clicker so that the investigator can more accurately time each swallow. The integrated clicker would also enable synchronizing the click information with recordings from the microphones and other sensors. Importantly, the clicker will only be required during algorithm training and will not be needed in the final product used by end users.

Due to differences in the sound quality between infants taking larger volumes of feed from a bottle and smaller volumes from a syringe, we analyzed these data sets separately. Smaller feed volumes taken by a syringe were more difficult to analyze and did not show a significant difference between swallow and nonswallow periods. Future versions of this device should include enhanced noise removal and sound amplification. This will make the device more useful for detecting and analyzing smaller swallow volumes in infants receiving smaller amounts of milk.

A key limitation of this study is the small sample size, which may limit the generalizability of the findings. Future studies with a larger and more diverse cohort are necessary to validate the accuracy of the Infafeed monitor and establish more robust conclusions. Expanding the study population will also allow for improved statistical power and a better understanding of interindividual variability in feeding characteristics. The exclusion of four recordings due to technical and data quality issues, may also impact the generalizability of the findings. Our result suggests a potential regression to the mean effect, where lower volumes appear to be overestimated. Future work will refine the model to address this, particularly by incorporating a larger dataset and optimizing the training of the volume estimation algorithm.

Another limitation of this study is the exclusion of breastfeeding. While this does not fully replicate all aspects of breastfeeding, it provided a controlled environment for initial feasibility testing. The device successfully identified distinct acoustic features during bottle and syringe feeding; however, the absence of breastfeeding data means that additional validation is required to confirm its ability to differentiate true swallows in natural breastfeeding scenarios. Unlike bottle and syringe feeding, breastfeeding involves complex dynamics which may influence the acoustic profile of swallows, which will be investigated in future studies to refine swallow detection accuracy in breastfeeding infants. The technical feasibility demonstrated in this study—such as the ability to distinguish swallows from nonswallow events and estimate intake volume—suggests that further development toward a fully functional device for breastfeeding infants is warranted rather than dismissed. Future studies will focus on evaluating the device in breastfeeding infants, considering additional variables such as infant positioning, milk flow, and natural feeding behaviors.

Conclusions

Use of the Infafeed Smart Feeding Monitor during bottle or syringe feeds was feasible. We were able to demonstrate the technical feasibility of automated milk intake estimation and a noticeable difference in the acoustic characteristics between swallow and nonswallow periods of the recordings, which will be useful in further studies of this monitor, and to develop automatic detection of swallows. Further studies with a larger cohort of infants consuming varying milk volumes are needed to enhance swallow detection and milk intake estimation accuracy over a wide range of volumes.

Clinical Significance

One of the primary reasons for early cessation of exclusive breastfeeding is maternal concern over insufficient milk supply, despite actual milk insufficiency being rare.[4–7] This perception often leads to unnecessary formula supplementation, which in turn can reduce breastfeeding frequency and milk production, ultimately contributing to early weaning.

The feasibility study conducted in bottle- and syringe-fed neonates demonstrated the potential of Infafeed to differentiate swallow vs nonswallow events. The strong correlation between acoustic features and milk volume per swallow, and the estimation of milk intake volume using linear regression, demonstrated the feasibility of Infafeed for automated monitoring of breastfeeding. By providing quantifiable, immediate feedback on neonatal milk intake, Infafeed has the potential to:

- Empower mothers by increasing breastfeeding confidence through objective milk intake measurements.
- Reduce unnecessary formula supplementation, thereby supporting exclusive breastfeeding continuation.
- Enable early identification of feeding difficulties, particularly in preterm or at-risk neonates, thereby improving neonatal nutrition, reducing the risk of dehydration and growth stunting.

If validated in larger studies, Infafeed could transform breastfeeding support strategies in both clinical and home settings, offering an accessible, low-cost tool to improve breastfeeding rates and long-term infant health outcomes globally.

Data Availability Statement

Data is available upon reasonable request to the corresponding author.

Ethical Approval

This study was approved by the Monash Health Human Research Ethics Committee (HREC/89481/MonH-2022-345330).

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REVIEW ARTICLE

Perioperative Care after Surgical Correction of Congenital Heart Defects in Premature Infants

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Abstract

The outcomes of premature infants with congenital heart defects following surgical correction can be improved with carefully planned and evidence-based management during the postoperative period. Many pathophysiological changes related to surgery-related tissue disruption and cardiopulmonary bypass include sodium (Na)/water overload, systemic inflammatory response syndrome (SIRS), and ischemia/reperfusion in the heart and other major organs are seen during this period. Focused intensive care is needed with close monitoring of cardiac function, tissue oxygenation, hemostasis, pain control, and sedation. There are also some center-specific needs; all care-providers need to reach a consensus on evidence-based protocols for initiation, maintenance, and weaning from assisted ventilation, which can facilitate earlier extubation and prevent ventilation-related complications. Close monitoring of the cardiac rhythm/function and the hemodynamic status can reduce critical organ dysfunction and SIRS. Measurement of specified laboratory parameters, and imaging such as chest radiography, echocardiography, and structural/functional assessment of other critical organs can help in monitoring these patients for signs of recovery. Monitoring of the sleep–wakefulness cycle, ambient noise and light control, glycemic control, monitoring of electrolytes and other metabolic parameters, feedings, nutrition, and mobilization can promote the quality of recovery. Individualized antibiotic prophylaxis may be needed based on specific defects, type of surgery, severity of illness, prior data, bacterial flora in the center, and assessments by other specialists. Finally, a checklist with clearlydefined management steps for possible needs prior to and after discharge can promote patient safety.

Keywords: Cardiac output, Cardiopulmonary bypass, Colloid, Crystalloid, Multiorgan dysfunction, Neonate, Newborn, Preload, Systemic inflammatory response syndrome, Third space.

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Key Points

- In most centers, infants born with severe congenital heart defects are evaluated for surgical management once they reach 2 kg in weight. Many of these infants are born premature/small-for-date and take some time to reach a weight/size threshold when they can sustain a major surgical procedure.
- The intra- and postoperative periods of these infants are complicated due to substantial tissue disruption due to surgical manipulation, sodium/water overload, the ensuing systemic inflammatory response syndrome (SIRS), and the suboptimal postoperative healing in various developing organs.
- The targets of pre-, intra-, and postoperative care after cardiac surgery include maintenance of cardiac function, tissue oxygenation, hemostasis, pain control, and sedation. Measurement of laboratory parameters and imaging can help in monitoring these patients for signs of recovery.
- The discharge planning should focus on normalization of sleep–wake cycle, nutrition, neurodevelopmental care, family support, communication with the primary healthcare providers, and clear plans for follow-up. Individualized antibiotic prophylaxis may be needed.
- Finally, a checklist of various needs prior to discharge and during follow-up can promote patient safety.

Introduction

In most neonatal intensive care units (NICUs), premature infants born with severe congenital heart defects (CHDs) are now evaluated for surgical management once they reach 2 kg in weight.[1]

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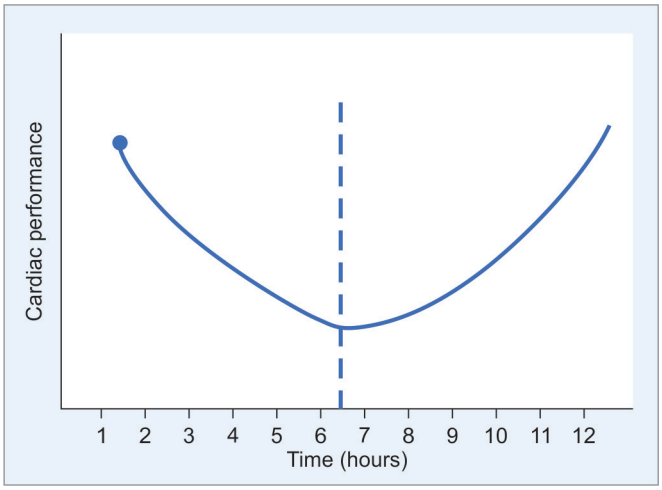

Fig. 1: Immediate postoperative period of hemodynamic instability that typically lasts 6–12 hours, but may extend up to 24 hours

Many of these infants are born very premature or are small-for-gestation and need to grow until they are more likely to sustain the surgical procedure.[2] Not surprisingly, the intra- and postoperative periods are complicated due to myocardial injury sustained during surgery, the ensuing SIRS, and the halting postoperative healing in various developing organs.[3,4] The sequelae of the intraoperative complications following cardiopulmonary bypass (CPB) and the surgical procedures can be transient or last for longer periods.[5] Understanding the pathophysiological changes during this period can facilitate prevention/timely identification and management of various systemic problems and complications.[3]

The pre-, intra-, and postoperative care of these infants is focused on (i) optimizing patient safety; (ii) timely detection and avoidance of multiorgan dysfunction; (iii) in some patients, maintenance of spontaneous breathing; (iv) supporting adequate cardiac output (CO) and end-organ O_2 delivery; (v) balancing intravascular and total body fluid volumes; (vi) ensuring pain control and patient comfort; (vii) minimize physical handling of the infant; and (viii) early initiation of enteral feeding and family-centered care.[3]

In the immediate postoperative period, the SIRS related to the CPB may lead to hemodynamic instability.[5] This period typically lasts 6–12 hours, but may extend up to 24 hours (a thematic depiction in Fig. 1).

In most patients, several factors influence the curve shown in Figure 1:[6–8]

- Severity of the underlying cardiac condition that may lead to biventricular dysfunction with multiorgan under-perfusion and SIRS;
- Intraoperative changes, including the degree of hemodilution, need for blood products, duration of aortic cross-clamping, and consequently, that of CPB, and the quality of myocardial protection;
- The results of surgical repair. Suboptimal repair and/or palliation may influence perioperative events.

The pathophysiological changes after cardiac surgery with CPB include:[9]

- *Sodium (Na)/water overload*: Fluids used for priming of the CPB circuit machine and the perioperatively administered crystalloids/colloids may change the Na/water balance.[10] Most of these fluids extravasate into the "third space" and the total intravascular volume might be relatively low.[11] Consequently, the infant may need continuous preload support to optimize the CO.[12] This increased total body fluid volume may need to be countered with generous use of diuretics, if not hemodialysis, during the recovery period in the first 24 hours after surgery.[9]
- *SIRS*: Surgical trauma and direct contact of blood-borne leukocytes to the external surfaces of the CPB circuit leads to leukocyte activation; this manifests with a SIRS with vasoplegia, coagulopathy, and multiorgan dysfunction.[13] Widespread activation of thrombin, complement, cytokines, neutrophils, mast cells, and other inflammatory mediators is typically seen in the first 12–24 hours; the SIRS might be prolonged depending on the duration of CPB. The CPB duration is a predictor of increased morbidity.[6–8]
- *Myocardial injury* may be related to the specific cardiac defect but can also be accentuated by perioperative factors such as (a) trauma caused by cardiotomy and mediastinal manipulation; and (b) ischemia and reperfusion during CPB and subsequent release of the aortic cross-clamp.[14,15] Protective countermeasures such as hypothermia and intermittent coronary perfusion with cardioplegic solutions can help to some extent.[16] The ischemia–reperfusion injury can aggravate any preexisting myocardial dysfunction during the first 12–24 hours after surgery. Based on data from adult patients, we are beginning to monitor high-sensitivity troponin levels to quantify these injuries.[17] We still need more information.[15,18,19]

Targets Of Pre-, Intra- And Postoperative Cardiac Operative Care

Adequate Oxygen (O_2) Delivery

We aim to optimize O_2 delivery (DO_2), which can be estimated as DO_2 (mL/kg/min) = CO (L/kg/min) × arterial O_2 content (CaO_2; mL O_2/dL).[20] The CO is the product of the heart rate (HR) × stroke volume (SV), whereas CaO_2 is governed by the hemoglobin (Hb) level and the arterial oxy-Hb saturation (SaO_2) and arterial O_2 tension (PaO_2) as of the following formula: $CaO_2 = (1.34 \times Hb \times SaO_2) + (0.0031 \times PaO_2)$.[21] The dissolved O_2 ($0.003 \times PaO_2$) is generally ignored, as this contributes little to the O_2 content and delivery (typically <0.3 mL/dL).[22] Clinically, the CaO_2 is estimated using the most recent Hb level and the average SpO_2 monitored continuously using a pulse oximeter. However, during surgery, when CPB is initiated, the pulse oximetry is no longer useful, as the CPB uses a continuous blood delivery instead of a pulsatile blood delivery. We usually substitute it with online continuous S_aO_2 and S_vO_2 monitoring.[21] Therapeutic targets to maintain adequate DO_2 include:

- *Hb concentrations:* The aim to keep a Hb level >12 gm/dL in first month for ventilated and >10 gm/dL for nonventilated infants

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after routine cardiac surgery with CPB. After the first month, the targets are >10 gm/dL and >8 gm/dL in ventilated and nonventilated infants, respectively.[23]

- *Hb saturations:* The accepted target of continuously monitored peripheral oxygen saturation (SpO_2) is >91% in premature and >94% for term infants in the immediate postoperative period.[24] These targets are particularly valid for those with a noncyanotic CHD. However, if the patient has had an intracardiac shunt, a Blalock–Taussig shunt, or a Glenn procedure, these values might be as low as 75–85%.[25] In cases with a single ventricle physiology, these values could be even lower. These values can be accepted if the pulmonary-systemic flow (Qp/Qs) ratio is adequate. Generally, hyper- and hypoxia should be avoided, and oxygenation limits should be individualized.

Cardiac Output

Pulmonary artery catheterization (PAC) is not possible for routine cardiac surgical assessment in most small infants. If it can be performed, intermittent or continuous assessment of CO can be obtained using PAC to stabilize the cardiac index (CI; = CO/body surface area) at ≥2 L/min/m^2.[26] Intravenous (IV) fluid therapy with or without inotropes and vasopressors can help achieve these hemodynamic targets.[22]

If PAC is not available, the CO may be estimated using surrogates of adequate O_2 delivery: (i) extremity perfusion; (ii) acid–base status; (iii) central venous oxygenation (S_cVO_2); (iv) urine output; (v) hemodynamic parameters; (vi) targeted neonatal echocardiography; (vii) point-of-care ultrasound (POCUS); (viii) near-infrared spectroscopy (NIRS); and (ix) pulse variability index.[27] When the signs of inadequate O_2 delivery are unresponsive to the standard resuscitative interventions (volume expansion and/or administration of low-dose inotropic support), POCUS, and transesophageal/transthoracic echocardiography can provide an accurate assessment of cardiac function.[28]

Hemostasis

One of the essential goals in postcardiac surgery care is ensuring balanced hemostasis. Blood loss from the chest tube output should reach <5–6 mL/kg/hour in the first postoperative hour and drop to <3–5 mL/kg/hour during the next hour.[22] High chest tube outputs may need corrections of any coagulopathy while maintaining a sufficient Hb level. If these goals are not achieved, surgical revisions might be needed. A high degree of vigilance is also needed for blood loss at other sites, such as the airways or hematuria.

In general, intensive care unit (ICU) transfers should be performed cautiously in a quiet and warm environment with care to prevent undue pain, hypothermia, and hospital-acquired infections. A judicious sedation of midazolam (0.01 mg/kg) can help. In some centers, dexmedetomidine has been found more useful as it does not suppress respiratory efforts.[27,29] The pain relief from caudal analgesia can work for about 12 hours. In our NICU, we use normo-flow nasal cannulas with flow rates of 2 L/min unless higher F_iO_2/flow rates are needed to maintain P_aO_2 >91% in premature and > 94% in term infants. Sometimes escalate the support if the F_iO_2 requirement is >40% for >30 min. Early detection of low CO is obtained by close monitoring of (i) rectal/peripheral temperature gradients (rectal probes are tolerated well); (ii) low urine output; (iii) age-appropriate mean arterial pressure; and (iv) tachycardia.[30]

Sedation

Our patients are usually sedated on arrival at the ICU. We usually plan to extubate most of these infants within 6 hours following cardiac surgery. Short-acting IV sedatives, such as dexmedetomidine, are usually used to facilitate early extubation. Intravenous sedation and analgesics with appropriate dosing for managing pain, agitation, and delirium is vital.[31]

Dexmedetomidine

It is an alpha-2 adrenergic agonist with sedative, analgesic, anxiolytic, and sympatholytic characteristics and is usually used to sedate patients after cardiac surgery.[32–34] In our hands, weaning from invasive mechanical ventilation has been possible while on sedation with small doses of dexmedetomidine infusion at about 0.2–0.4 μg/kg/hour. It causes less respiratory depression than other sedative or hypnotic agents.[35–41] However, the experience has not been the same at all ICUs.[42–45] It can cause hypotension and bradycardia at high doses, but these adverse effects are manageable.

Propofol

It is a potent IV anesthetic agent with a very short half-life and is useful when used in continuous infusions.[46] In neonates, propofol has been avoided because of the risk of severe hypotension. In more mature infants, an IV loading dose of 0.5–1 mg/kg followed with a 1–4 mg/kg/hour continuous IV infusion can be useful; the patient should be closely monitored for signs of the propofol-related infusion syndrome, which manifests with metabolic acidosis, arrhythmias, acute renal failure, rhabdomyolysis, hyperkalemia, and cardiovascular collapse.[47] Propofol has been used in children after cardiac surgery if they need longer invasive mechanical ventilation or for patients who have severe hemodynamic instability and require deeper levels of sedation. The hemodynamic side effects are minimized by using lower doses.[48,49]

Medications to Avoid

Benzodiazepines should be avoided in the postoperative care of routine cardiac surgery because of the risk of altered sensorium. This risk is higher with continuous infusions. These agents may also increase the duration of mechanical ventilation and the length of hospital stay.[50]

Analgesia

General Considerations

Multimodal pain management is a critical part of early postoperative management for cardiac surgical patients.[51–58] Both the Enhanced Recovery After Cardiac Surgery Society and the Society of Cardiovascular Anesthesiologists recommend multimodal strategies that specifically spare opioid usage. However, age-adjusted pain management plans can facilitate recovery.[51,59] In neonates, nonpharmacological measures, such as nonnutritive sucking, swaddling, or facilitated tucking, massage, and others, can be considered as a part of multimodal pain management.[58,60] Systemic nonopioid analgesics with regional and local anesthetic methods, and careful opioid use can also be helpful.[51–53,59,61–63] Multimodal pain management plans prior to, during, and after cardiac surgery may decrease the perioperative opioid needs up to 30%.[32,64,65]

Importance of Adequate Analgesia

Pain-scoring tools are used at specific periods for both ventilated and nonventilated patients to allow early identification and treatment of acute pain after cardiac surgery.[66] Failure to attain proper analgesia level may lead to some complications after cardiac surgery that include:

- *Pulmonary complications*: Respiratory splinting to protect from pain after median sternotomy or thoracotomy may cause pulmonary insufficiency and also curtail pulmonary protection mechanisms, such as mucus flow, which may predispose to pneumonia and possible reintubation.
- *Cardiovascular complications*: Pain is associated with a high sympathetic output through increased levels of circulating catecholamines. This state of high sympathetic output may lead to serious effects by increasing myocardial O_2 demand and increase the incidence of arrhythmias, such as atrial fibrillation.[64] It may also lead to hypoxemic crisis in patients with obstruction to pulmonary flow and/or pulmonary hypertension.
- *Altered sensorium*: Although giving analgesics and sedatives can lead to delirium, acute uncontrolled pain may also be an associated factor, especially in sick or frail patients.[67]
- The development of constant *postoperative pain* on the third postoperative day may increase the risk of developing persistent pain syndromes.[60,64,68]

Specific Agents and Techniques

In our ICU, we have tried to limit the use of opioids and use acetaminophen whenever possible.

Opioids

For patients with pain, an IV opioid may be needed. Fentanyl is a judicious selection as a bolus, scheduled administration, or continuous infusion.[69] It can be used in intermittent IV doses for both preterm and term neonates. The initial dose is 1–3 μg/kg/dose pushed over at least 5 minutes to avoid adverse effects such as chest rigidity. The dose may be repeated every 2–4 hours, as needed. It can also be used as a continuous IV infusion. In some infants who show signs of pain, a loading dose of 1–2 μg/kg can be given once over 5–30 minutes followed by a continuous IV infusion of 0.5–1 μg/kg/hour. This infusion range of 1–3 μg/kg/hour is then titrated to achieve the desired effect. The typical maximum dose is 50 μg/dose; however, a higher maximum dose of 100 μg/dose can sometimes be used in critically ill patients in the PICU/NICU.[3]

After extubation, oral opioids like morphine may also be useful. Judicious opioid use can help minimize or avoid prolonged intubation due to excessive sedation and respiratory depression.[54,70,71] Altered gut motility is less frequent in young infants, but ileus can still be seen when high doses are used for prolonged periods, but this is not seen very often in infants.[52,56,71–76]

Nonopioid Systemic Analgesics

These agents may be considered during and after cardiac surgery; they include dexmedetomidine, acetaminophen, ketamine, and others.[32,51–53,62,63,77]

Dexmedetomidine

See above.

Acetaminophen

It is used in preterm infants of 28–32 weeks' gestation.[78] The usual oral dose is 10–15 mg/kg/dose every 6–12 hours as needed for a maximum daily dose of 40 mg/kg/day. For those with gestational age of 33–36 weeks or term newborn babies <10 days of age, 10–15 mg/kg/dose can be given orally every 6–8 hours with a maximum daily dose of 60 mg/kg/day. In term newborns older than 9 days of postnatal age, an oral dose of 10–15 mg/kg/dose can be given every 4–6 hours. A maximum of 5 doses in 24 hours or 75 mg/kg/day should not be exceeded.[79]

The use of opioids, expressed as morphine equivalents, in the first 24 hours after surgery is typically lower in those receiving acetaminophen. The IV is administered at 7.5–15 mg/kg/dose every 6 hours with a maximum daily dose of 60 mg/kg/day. For rectal use, a loading dose of 40 mg/kg for one dose is administered after surgery. A maintenance dose of 20–25 mg/kg/dose every 6 hours, as needed, for 2–3 days has been suggested if further pain control is required postoperatively. A maximum daily dose of 100 mg/kg/day should not exceed 4,000 mg/day; durations of longer than 5 days have not been evaluated.[80–83]

Other Agents

Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually avoided because of cardiovascular and renal adverse effects.[63,84,85] However, this effect is rarely clinically relevant in those with normal postsurgical renal function.[75,86–88] If a patient has a persistent pain refractory to opioids and acetaminophen, the NSAIDs can be added, for their cyclooxygenase (COX)-1 and COX-2 effects, to limit the duration of pain in some patients with acceptable renal function and without a substantial risk of bleeding or acute kidney injury.[84,89–93]

Clinical Management

Imaging Considerations

A chest X-ray is requested shortly after arrival to the ICU to ascertain the correct position of the endotracheal tube and of the vascular line tip; in addition, the images can help check for lung pathology like pulmonary edema, atelectasis, or pneumothorax. Bedside POCUS lung can be used to assess the possibilities of pneumothorax, atelectasis, pneumonia, pulmonary embolism, diaphragmatic excursion abnormalities, pulmonary effusion, hemothorax, and other postsurgical problems.[94]

Implementing Mechanical Ventilation

Setting a target fraction of inspired oxygen concentration (FiO_2) is based on saturation targets in the operating room, during transport, and on arrival to the ICU, and is then adjusted as necessary to aim for desired tidal volumes and $PaCO_2$ levels. Continuously monitoring transcutaneous or end-tidal carbon dioxide ($EtCO_2$) can be helpful per the preference/experience of the staff. Intermittent arterial blood gases to assess arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), and acid–base status can help evaluate the ventilatory status of the patients. Implementing lung-protective ventilation strategy in continuation with the intraoperative management may reduce the incidence of postsurgical pulmonary complications:[95,96] (i) low tidal volume (V_T) of 3.5–6 mL/kg working body weight; (ii) respiratory rate (RR) 20–60/minute then adjusted depending on $EtCO_2$ monitoring and $PaCO_2$ in blood gas; (iii) positive end-expiratory pressure (PEEP) of 5–8 cm H_2O; (iv) implementation of higher PEEP levels may help improve oxygenation in some patients with pulmonary edema or altered lung mechanics, but we need to be cautious to not compromise the right ventricle preload; (v) plateau pressure (PP) maintained at <20 cm H_2O with adjustments of V_T, (vi) controlling flow, pressure, and volume graphics; (vii) watching important loop dynamics; (viii) use of noninvasive blood gas monitoring might be useful; and (ix) low driving pressure or delta wave (PP-PEEP) at <15 cm H_2O.

Weaning from Mechanical Ventilation

After a cardiac surgical procedure, based on the experience in the ICU, the infant should be carefully evaluated/monitored for

extubation and conversion to nasal intermittent positive-pressure ventilation.[51,65,97–99] Prolonged ventilation is associated with increased morbidity, mortality, and cost.[95,99] To facilitate early extubation, appropriate pre- and intraoperative management strategies are continued in the postoperative period, which may include (i) multimodal opioid-sparing pain management; (ii) limited use of benzodiazepines; (iii) reversal of neuromuscular blocking agents at the end of the procedure; (iv) use of lung-protective ventilation; (v) temperature control; (vi) ensuring hemostasis; (vii) careful fluid management; (viii) use of corticosteroids; and (ix) observation for signs of abstinence syndrome when high opioid doses were used.

Reversal of Residual Neuromuscular Blockade

It is advisable to avoid rapid reversal of residual neuromuscular blockade before the patient has been rewarmed to more than 36°C as this might lead to increased O_2 consumption.

Neostigmine: It is used to reverse the nondepolarizing neuromuscular blockade in postsurgical periods.[100] Once rewarming is complete, the neuromuscular blockade can be reversed in a combination with glycopyrrolate or sugammadex.[100,101] In the neonatal period, a dose of 0.03–0.07 mg/kg can be useful. The maximum cumulative dose of neostigmine is 0.07 mg/kg. Furthermore, a 0.03 mg/kg dose can typically reverse the shorter half-life neuromuscular blocking agents (NMBAs) such as rocuronium. However, a 0.07 mg/kg dose is advisable for longer half-life NMBAs such as vecuronium and pancuronium.[102]

Glycopyrrolate: In newborn infants, a single IV dose of 4–10 μg/kg is acceptable, but it is not the preferred vagolytic. An IV dose of 0.2 mg for each 1 mg of neostigmine or 5 mg of pyridostigmine is advisable.[103]

Sugammadex: Dosing is based on body weight to reverse rocuronium- or vecuronium-induced blockade. For a moderate degree of neuromuscular block, a single IV bolus of 2 mg/kg over 10 seconds can help achieve reversal.

Once the patient is active, weaning from invasive mechanical ventilation is initiated. Rewarming and early extubation strategies are associated with better outcomes.[27] Patients with preoperative hypoxemia or severe chronic obstructive lung disease problems may need a high-flow nasal cannula or noninvasive ventilation after extubation for a certain period of time.[103,104]

Hemodynamic Management

Circulatory Support

Inotropic support and vasoactive therapy, including inotropes, vasopressors, and vasodilators are frequently used during postcardiac surgical care to support left ventricular (LV) and/or right ventricular (RV) function, especially in the initial 6–12 hours postbypass period. These medications are then weaned if the hemodynamic parameters are maintained. The selection of inotropic and vasoactive medications and their doses can be changed as indicated. Once the pathophysiological changes related to CPB and due to low CO are resolved, these agents can be weaned off.[105,106]

Mechanical Circulatory Support

Postcardiotomy cardiogenic shock occurs in 0.2–6% patients after open-heart surgery.[107,108] Temporary mechanical circulatory support, such as with an intra-aortic balloon pump counter-pulsation, percutaneous or implantable ventricular assist devices, or extracorporeal membrane oxygenation (ECMO), can be used for support if there is refractory ventricular dysfunction with persistently low CO.[102] These devices are typically inserted in the intraoperative postbypass period. The selection of a circulatory-assist device depends on the hemodynamic factors of the patient, surgical preferences, and institutional resources. Some patients may need ECMO.

Management of Arrhythmias

Normal sinus rhythm is needed to maintain optimal CO. This rhythm ensures sufficient blood filling by providing an atrial contribution to a synchronized ventricular contraction. The management of postoperative arrhythmias begins with assessment and correction of reversible causes, such as hyperthermia, electrolyte imbalance, inadequate doses or type of inotropes, and hypovolemia. Early use of a beta-blocker might be a strategic intervention. Metoprolol is administered with an immediate IV dose of 0.1–0.2 mg/kg with a maximum dose of 10 mg/dose. The long-term treatment is usually provided with an enteral dose of immediate-release (metoprolol tartrate) at 0.5–1 mg/kg/dose twice daily with a maximum daily dose of 6 mg/kg/day on postoperative day 1 or as soon as the hemodynamics are normalized. Subsequent doses are titrated upward to achieve a heart rate between 70 and 90 beats per minute while maintaining adequate CO and blood pressure (BP).

Management of Cardiac Arrest

Cardiac arrest may occur at any time after cardiac surgery, although most occurrences are seen in the first 5 postoperative hours.[109,110] The incidence was 0.7% in the first 24 hours after surgery in one series of nearly 4,000 patients.[109] Causes include myocardial ischemia, significant bleeding, cardiac dysfunction such as with cardiac tamponade or tension pneumothorax, and arrhythmias such as ventricular fibrillation, pulseless ventricular tachycardia, or loss of temporary pacemaker capture in a pacer-dependent patient.[109,111,112] In the first few hours after CPB, most of these causes are reversible. There are critical differences in the management of cardiac arrest in the intraoperative or ICU setting after open cardiac surgical procedures compared with standard pediatric advanced cardiac life support (PACLS) management protocols: (i) external cardiac compressions are not initiated immediately due to concern for the disruption of the surgical repair. However, this depends on the institutional practice and the seriousness of the situation; (ii) administration of a full standard PACLS dose of epinephrine is avoided, since this may lead to extremely high BPs that could disrupt arterial suture lines. Instead, only half of the usual doses of epinephrine may be administered with continuous reassessment; (iii) administration of atropine for asystole or severe bradycardia is avoided. Instead, pacing is initiated. All patients returning to the ICU after cardiac surgery should have pacemaker cables for rapid initiation of pacing if needed.

The following specific management strategies are employed; these have been adapted from adult postcardiac care.[113] If VF or pulseless VT is identified, three successive defibrillation shocks should be administered. Defibrillation has a success rate of 78% after the first shock compared with 35% and 14% after the second and third shocks, respectively.[111] Amiodarone (5 mg/kg) has been used with a rapid bolus followed by two repeated doses to a maximum total dose of 15 mg/kg during acute treatment.

If asystole or severe bradycardia is identified, pacing is initiated. The pacemaker is set for dual chamber pacing (DDD mode at 80–120 bpm at a max output voltage of 20 milliamps atrial and 25 milliamps ventricle.[113] If a pulseless electrical activity (PEA) is noted, the pacing is interrupted to ensure the underlying rhythm is not VF. If PEA is confirmed, proceed with external cardiac compressions while opening the chest as described below. If VF, VT, asystole, severe bradycardia, or PEA is present and unresponsive to initial defibrillation or pacing after 1 minute, the management must escalate as follows: (i) initiate external cardiac compressions while the chest is opened through the existing fresh sternotomy as expeditiously as possible (within 5 minutes); (ii) during manual cardiac massage, mechanical ventilation and sedation medications are discontinued, and manual bag ventilation is employed, using a fraction of inspired oxygen (FiO_2) set at 1.0 and a rate of two breaths for every 30 compressions; (iii) administer epinephrine boluses at half doses rather than standard PALS doses, which may lead to extremely high BP that could disrupt arterial suture lines after restoration of spontaneous circulation.[111]

If the chest needs to be re-opened for any reason, we (a) initiate two-handed internal cardiac massage at the rate of 100–120 bpm. The two-handed internal cardiac massage technique involves pressing the heart like a pancake with two flattened hands and straightened fingers to avoid pushing a thumb into an atrial chamber.[113] In patients with an intra-atrial BP (IABP) monitoring device in place, the triggering mode may be switched during cardiac massage from the use of the electrocardiogram to the arterial pressure tracing; (b) use internal defibrillation at 2 J/kg in the first attempt, then at 4 J/kg in the second attempt, then at 4 J/kg or higher in the subsequent attempts until a max dose 10 J/kg, or adult maximum (200 J, biphasic; 360 J monophasic); and (c) continue resuscitation with internal cardiac massage, epinephrine, internal defibrillation, and/or pacing as indicated until the heart restarts contracting or until resuscitation efforts are terminated due to futility.

Detection and Management of Altered Sensorium or Stroke

Altered Sensorium

Screening for postoperative altered sensorium should be part of standard postoperative orders after neonatal and pediatric cardiac surgery.[49,50] Increased risk of delirium occurs in patients with risk factors such as frailty or obstructive sleep apnea.[110,114,115] Both pharmacological and nonpharmacological analgesia is used as the first-line treatment for both prevention and treatment of delirium.[56] These include: (i) standardized sensory inputs with hearing aids, glasses, music, and others; (ii) cognitive stimulation; (iii) encouraging sleep–wakefulness cycles; (iv) adequate hydration and nutrition; (vi) investigating known treatable causes of altered sensorium such as pain or medications, medication withdrawal, and some superimposed medical conditions.

Pharmacologic interventions, such as with dexmedetomidine, quetiapine, olanzapine, and haloperidol, may be used in some centers for selected patients.[52,114]

Stroke

Asymptomatic stroke is more common in adults than infants after cardiac surgery.[116] The management of acute ischemic stroke occurring in the postoperative period after cardiac surgery is not very different between adult and pediatric patients. The management may include endovascular thrombectomy and/or intra-arterial thrombolysis.[117]

Glycemic Control

We maintain blood sugar (BS) level in the range of 4–8 mmol/L (74–144 mg/dL) using a continuous IV insulin and/or dextrose infusion with nomogram(s) based on frequent (hourly) BS assessment. There is no difference in glycemic control between the postbypass period during cardiac surgery and other critical care periods.[118] Poor glycemic control around the surgery can lead to increased morbidity and mortality.[119,120]

Hyperglycemia is frequently seen during and after CPB. Many infants develop stress-induced hyperglycemia and may need insulin therapy.[121] A dose of 0.1–0.2 units/kg is given and then titrated to maintain plasma glucose levels. There should be clear hyperglycemia and hypoglycemia protocols for newborns and infants.

Others

These patients have a high severity of illness and need close monitoring for specific organ failure such as kidney and liver. Some infants need mineralocorticoids to support BP and Na/potassium balance. In our experience, the overall fluid/electrolyte needs have to be individualized. Monitoring central and peripheral body temperatures is also a key component of intensive care. In addition to continuous observation by neonatologists, pediatric intensive care specialists, cardiologists, cardiac surgeons, and anesthesiologists, we include many other services, such as pulmonologists, nephrologists, hematologists, pain control, respiratory services, occupational and physical therapists, and social work. Some families have also requested for religious support.

Diet and Feeding

There are unit-based protocols for starting enteral diets in clinically stable patients prior to or after extubation. In newborns, minimal enteral feeding could possibly help in preventing fasting gastropathy. Although hemodynamic instability, with or without the need for significant vasopressor support, has been regarded as a contraindication to enteral feeding, newer protocols are more permissive and encourage feedings in euvolemic patients with good tissue perfusion.[122] If a patient cannot tolerate enteral feedings, oral immune therapy can be started at 0.2 mL every 2–4 hours of expressed mother's own or donor breast milk at both angles of the mouth. If human milk is not available, a term (20 kCal) formula can be used. We have also used a semi-elemental formula in selected patients. Feeding protocols have helped. If the decision or the conditions might affect enteral feedings for ≥3 days, then it is preferred that the total parenteral nutrition be initiated.

In our own NICU, we have been relatively conservative in starting enteral nutrition; most patients are still started within 24–36 hours on partial or total parenteral nutrition to prevent a catabolic state.[121] We have been reluctant in feeding infants with instability of vital signs, those who are being treated with narcotics or inotropes, or have abdominal distension, vomiting, or prefeeding residuals ≥25%. An indirect assessment of bowel perfusion can also help in these decisions; we avoid feeding infants with hypotension, tachycardia, urine output <1 mL/kg/hour, delayed capillary refill time, or sluggish/negative bowel sounds. Serum lactate levels should be closely monitored before starting oral feeding. Bowel

ultrasound examination and ancillary diagnostic detectors of bowel perfusion such as NIRS of the mesenteric area and Doppler of the splanchnic and mesentery artery can help.[80,81,83]

Mobilization

Many ICUs initiate movements along an active range of motion with help from physiotherapy services. This is an extension of the perceived benefits in critically ill older patients; further studies are needed for infants.[123] After prolonged sedation, young infants may begin to show adverse effects such as decreased circulating blood volume, loss of muscle mass, insulin resistance, and altered sleep patterns.[39] Repositioning infants every 4–6 hours after the surgical procedure may help.

Neurophysiological Developmental Care

In older patients, sleep regulation is believed to improve recovery, decrease pain, and reduce admission time. Studies are needed in infants. Sound control down to <70–90 decibels are advisable. Use of ear plugs or adapting soft music or recorded maternal heartbeats are used in some centers. Similarly, control of ambient light to mimic the diurnal cycle can promote physiological sleep patterns. Covering of the incubator or using dark eye googles are additional measures used in some units. Clustering of monitoring/care interventions to minimize handling of these infants to four to six times per day is advisable. Using a nest bed, safe coverings, and swaddling may increase contented relaxed sleep. Use of pain scoring scales and increasing pleasant stimuli, such as the presence of parents, sucrose suck, use of pacifiers, and use of safety space around the bed, can need for analgesics/sedation, improve sleep patterns, weight gain, and neurophysiological development.[124]

Venous Thromboembolism Prophylaxis

Children and adolescent patients who have undergone cardiac surgery show a moderate risk of venous thromboembolism due to the duration of intra-/postoperative immobility.[122] The risk is lower in infants, but we still need careful studies to detect cerebral and pulmonary thromboembolism that might not be clinically obvious. In young infants with CHDs who have received high-risk central venous lines; undergone procedures for diversion of systemic blood flow to the pulmonary artery such as a Sano shunt, Blalock–Taussig shunt, central shunts; or those who have a known hypercoagulable state or a history of previous thrombosis, thromboprophylaxis is achieved in the neonatal period by a continuous IV heparin infusion at 10–15 units/kg/hour, and this low dose is advisable in infants too. There is some variation in existing guidelines and institutional protocols for pharmacologic prophylaxis after cardiac surgery.[39,125]

Criteria for Discharge from ICUs [NICU/Pediatric ICU (PICU)]

In the postoperative period, we focus on early extubation after a few hours, prevention and treatment of nausea and vomiting, pain control, maintenance of sleep–wake cycle, delirium screening, early initiation of movements, and prompt and adequate provision of nutrition. Invasive monitors and urinary catheters are removed as soon as possible, even on the first postoperative day. Although institutional practices vary, pleural and mediastinal drains are typically removed if output is <100 mL in an 8-hour shift for two shifts. If the criteria are met, most patients who have undergone cardiac surgery can be transferred to a lower level of monitored care. Risk factors for re-admission to the ICU include low LV ejection fraction, renal failure, surgical re-exploration for bleeding, and need for controlled ventilation, and a catabolic state.[31,126]

Antibiotics Prophylaxis

Antibiotic selection should be based on the type of cardiac procedure and the phase of care. Antibiotic dosing should follow guidelines based on age and phase of care in addition to the result of cultures and the consultation with pediatric ID. For surgical procedures performed in the ICU, antibiotic prophylaxis should be selected based on the pre-/intraoperative recommendations.[126–128] Even if the patient is already receiving antimicrobials for postoperative prophylaxis from another procedure, appropriate antibiotic prophylaxis should be re-dosed before a new procedure. For instance, if a patient undergoes chest closure in the unit, cefazolin should be given within 60 minutes prior to the procedure unless the previous dose was given within the intraoperative re-dosing interval (4 hours). The duration of prophylaxis should be limited, generally to 48 to 72 hours regardless of the presence of line or drains. However, gestational age and postnatal age should be considered while making the decision. Antibiotic allergies are fortunately uncommon in infants. If needed, the team should refer to the inpatient beta-lactam allergy guidelines. Many patients with beta-lactam allergy can tolerate cefazolin, which provides more effective surgical-site infection prophylaxis than vancomycin. For those with a history of colonization/infection with methicillin-resistant *Staphylococcus aureus*, vancomycin should be added to the prophylaxis regimen.[126–128]

Long-term Monitoring of Growth and Development

Neonate and infants who undergo cardiac surgery for CHD may have several long-term neurodevelopmental consequences.[127] These may include:

- Many children with complex CHD experience neuro-developmental and psychosocial impairments that impact their quality of life. This can include cognitive, motor, and language delays.
- Brain insults are common, particularly in the frontal and temporoparietal white matter regions in newborns and infants during and after cardiac surgery.
- Children who have undergone cardiac surgery may have lower cognitive and motor functions, in addition to potential language and learning problems.
- During adolescence, many of these children require educational and psychosocial services to support their development.
- These neurodevelopmental impairments can persist into adulthood, which may affect educational achievements, employment, and the overall quality of life.

Early detection and intervention are vital for improving outcomes. Multidisciplinary follow-up plans, including regular neuromotor and psychological evaluations, can help address these issues.[127]

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REVIEW ARTICLE

Epigenetic Regulation of Macrophage Polarization

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Abstract

Increasing data shows that macrophages, the primary immune cells in the growing fetus/neonate, retain an innate immune memory of prior stimuli. This memory is rooted in epigenetic regulation of lineage- and tissue-specific transcription either to enhance the responses or to induce tolerance to repeated exposures to a stimulus. As we understand, epigenetics refers to the study of heritable information transmitted during cell divisions that can alter gene expression via inclusion of chemical tags but no changes in the DNA sequence. We now recognize the lineage-determining transcription factors as important mediators that can make the local chromatin more accessible to other factors; one example is the erythroblast transformation-specific gene PU.1 (purine-rich sequence binding protein 1). The PU.1 can upregulate the basal activation state of many promoters by increasing histone H3 lysine 4 trimethylation (H3K4me3). There are several other newly discovered regulators that perform similar regulatory roles. These mediators enhance macrophage differentiation into several phenotypes essential for host defense or tissue homeostasis in response to environmental stimuli. The two ends of this polarization spectrum include the classically-activated (M1) macrophages induced by interferon-γ and microbial products; and the alternatively-activated (M2) macrophages induced by the T-helper 2 cytokines interleukin (IL)-4 and IL-13. The M1 macrophages participate in host defense and clearing pathogens, whereas all the known subtypes of M2 cells promote resolution of inflammation and tissue repair. Maladaptive changes in macrophages can disrupt the normal sequence of immune/inflammatory responses and predispose to disease states. The review summarizes our current understanding of the involved mechanisms; this information can help understand the immune responses in neonates who are yet to develop mature neutrophil function or adaptive immunity and are largely dependent on mononuclear cells for immune defenses.

Keywords: Epigenetics, Hematopoiesis, Hematopoietic stem cells, Infant, Lineage-determining transcription factors, Macrophages, Macrophage polarization states, Monocytes, Neonate, Newborn.

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Key Points

- Epigenetics is the study of stable, heritable changes in gene expression that involve chemical modifications but not in the actual sequence of nucleotides. Some mechanisms include DNA methylation, interaction with noncoding RNAs, and posttranslational modification of histones.
- Tissue-resident macrophages are derived from the yolk sac progenitors and hepatic/bone marrow-derived monocytes. Emerging data show several subpopulations with varying effects; the differentiation of these subgroups likely involves epigenetic changes.
- Gene loci relevant for polarized macrophage phenotypes exist in repressed, poised, and active subgroups.
- The purine-rich sequence binding protein 1 (PU.1) plays a key role in the differentiation of macrophage lineages. Several downstream genetic and epigenetic mechanisms have been defined.
- Changes in macrophages can cause a broad spectrum of maladaptive immunity and inflammation that are causative factors of disease and, thus, represent key therapeutic targets.

Macrophage Development and Polarization

Origin of Macrophages

In the embryo, macrophages arise from multiple progenitors: (a) primary committed lineages independent of the transcription factor cellular factor Myb or the erythromyeloid progenitors in the yolk sac (YS); (b) those in the aorta-gonad-mesonephros zone;

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and (c) the hematopoietic stem cells in the liver and the bone marrow.[1–4] A late c-Myb-dependent wave generated in the fetal liver and the bone marrow produces multiple hematopoietic lineages, including monocytic intermediates throughout life; these include microglia in the brain, Kupffer cells in the liver, osteoclasts in the bones, and other tissue-resident macrophages and dendritic cells (DC).[5–7] During hematopoiesis, a multipotent stem cell again branches out to various tissues.[8] Unlike the monocyte-derived macrophages (MDMs), tissue macrophages originating from the YS have some self-regenerating properties.[9]

Resident macrophages in various tissues express specific genes following integration of transcriptional and epigenetic regulators. The MDMs are derived from circulating monocytes that migrate into tissues and express signal-specific genes during differentiation. Minor epigenetic modifications can happen with environmental changes such as those seen during infections; these cells can eliminate pathogens and restore tissue integrity.[10,11] In MDMs, epigenetic changes are coordinated by myeloid lineage- and tissue-specific transcription factors. There are many "topologically-associated domains (TADs)" where DNA looping can promote the interaction of genes with *cis*-acting regulatory elements; a protein ring consisting of cohesin can bind a DNA-binding protein called CTCF (CCCTC-binding factor) to establish TAD boundaries.[12] The circumscribed regions contain relatively stable chromatin loops, which can prevent/interrupt enhancer-promoter contacts.[13–17] Many embryonic cells contain TADs marked by repressive histone modifications such as histone H3 lysine 27 trimethylation (H3K27me3).[18–20] Some TADs correspond to nuclear lamina-associated domains.[21]

In various tissues, macrophages are enriched for DNA binding sites for local enhancers and recognition motifs for the corresponding transcription factors.[22] Lineage-determining transcription factors or pioneer factors/master regulators can open the local chromatin to merge with other factors.[23] One example is the ETS (erythroblast transformation specific; a conserved DNA-binding domain in specific proteins to bind to DNA) family member PU.1 (purine-rich sequence binding protein 1), which is associated with the basal activation state and trimethylation of histone H3 lysine 4 (H3K4me3) of many promoters. It occupies most macrophage enhancers to maintain H3K4me1 and activates many cell-specific enhancer-like elements.[24] The PU.1 also interacts with macrophage-specific enhancers and increases chromatin accessibility by binding the CCAAT/enhancer binding proteins (C/EBP), interferon regulatory factor (IRF), nuclear factor kappa B (NF-κB), and the activator protein-1 (AP-1).[25] It increases nucleosome remodeling and histone modifications to prime DNA, leading to differential activation of enhancers in response to H3K4 monomethylation at different places in the genome.[24] The binding of secondary signal-dependent transcription factors establishes tissue-specific enhancers and regulates gene expression.[26]

Monocyte-to-macrophage Transition under Stimulation

The MDMs are seen in the fetal/neonatal intestine in larger numbers in some tissues, such as the intestine and skin. In these organs, monocytes are viewed as an intermediate developmental stage between bone marrow precursors and tissue macrophages.[27] In addition, blood monocytes migrate to inflammatory tissues and differentiate into MDMs that can restore tissue integrity and eliminate the pathogen.

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Initial Inflammatory Activation of MDMs

Toll-like receptor (TLR) ligands, such as LPS, and Th1 cytokines, including IFN-γ, elicit M1 activation alone or in combination and can affect epigenetic processes and lead to epigenetic modifications.[28] TLR4 and analogous receptors are key sensors in the M1 response that triggers inflammation through mitogen-activated protein kinase (MAPK), NF-κB, and IRF gene networks, which have downstream genes that encode inflammatory cytokines, such as CXCL10, IL-1β, IL-6, IL-12, p40, and tumor necrosis factor (TNF).

Epigenetic Regulation of Macrophage Polarization

Macrophages show several polarized phenotypes. Increasing information suggests that these are largely rooted in epigenetic differences, which explains the plasticity in transition between cellular programs.[2] This polarization involves exposure to microbial flora, host cytokines, and other environmental cues; which alter the interaction among transcription factors, DNA, and downstream signaling pathways.[29–32] The determinants of the epigenetic landscape include DNA methylation, three-dimensional changes in chromatin, and proteins bound to gene regulatory promoters and enhancers; these changes regulate gene expression and functional outcomes.[33] The differences in the chromatin structure can alter its accessibility and consequent genomic localization of "signaling transcription factors," such as NF-κB and the STATs (signal transducer and activator of transcription).[34,35] These structural changes can get remodeled following further exposure to polarizing stimuli, and thereby recalibrate the responses to successive stimuli.

Polarizing Factors and Macrophage Phenotypes

Macrophage polarization states (Table 1) are defined by the inducing stimulus and by the ensuing patterns of gene expression, which determine function.[36–39] A variety of activation states are being defined (Fig. 1). Infection or tissue injury activates macrophage host defense functions like microbial killing and production of cytokines and chemokines.[36–39] This is one end of the activation spectrum, labeled as the classical activation (also termed M1) and is induced by interferon (IFN)-γ and microbial products such as TLR ligands. An alternative activation state (M2) is induced by the T-helper (Th)2 cytokines interleukin (IL)-4 and IL-13.[36,37,40]

The M1 or classically-activated macrophages, are proinflammatory cells. These are characterized by efficient antigen presentation, high bactericidal activity, and the production of proinflammatory cytokines and reactive oxygen and nitrogen species.[41]

The M2 or alternatively-activated macrophages, have immunoregulatory functions. These cells express anti-inflammatory cytokines and are not as effective as M1 cells in the production of proinflammatory cytokines and antigen presentation. These cells are primarily regulatory, and promote tissue remodeling, wound healing, angiogenesis, antihelminth responses, and possibly, atopy. In premature and term neonates, macrophages show relatively

Table 1: Differences between M1 and M2 polarization states

M1	*M2*
M1-like macrophages (induced by IFNs, granulocyte macrophage colony-stimulating factor (GM-CSF), lipopolysaccharide (LPS), and other microbial products) are potent microbial killers, generate inflammatory cytokines, but may lead to toxicity and collateral tissue damage.	M2-related macrophages (induced by IL-4/13, IL-10, transforming growth factor (TGF)-β, glucocorticoids, and immune complexes) promote tissue function under physiological conditions, preserve function during times of stress, restrain and resolve inflammation after infection or injury, and promote repair and wound healing.
Core aspects of M1 macrophages are high expression of major M1 effector molecules like TNF, IL-1 and IL-12, antimicrobial molecules, reactive oxygen/nitrogen intermediates, and IFN-induced genes-Th1-recruiting chemokines CXCL9 (C-X-C motif chemokine ligand 9) and CXCL10 (C-X-C motif chemokine ligand 10).	Core aspects of M2 macrophages are expression of scavenger receptors, growth factors (heparin binding epidermal growth factor and insulin-like growth factor), Th2 chemokines (CCL18 and CCL22), and suppressors of inflammation and immunity like IL-10 and indoleamine 2,3-dioxygenase.[39] Macrophage colony-stimulating factor (M-CSF) shows a predisposition to an M2 phenotype, resulting in suppression of inflammatory activation and inappropriate responses to innocuous stressors.[44,45]

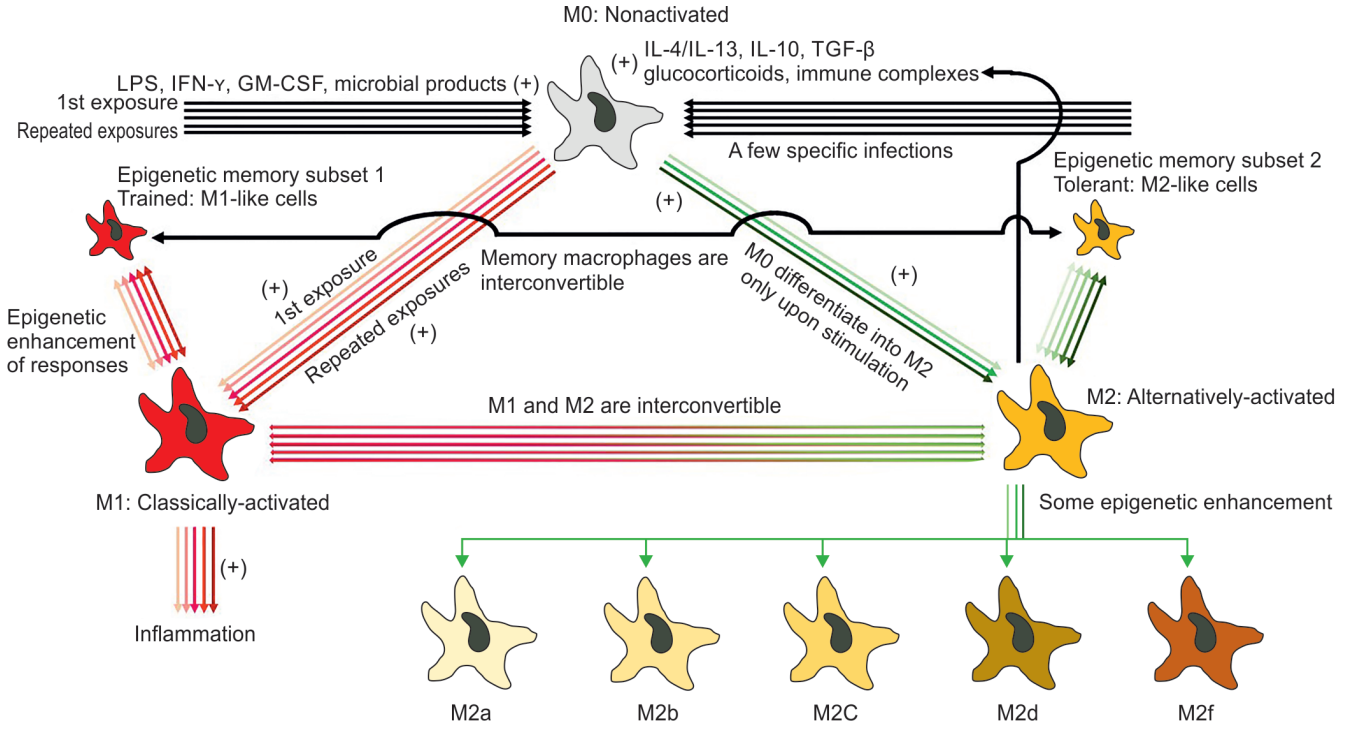


Fig. 1: Differentiation of MDMs. The neonatal immune system shows an inflammatory bias as compared with adults, with a predominance of the M1 lineage and a relative immaturity of anti-inflammatory systems. Repeated stimulation with stimuli such as TLR agonists leads to epigenetic enhancement and progressive amplification of the innate immune/inflammatory responses. The figure shows macrophages differentiating in the categories M0 (gray), M1 (deep red), and M2 (amber). The deepening of shades in the arrows in M0 to M1, M1 to memory M1, and the inflammatory responses shows progressive amplification of these responses with multiple exposures. Single- vs double-headed arrows show unilateral or reversible responses. Fewer arrows in the M0 to M2 differentiation (green) shows that such differentiation is relatively limited in infants. The smaller size of the memory macrophages is a graphic representation of the smaller number in these cohorts, and not a morphological difference. M with added letters show the categories of macrophages. [Some components of the figure were adapted with permission from *Maheshwari A. Innate immune memory in macrophages. Newborn 2023;2(1):60–79*]

strong M1 profile, which predisposes them to conditions such as necrotizing enterocolitis.[42,43]

Subtypes of M2 Macrophages[4]

M2 macrophages are a relatively heterogeneous group, comprising of five subcategories with distinct inflammatory functions and physiological roles (M2a, M2b, M2c, M2d, and M2f (Fig. 1 and Table 2).[4] M2a are activated by the cytokines IL-4 and IL-13, and regulate the expression of platelet-derived growth factor-BB and TGF-β. These cells support pericyte and smooth muscle differentiation. Upon activation by immune complexes, IL-1β, pathogen-associated molecular patterns (PAMPs), and TLR ligands, these cells express inflammatory cytokines (IL-1, IL-6, and TNF), and anti-inflammatory IL-10.[46–48] They are involved in altered regulation of the PI3K/Akt/ FoxO3a pathway.[49] M2c macrophages are activated by IL-10, TGF-β, and glucocorticoids.[50] They express MMPs and IL-10, TGF-β, and pentraxin-3.[50,51] They are involved in vascular remodelling.[52] M2d macrophages are activated by TLR agonists and adenosine A2A receptor agonists.[53,54] They suppress inflammatory responses.[55] They regulate the expression of IL-10

Table 2: Macrophage subpopulations

Macrophage subpopulation	*Activation*	*Function*	*Biological processes*
M0 (naïve, unstimulated macrophages)			
M1 (classically activated, inflammatory macrophages)			
	• Activated by LPS and IFN-γ. • Macrophage-produced inducible nitric oxide synthase.[52] • Macrophage-produced IL-12, IL-18, and IL-2.[59] • GM-CSF.	• Proinflammatory, antimicrobial. • Regulate angiogenesis.[52,60,61]	• Activate Tie-signaling.[58] • Promote endothelial cell chemotaxis, and cell migration in angiogenesis.[62]
Innate immune memory (IIM) macrophages			
Trained (M1-like)	• Epigenetic reprogramming, especially histone modification.[63] • After stimulation, H3K4me1 levels and the binding of TFs increase at latent enhancers. • Increased H3K4me3 at promoters of innate immunity genes.	• Memory of previous infections, which can rapidly recruit and activate innate immune cells.[10] • Rapid induction of inflammatory mediators upon secondary infections with pathogenic bacteria and *Candida* spp.[64]	• Host defense. Particularly important in neonates and young infants before adaptive immunity becomes functionally adequate.[65]
Tolerized (M2-like)	• Including nucleosome remodeling, the reduced recruitment of transcription factors and chromatin remodeling complexes, and histone modification. • NF-κB-associated inhibitory mechanisms.	• Memory of previous infections; can suppress unduly severe inflammatory responses.[66]	• Host protection. May protect young infants, who are still developing adaptive responses, from severe tissue damage.[66]
M2 (alternatively-activated/immunoregulatory, anti-inflammatory, prohealing macrophages)			
M2a	• Cytokines, IL-4, and IL-13.[39]	• Regulate the expression of platelet-derived growth factor-BB and TGF-β.[52]	• Support pericyte and smooth muscle cell differentiation.[58]
M2b	• Immune complexes, IL-1β, and molecules with PAMs. • Immune complexes and TLR ligands.[56]	• Express inflammatory cytokines (IL-1, IL-6, and TNF), and anti-inflammatory IL-10.[48]	Altered regulation of the PI3K/Akt/FoxO3a pathway.[49]
M2c	• IL-10, TGF-β, and glucocorticoids.[50]	• Express MMPs. • Express IL-10, TGF-β, and pentraxin-3.[51]	• Vascular remodeling.[52]
M2d	• TLR agonists. • adenosine A2A receptor agonists.[54]	• Suppress inflammatory responses.[55]	• Regulate the expression of IL-10 and VEGF.[56]
M2f	• Phagocytosis of apoptotic cells.[57] • Upregulate TGF-β_1.[58]	• Express anti-inflammatory mediators.[58]	• Regulate vascular permeability.[58]

[adapted with permission from *Maheshwari A. Innate immune memory in macrophages. Newborn 2023;2(1):60–79*]

and vascular endothelial growth factor (VEGF).[56] M2f macrophages are activated by phagocytosis of apoptotic cells and upregulate TGF-β1.[57,58] They express anti-inflammatory mediators and regulate vascular permeability.[58]

Macrophage Polarization States

Epigenetic changes are paramount to initial inflammatory activation (M1) by TLRs, induction of an IFN response by the microbiome, or LPS; transition from an M1 to a tolerant/M2-like phenotype or to a tolerant DC phenotype after TLR or TNF stimulation; inhibition by IL-10; M2 polarization by M-CSF and IL-4; and/or polarization toward the osteoclast pathway by RANKL (receptor activator of NF-κB ligand).[67–87] Epigenetic transcriptional memory bestows the molecular foundation of polarizing signals into a coherent phenotype, and reprogramming for specific responses to environmental stressors.

The pattern of histone marks behaves like a cryptic message to be "read" by additional chromatin regulators and transcriptional coactivators/corepressors (Co-R) to determine the rates of transcription initiation and elongation. There is an equipoise of positive and negative histone marks at gene promoters and distal regulatory elements (enhancers) which synchronizes transcription rates.

The gene loci relevant for polarized macrophage phenotypes exist in four states (details in Table 3).[30–33]

- Repressed: Closed chromatin conformation shows negative marks on histones; refractory to induction of transcription by stimuli.
- Poised: Both partially open and partially closed chromatin regions. Open regions show activating histone marks and a prebound RNA polymerase II near the transcription start site. Partially closed regions show repressive histone marks and Co-R complexes.
- Active: Open chromatin shows active histone marks and ongoing transcription.
- Deactivated: Nucleosome remodeling with decreased histone acetylation and inactive inflammatory genes.

Table 3: Epigenetic regulation of inflammatory cytokine gene regulation in macrophages

Repressed	In cells that do not express inflammatory cytokines, corresponding gene loci exhibit inaccessible chromatin, occupancy by transcriptional repressors and Co-R, and negative histone marks.
Poised	Genes are maintained in a poised state of low or nonproductive basal transcription but high responsiveness to extracellular stimuli by a balance between positive and negative epigenetic marks. During macrophage differentiation, pioneer factors (PU.1) bind to cytokine gene promoters and enhancers to facilitate the opening of chromatin by nucleosome remodeling, histone acetylation, and promotion of positive methyl marks (H3K4me3 at promoters and H3K4me1 at enhancers). Activating histone marks [H3K4me3, H3K9/14ac (histone H3 acetylated at lysines 9/14)], a chromatin configuration that is at least partially-open, and in some genes, a prebound RNA polymerase II (pol II) located near the transcription start site. Repressive histone marks such as H3K9me3 and H3K27me3, Co-R complexes, and partially closed chromatin (requiring positive histone marks and nucleosome remodeling for transcription factor binding) restrict transcription.
Active	Enhancers of active genes are characterized by occupancy by p300, H3K27-Ac (acetylation of the lysine residue at N-terminal position 27 of the histone H3 protein), and low levels of transcription of noncoding enhancer RNA. Stimulation of macrophages by TLR ligands releases Co-R, increases histone acetylation, and leads to nucleosome remodeling by Brahma-related gene (Brg)-1 and recruitment of signaling transcription factors such as NF-κB. These changes increase active transcription through the recruitment of general transcription factors and RNA polymerase II.
Deactivated	Inflammatory genes are deactivated by occupancy by transcriptional repressors, decreases in histone acetylation by histone deacetylases (HDACs), and nucleosome remodeling by the nucleosome remodeling and deacetylation (NURD) complex that also contains HDACs.

M1 Macrophage Activation

The neonatal immune system has a strong proinflammatory bias.[88–91] The TLR signaling is particularly active with enhanced activity of MAPKs, NF-κB, and the IRFs. These pathways also induce inflammatory cytokines such as TNF, IL-1β, IL-6, IL12, p40, and chemokine CXC ligand 10 that are consistently seen in acute M1 responses.[30,31,33]

In the absence of TLR signaling, inflammatory cytokine gene transcription is restrained ("poised" state) by gene-specific repressive mechanisms. Gene loci inhibited by repressors such as B-cell leukemia-6 and nuclear receptors that engage Co-R complexes (HDACs and histone demethylases) help restrain positive histone marks.[32,74] Inflammatory gene loci also contain negative histone marks H3K9me3, H3K27me3, and H4K20me3; and possibly alter nucleosome positioning and chromatin accessibility of genes such as IL-12b.[67,69,73,92–95] The TLR stimulation can "release" these epigenetic "brakes" via reduced binding of B-cell lymphoma protein 6 and Co-R from gene loci and concomitant activation of demethylases such as Jumonji domain-containing protein (JMJ)-D3, JMJD2d, lysine demethylase 1B, and plant homeodomain finger 2 that erase the negative histone marks H3K27me3, H3K9me3, and H4K20me3.[67,73,93,94]

Induction of a subset of genes that includes IL-6 and IL-12b requires nucleosome remodeling by the ATP-dependent complex BAF (barrier-to-autointegration factor; also termed as the SWItch/Sucrose Non-Fermentable (SWI/SNF), an ATP-dependent chromatin remodeling complex).[68,69] This facilitates recruitment of signaling transcription factors such as NF-κB, an increase in positive histone marks such as H3S10p (histone H3 serine 10 phosphorylation), H4-Ac (histone H4 acetylation), and H3K4me3, and release of paused pol II to promote transcription elongation. Enhancers are also activated, as shown by recruitment of the histone acetyltransferase (HAT) p300, increased histone acetylation, binding of signaling transcription factors, and transcription of enhancer RNA.[24,71,75,96–98]

An inhibitor of bromodomain and extraterminal domain proteins (iBET) disturbs engagement of BET proteins and acetylated histones to block expression of TLR4-induced genes. It has shown efficacy in mouse models of endotoxin toxicity and sepsis.[99] The iBET and related compounds JQ1 and iBET151 suppress the expression of the Myelocytomatosis Viral Oncogene Homolog (Myc) gene.[100] Inhibitors of LSD1, JMJD3, ultrathorax (UTX) histone demethylases, and HDAC inhibitors can also suppress inflammation.[101] Targeting chromatic regulators could also help in gene- and patient-specific therapy. TLR-induced expression of core M1 inflammatory cytokines is transient, and gene expression is subsequently repressed to near-baseline levels. Nuclear receptors, TLR-induced transcriptional repressors ATF3 (activating transcription factor 3), and hairy and enhancer of split (Hes)-1, feedback inhibitors induced by IL-10, and the p50 NF-κB subunit can recruit Co-R complexes that contain HDACs and histone demethylases and decrease gene expression.[32,83,102–106]

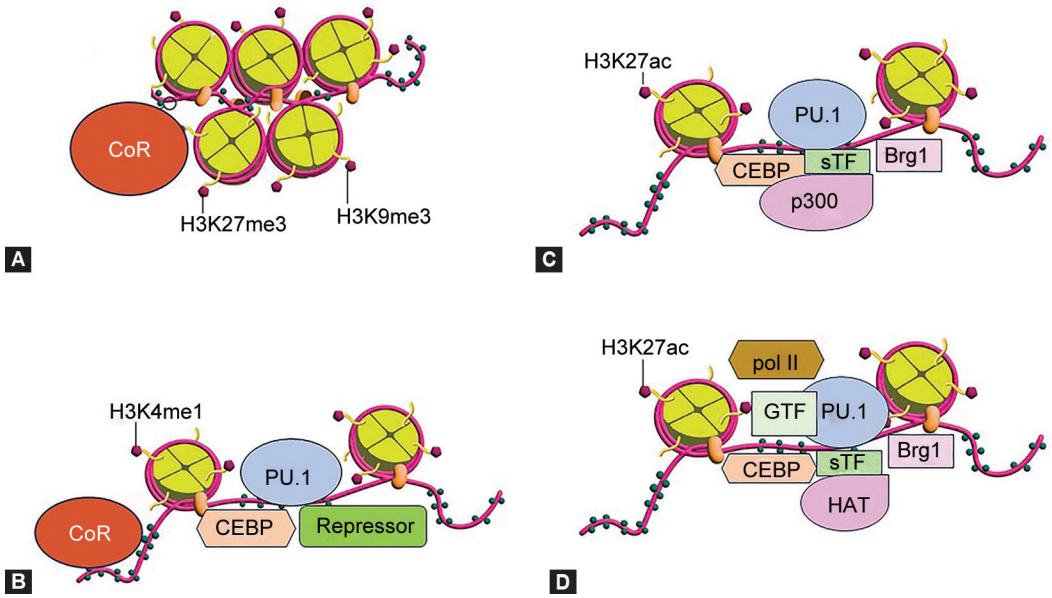
Priming of the M1 State

Interferons prime macrophages for intensified and protracted expression of inflammatory cytokine genes on encountering PAMPs. Low homeostatic levels of IFN-β and downstream Janus kinase (Jak)–STAT signaling maintain macrophages in a primed state of increased readiness to respond rapidly and strongly to infectious challenges.[107]

Several TLR ligands and TNF induce an autocrine IFN-β–Jak–STAT loop that is an important component of M1 activation.[38,108] HDAC3 plays a key negative role in this process; diminished histone acetylation may be an indirect effect, where repression of genes such as Ptgs1 (prostaglandin-endoperoxide synthase 1) can promote LPS-mediated inflammation.[77] Interferon-γ is the most potent M1-activating cytokine and acts as an enhancer of a TLR-induced inflammatory activation state. Interferon-γ and STAT1 are associated with nucleosome remodeling and opening of chromatin and may prime formation of new enhancers that augment gene expression.[109,110] The HDAC inhibitors can possibly be useful for clinical translation; these suppress induction of various inflammatory and IFN target genes.[111]

M1 to M2 Transition

Acute activation of macrophages by TLR ligands or TNF is transient and is followed by a state of tolerance.[112] Tolerant macrophages exhibit a selective defect in the induction of a subset of genes, including inflammatory cytokine genes, decreased chromatin



Figs 2A to D: Epigenetic regulation of inflammatory cytokine gene loci in macrophages. (A) Enhancer in repressed state; (B) Enhancer in poised state; (C) Enhancer in active state; and (D) Promoter in active state. The PU.1 is a transcription factor that binds the purine-rich PU-box sequence seen near promoters; CoR is a cold-responsive gene; the notations H3K27 indicate methylation of histone H3 protein at the specified lysine (K); CEBP is a member of the CCAAT/enhancer binding protein family of transcription factors; sTF-1 is a putative insulin gene transcription factor; Brg1 is a Brahma-related gene 1-encoded adenosine-5′-triphosphate (ATP)-dependent catalytical subunit of the switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complexes; p300 is a transcription coactivator that mediates histone 3 lysine 27 acetylation; pol II is a nuclear RNA polymerase; GTF is a glucosyltransferase; and HAT is the histone acetyltransferase 1

accessibility, and lesser recruitment of transcription factors such as p65. Decreased ease of chromatin access can be attributed to decreased TLR-induced recruitment of Brg1-containing nucleosome remodeling complexes, and complex changes in histone acetylation and methylation. Nontolerized genes maintain an open chromatin state. Interferon-γ prevents tolerance by preserving expression of the receptor-interacting protein 140 (RIP140) coactivator and promoting TLR-induced chromatin accessibility upon secondary TLR challenge.[110,113]

A key mediator of the alternative activation of macrophages is the histone demethylase JMJD3, which promotes the expression of the transcription factor IRF4; it removes the negative H3K27me3 marks at the Irf4 locus to achieve these results.[86] In growing infants, JMJD3 might play an important role in increasing nuclear factor of activated T-cells c1 expression and consequently, RANKL-induced differentiation down the alternative osteoclast pathway.[87] The HDAC3 regulates IL-4-induced M2 polarization by deacetylating enhancers of IL-4-induced M2 genes.[85] Histone methylation and acetylation are paramount to M2 polarization.

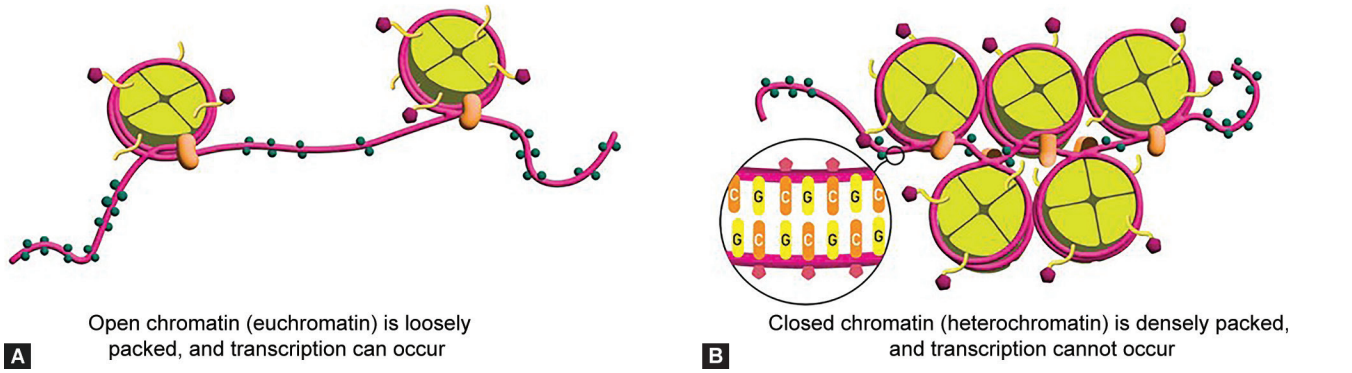
Maturing Macrophages Can Alter Tissue Homeostasis

Tissue-resident macrophages include those derived from the YS progenitors and fetal/adult MDMs. Despite different ontogeny, these cells show intrinsic anti-inflammatory and immunosuppressive functions. Tissue macrophages are primed to respond rapidly to subsequent challenges, maintaining low levels of constitutive IFN-β and downstream JAK–STAT signaling.[107] Commensal microbiota play an important role in IFN expression.[76,114] PU.1 is indispensable to macrophage development in most of the tissues. The enhancer of Spi1, which controls the expression of PU.1, has H3K4me2 and H3K27ac marks in all macrophage populations (Figs 2 and 3).[115]

Microglia are resident macrophages in the brain and spinal cord that are entirely derived from the YS during embryogenesis, as seen in the privacy behind the blood–brain barrier. The Spalt-like transcription factor-1 is a microglia-specific transcription factor regulated by enhancers which are open and active only in these cells.[116] It controls transcriptional regulation that maintains microglial identity and physiological properties as a critical factor for homeostasis in the brain.[117]

The intestine contains the largest pool of macrophages among the tissues.[118] Embryonic precursors seed the intestinal mucosa and multiply substantially in the neonatal period.[119] Bone marrow-derived monocytes begin to replace the original macrophages around the time of weaning, and these differentiate locally into mature tissue macrophage populations in the lamina propria to help promote gut homeostasis. Intestinal macrophages are enriched for RUNX (Runt-related transcription factor) family motifs; RUNX3 is highly expressed in these cells.[116] The gut microbiome is an important regulator of the macrophage populations in the intestine (Fig. 1).

Alveolar macrophages differentiate from fetal liver monocytes depending on the colony-stimulating factor 2 (CSF2; GM-CSF) through the induction of peroxisome proliferator-activated receptor-γ.[120] Embryonic macrophages and fetal monocytes colonize the developing lung.[121] These macrophages can be seen in the saccular stage of lung development, when fetal monocytes, not embryo-derived macrophages, are the main precursors of alveolar macrophages. Transcriptional inhibitors BTB Domain And CNC Homolog 2 (Bach2) and also Bach1 promote alveolar maturation.[122] The long noncoding RNA (lncRNA) MEG3-4 (maternally expressed gene 3–4) is a tissue-specific regulator of inflammatory responses in alveolar macrophages during bacterial infections through the transcriptional regulation of immune response genes.[123]



Figs 3A and B: Chromatin condensation state affects gene expression. (A) Euchromatin state: stimulation with a pathogen/danger signal demethylates DNA, decondenses chromatin, and makes these genes accessible for transcription; (B) Heterochromatin state: chromatin housing the immune response genes in naïve macrophages is highly condensed and inaccessible due to high DNA methylation and is either not transcribed at all or at very low levels. [Some components of the figure were adapted with permission from *Singh S, Frydrysiak-Brzozowska A, Ayad AEB, et al. A primer on epigenetic changes: The more we know, the more we find in fetuses and infants. Newborn 2024;3(3):219–232]*

Splenic macrophages begin to appear in growing infants. The mature spleen in growing infants shows three typical zones—the marginal zone (MZ), red pulp, and white pulp, and each contains specific macrophage subpopulations.[124] The MZ macrophages that differentiate under the influence of the expressing nuclear receptor Liver X receptor alpha remove apoptotic cells.[125,126] These macrophages express transcription factor Spi-C, a PU.1-related transcription factor.[127]

The abdominal cavity shows at least two distinct macrophage subtypes.[128] Large peritoneal macrophages contribute to most of the peritoneal cavity macrophages, but these are rapidly replaced by smaller macrophages after stimulation. This new population of macrophages efficiently removes apoptotic cells. The localization and polarization of peritoneal macrophages is regulated by the retinoic acid-induced GATA-binding factor 6, a specific transcription factor that alters the transcriptional and epigenetic properties of these cells.[129] A key downstream regulator is the retinoic acid receptor beta (Rarb) gene, which promotes H3K27ac specifically in peritoneal macrophages.[26] The Rarb gene enhancer is poised in other tissues but remains active in peritoneal macrophages because of locally produced retinoic acid.[130]

Epigenetic Modifications in Macrophages during Inflammation

Changes in macrophages can cause a broad spectrum of maladaptive immunity and inflammation that are causative factors of disease and thus represent key therapeutic targets.[131] Immune response associated with sepsis is greatly impacted by macrophage epigenetic landscape. For instance, HDAC6 inhibitors decrease proinflammatory mediators, inhibit macrophage apoptosis, and promote bacterial clearance.[132] The expression of several microRNAs (miRNAs) is altered in neonatal sepsis and could be possible therapeutic targets. For instance, miRNA-Let7A (let-7a) is decreased in sepsis due to gram-negative bacilli; it regulates the TLR4-mediated sepsis-induced inflammatory response.[133] The lncRNA Nuclear Enriched Abundant Transcript 1 is upregulated in sepsis. Decreased macrophage levels of microRNA-141 also increased the inflammation.[3]

Macrophage functions are altered in hypoxic–ischemic encephalopathy, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, and renal failure. Macrophage epigenetics can show prognostic markers and might provide useful immunomodulatory treatments for neonates, and even adults.[3,134,135]

IIM in Macrophages

The IIM of macrophages impacts immune responses to ensuing stimuli. It is classified as tolerance and training. It is also seen in in tissue-resident mononuclear phagocytes such as microglia.[136] In trained immunity, the first stimulation induces long-lasting histone marks. Later hits alter macrophage properties with H3K27ac and H3K4me3 and induce tolerance.

Tolerance

Acute inflammatory TLR activation of macrophages is a transient, tightly-regulated process.[112] The activation state is transient and is followed by tolerance, indicating that this is a self-limited response to stimuli despite sustained action of the agonist.[4] The TLR-induced responses include selective and transient silencing of proinflammatory genes and the priming of the second-class genes of M2 activation.[81] Following the first LPS exposure, anti-inflammatory genes are altered in the second stimulation, thereby increasing the efficiency of innate host defense. This LPS tolerance is mainly controlled by epigenetic regulation, including nucleosome remodeling, reduced recruitment of transcription factors and chromatin remodeling complexes, and histone modifications.[137] This process involves silencing of proinflammatory and priming of anti-inflammatory genes in tolerant macrophages through differential alteration of chromatin at promoters of pro- and anti-inflammatory genes. The NF-κB-associated inhibitory mechanisms can lead to tolerance by recruitment of the NCOR-HDAC3-P50 repressive complex into targeted genes.[107] It can also recruit histone methyltransferase G9a to promoters to induce H3K9 methylation and binding of the heterochromatin protein 1, leading to epigenetic silencing.[138]

Noncoding RNAs, especially miRNAs, can regulate macrophage tolerization. The miRNA-146a induces TLR signaling tolerance following a primary stimulus with Myeloid differentiation primary response 88-dependent TLR pathways.[139] The miRNA-221 and miRNA-222 regulate BRG1 and, consequently, functional reprogramming of macrophages during LPS tolerization.[140]

Trained Immunity

The traditional view that only the adaptive immune system can build immunological memory no longer holds true at present. In

organisms lacking adaptive immunity, such as invertebrates, the innate immune system can mount long-term memory for resistance to reinfection.[141]

Microglia develop a "trained" IIM after repeated exposures to infectious stimuli.[142] This epigenetic reprogramming is marked by higher H3K4me1 levels and TF binding on the promoters of "latent" enhancers, which revert to baseline after cessation of stimulation.[143] The progressively stronger cellular responses with repeated stimulation have been further linked with increased H3K4me3 on promoters of canonical mediators, such as the TLR-activated adaptor Myd88 and downstream cytokines, TNF, IL-6, and IL-18.[63]

Trained immune genes interact with lncRNAs through βG and its receptor dectin-1. The upstream master lncRNA of inflammatory chemokine loci form chromosomal contacts at the promoters of the key chemoattractants such as ELR$^+$ CXC-ligand (CXCL) chemokines – IL-8/CXCL8, CXCL1, CXCL2, and CXCL3, and *cis*-directs the protein complex of WD repeat-containing protein 5 (WDR5) and mixed lineage leukemia 1 (MLL1), facilitating H3K4me3 epigenetic priming before transcriptional activation.[144–146]

Innate immunity training plays a vital part in disease prevention. Bacillus Calmette–Guérin (BCG) can be used to train macrophages *ex vivo* and thereby provide cross-protection.[147] The ability of macrophages to transmit memory phenotypes to offspring and provide sustained protection remains unclear, mainly due to the short lifespan of macrophages. Long-term IIM is vital to developing a robust immunity.

Epigenetic Mechanisms of IIM in Macrophages

Emerging evidence shows macrophages show and mature with epigenetic memory of recent inflammatory exposures. In one study, an epigenetics compound library was screened that affects trained immunity or LPS tolerance in macrophages using TNF as a readout.[148] The investigators tested 181 compounds, where 1 showed suppressive effects and 2 promoted β-glucan (βG)-trained TNF production. In contrast, inhibitors of Aurora kinase, histone methyltransferase, histone demethylase, HDAC, and DNA methyltransferase suppressed LPS tolerance. Several proteins previously unknown to be involved in IIM, such as O^6-methylguanine-DNA methyltransferase, Aurora kinase, lysine-specific histone demethylase 1 (LSD1), and protein arginine methyltransferase 5 were revealed. Protein network analysis revealed that the trained immunity targets are linked via Trp53, while LPS tolerance targets form three clusters of histone-modifying enzymes, cell division, and base-excision repair. In trained immunity, the SETD7 [Su(var)3-9, Enhancer-of-zeste and Trithorax (SET) domain-containing 7, histone lysine methyltransferase] was identified, and its expression was increased during βG treatment. The LPS priming increased LSD1 expression, whereas siRNA-mediated reduction resulted in increased expression of IL-1β in LPS tolerance. This study confirmed the importance of epigenetic modifications in IIM and provided potential novel targets for intervention.

In *Candida* infections, macrophage memory is trained by βG-induced epigenetic changes such as enhanced trimethylation of histone H3 at lysine 4 (H3K4me3).[149,150] This H3K4me3 marker is located on the promoter regions of IL-6, TNF, and IL-1β, and has been associated with increased expression of these cytokines, thereby enhancing the response to secondary stimulation in infections.[150–152] H3K4me3 is also upregulated following *in vitro* stimulation of human monocytes trained by oxidized low-density lipoprotein. These cells show TLR-2 and TLR-4 activation with higher expression of IL-6, IL-8, IL-18, and TNF, monocyte chemoattractant protein 1/CC-ligand 2, and matrix metalloproteinases.[153]

Kleinnijenhuis et al. also reported that the protective effect of monocytes against secondary reinfection after primary BCG vaccination in healthy volunteers was mediated by H3K4me3, accompanied by the production of the inflammatory cytokines IFN-γ, TNF, and IL-1β increasing several-fold in response to infections by nonspecific bacterial and fungal pathogens.[152] Moreover, the inhibition of histone methyltransferase was found to be associated with a significant reduction in BCG-induced macrophage memory.

A stable differential DNA methylation pattern was observed in peripheral blood mononuclear cells (PBMCs) isolated from BCG-vaccinated individuals compared with counterparts without BCG vaccination. Gene ontology analysis revealed that promoters with altered DNA methylation patterns were strongly enriched among immune-related genes, thereby enhancing the resistance of macrophages to mycobacteria.[154,155] In another study, a global methylation analysis of PBMCs showed more than 1,000 differentially methylated regions (DMRs) between tuberculosis patients and healthy controls. After completion of treatment, the number of DMRs increased to nearly 4,000; most of these genes were associated with the autophagy-related pathways.[156] When alveolar macrophages were infected with *Mycobacterium tuberculosis*, a distinct DNA methylation profile enriched in the pentose phosphate pathway, T-cell migration, and IFN-γ production pathways was seen.[157]

Macrophage Epigenomics

Transcriptomes and the epigenomes of three populations of macrophages derived from healthy human monocytes *in vitro* were analyzed. These cells were maintained in culture in 10% pooled human serum for 6 days. In the first 24 hours, the monocytes were maintained as control or were exposed to βG or LPS. On the 6th day, βG-treated cells were consistently proinflammatory with enhanced efficiency in phagocytosis.[158] Hence, these were viewed as "trained."[159] In contrast, LPS-exposed MDMs showed downregulation of IL-6 and TNF expression and were labeled as "tolerant."[63] In both instances, these 6th day macrophages showed some functional memory of the stimuli.

In human studies, a part of the macrophage genome begins to show nucleosome-borne epigenomic dynamics following exposure to PAM patterns. The three major macrophage subtypes (M0, M1, and M2) show consistent differences in the transcriptome (Fig. 1). Controls, trained, and tolerant macrophages display transcriptomic differences at all levels, including interactions with extracellular matrix, signal receptors, metabolite transporters, organelle and cytoplasm constituents and signaling pathways, RNA processing, and transcription factors. About 200 TFs, 100 kinases, and 20 epigenetic enzymes were differentially expressed following monocyte-to-macrophage differentiation.[147] For instance, monocytes uniquely express lysine (K)-specific demethylase 6B (KDM6B; also called JMJD3). The E-box binding C2H2 (cysteine-2/histidine-2) zinc finger TF Snail family transcriptional repressor 1 (SNAI1) of monocytes is largely replaced by its SNAI3 paralog in macrophages. The NF-κB regulator IRAK3 (IL-1 receptor-associated kinase 3) is epigenetically upregulated in LPS-paralyzed macrophages; the G-coupled receptors such as the Adora receptors and many cAMP (cyclic adenosine monophosphate) signal transduction factors are expressed differentially in control, βG-trained, and trained macrophages.[147]

Conclusion

Epigenetic changes are an important mechanism by which macrophages differentiate into various functional subgroups. The evidence for plasticity between M1 and M2, and within the M2 subgroups supports this construct.[160] However, M1 macrophages do not show consistent reversibility in responses following IL-4 treatment.[161] Trained cells show considerable remodeling in metabolic pathways, as seen with increased glycolytic capacity, in some steps in the tricarboxylic acid cycle, and in cholesterol metabolizing enzymes.[147] These metabolic changes likely affect chromatin modifications through altered availability of the writers and erasers of histone modifications.[162–165] Macrophages are particularly important in the immune profile of neonates, and hence, further work is needed to understand the molecular mechanisms of activation of various subcategories of these cells.[166–169]

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CASE REPORT

Neonatal Small Colon Syndrome in Infants of Diabetic Mothers: Is It Always a Transient Condition?

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Abstract

Objective: We describe an infant of diabetic mother (IDM) with an unusually severe, extensive, and persistent neonatal small colon syndrome (NSCS).

Case presentation: We report a 36-week-gestation female IDM who developed signs of intestinal obstruction at about 6 hours after birth. A contrast enema showed a small-caliber distal small intestine and colon. There was no clinical improvement over next 2 weeks, and so an exploratory laparotomy was performed; the involved bowel contained viscous meconium with pellets. Histopathological examination showed normal bowel histoarchitecture with an appropriate morphology/number of ganglion cells. A double barrel enterostomy was created, and the distal gastrointestinal tract was regularly flushed. She has since shown good improvement and has been discharged on full, exclusive breastfeeds. Laboratory investigations, including blood counts and chemistries, thyroid function, and screening for cystic fibrosis (CF) were reassuring. Our working diagnosis is an unusually severe/extensive NSCS. We have followed this infant for gastrointestinal symptoms now for 3 months since discharge.

Conclusion: Neonatal small colon syndrome may not always show prompt, spontaneous resolution. It should be included in the differential diagnosis of a newborn infant with unusually prolonged signs of intestinal obstruction. Some infants may require surgical management with ostomy formation.

Keywords: Case report, Contrast enema, Cystic fibrosis, Double barrel stoma, Gestational diabetes, Hirschsprung disease, Infant, Intestinal obstruction, Maternal diabetes, Meconium pellets, Neonate.

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Key Points

1. We describe the clinical course of an infant of diabetic mother (IDM) with an unusually severe and prolonged neonatal small colon syndrome (NSCS).
2. This infant had a prolonged period of feeding intolerance with abdominal distension, tenderness, bilious vomitings, and hypoactive bowel sounds. Radiographs showed dilated bowel loops with no rectal gas. A contrast study showed a small-caliber distal small bowel and colon.
3. An exploratory laparotomy was performed at 2 weeks of postnatal age. The involved bowel contained viscous meconium with pellets. A double barrel stoma was created and distal bowel was serially flushed. The infant improved gradually and has been discharged on full, exclusive breastfeeds.
4. We need to note that NSCS may not always show prompt, spontaneous resolution. It should be included in the differential diagnosis of a newborn infant with unusually prolonged functional intestinal obstruction.

Introduction

We recently treated an IDM with NSCS. She did not respond to conservative management, and an exploratory laparotomy had to be performed after 2 postnatal weeks. This infant had been evaluated for many differential diagnoses, but the clinical course was a reminder that NSCS should be considered as a possibility in infants with prolonged functional intestinal obstruction that extends beyond the left colon even if they are born at near-term/term gestation.[1]

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Conflict of interest: None

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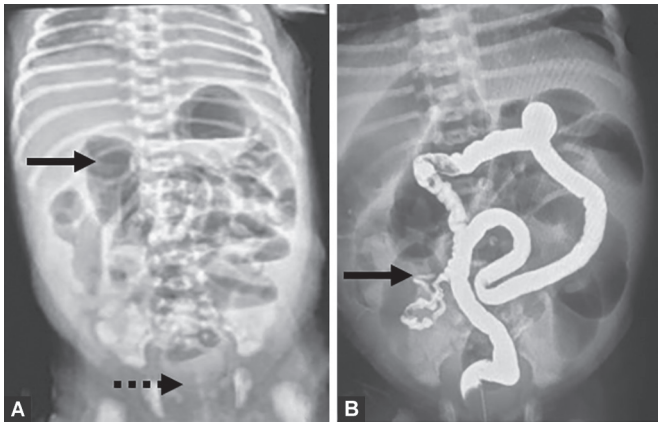
Case Description

We recently treated a 36^{+3} weeks' gestation female neonate born to a 28-year-old G_1P_0 mother by an elective Cesarean section. The pregnancy was nonconsanguineous; antenatal history was



Figs 1A and B: (A) Serial radiographs showing dilated proximal bowel loops with collapsed distal bowel (arrow) and absence of rectal shadow (broken arrow); (B) Contrast enema study showing a small caliber of the colon and distal small intestine (arrow)

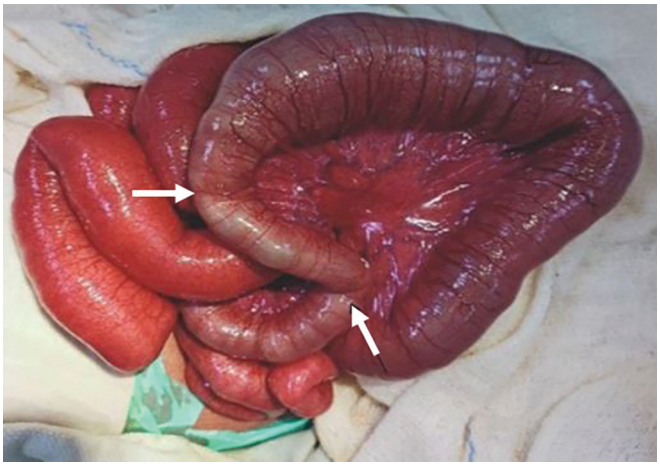


Fig. 2: Intraoperative finding of dilated jejunum and ileum till 40 cm proximal to ileocecal junction, with significant dilatation of the loop of ileum with thickened meconium just proximal to the area of narrowing

marked by gestational diabetes since 31^{+4} weeks (HbA1c = 6.14%, abnormal oral glucose tolerance test). The mother was managed with dietary modifications, but did not require any medications.[2] Her subsequent blood sugar values were within normal ranges. Antenatal sonography showed a normal amniotic fluid index and no fetal abnormalities.[3,4]

At birth, the neonate responded well without the need for active resuscitation; Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. Anthropometric measurements showed that she was large-for-date (weight 3,790 gm; >95th percentile), but the head circumference (34 cm) and body length (50 cm) were appropriate for gestational age.[5] The neonate was roomed-in with the mother and started breastfeeding. However, she developed abdominal distension with bilious vomiting after 6 hours and was transferred to the neonatal intensive care unit. Her vital parameters were all within normal limits. The abdomen was distended, tense, and tender with hypoactive bowel sounds; there was no hepatosplenomegaly, and the rest of the physical examination was unremarkable. The neonate was kept *nil per oral* (NPO) with only intravenous fluids. An orogastric tube was placed, and gastric aspirates were monitored.

She first passed some pellets of meconium at 20 hours after birth but continued to have bilious aspirates. The abdominal radiograph showed dilated bowel loops with no rectal gas shadow (Fig. 1A). Serial radiographs showed minimal change. A contrast enema performed on postnatal day 2 showed a narrow, small-caliber distal small intestine and colon (Fig. 1B). Postenema, the infant intermittently passed a few stool pellets but continued to show abdominal distension, tenderness, and persistent bilious aspirates.

We measured complete blood counts, serum calcium levels, and thyroid function tests, which were all within normal ranges. Considering that we were observing an IDM, NSCS was considered a likely possibility but it was unusually extensive. Meconium plug syndrome was also plausible, but again, considering the extensive radiographic changes, it had to be a diagnosis of exclusion. Cystic fibrosis (CF) with meconium ileus was considered; the estimated incidence of CF in Asia is 1 in 10,000–12,000, but the data from India are limited.[6] In our own experience, it is seen very infrequently. The medical community in India has conflicting views about the incidence of CF in this region, and so we screen all infants with consistent symptoms.[7] This patient tested negative for the immunoreactive trypsinogen assay.[8] Hirschsprung disease was considered, but a clear transitional zone was not seen on the contrast study.[9,10]

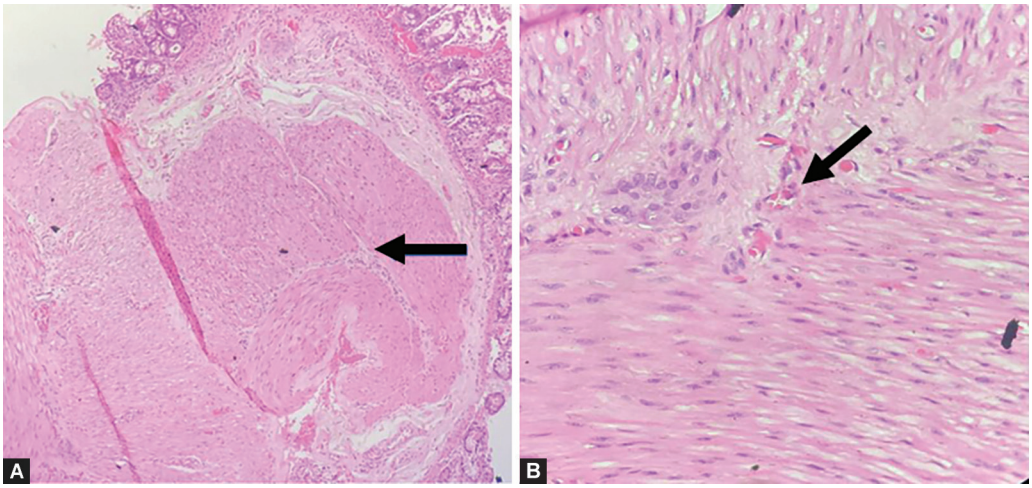
There was no improvement in neonate's condition until 2 weeks. An exploratory laparotomy was performed, which showed a large number of meconium pellets in the colon, ileum, and distal jejunum that had to be gently milked out for extraction. The small intestine showed some dilatation until about 40 cm proximal to the ileocecal junction; the distal bowel segments contained thick meconium and meconium pellets (Fig. 2). A double barrel ileostomy was performed. A punch biopsy drawn from a site distal to the stoma showed normal histoarchitecture (Fig. 3A) with normal-looking ganglion cells in usual numbers (Fig. 3B).

After surgery, the neonate was continued on parenteral nutrition. Feedings were started cautiously on postoperative day (POD) 10. The stool output initially remained limited to thick pellets, and so we irrigated the stoma several times every day with *N*-acetylcysteine.[11] She gradually began to tolerate feedings to reach full volumes by POD 14. She was discharged at 1 month after birth on full, exclusive breastfeeds. She has now been followed up for 3 months and has shown normal growth and neurodevelopment. An end-to-end anastomosis with stoma closure is being planned.

Discussion

Neonatal small colon syndrome is a condition characterized by features of large bowel obstruction in an otherwise healthy neonate; 40–50% of these patients are IDMs.[12] The pathophysiology is believed to be related to the smooth muscle constricting effects of glucagon and increased sympathetic activity resulting from hypoglycemia at birth. Additionally, functional immaturity of the ganglion cells and abnormalities in the autonomic nervous system may contribute to this condition.[13]

Early descriptions of meconium-related functional intestinal obstruction differentiated between two different presentations. Symptoms related to a meconium plug located in the colon were usually relieved after the meconium was excreted following conventional treatment. The presence of more viscous, sticky meconium in the small intestines with poor response to conventional treatment, consequently requiring surgical intervention, has also been described.[14,15]



Figs 3A and B: Normal histopathology of tissue biopsy samples: (A) Full-thickness biopsy showing an intact myenteric plexus between the muscularis externa layers (40×, hematoxylin and eosin); (B) Higher-magnification photomicrographs (400×, hematoxylin and eosin) showing normal morphology and number of ganglion cells

Our index case was a near-term infant. Her clinical features of prolonged nonobstructive intestinal dysfunction due to viscous meconium have previously been seen more often in very premature infants with a maternal history of hypertension, magnesium sulfate therapy, Cesarean delivery, and diabetes mellitus.[15,16] Yamoto et al. noted an association with intrauterine growth retardation.[17] Okuyama et al. found twin pregnancies, prolonged rupture of membranes, and the use of maternal steroids as risk factors.[18] In their cohort, low birth weight, fetal distress, maternal DM, and the maternal use of steroids independently increased the risk of these clinical features.

Neonatal small colon syndrome often shows clinical features suggestive of lower intestinal obstruction, similar to those seen in meconium plug syndrome, meconium ileus, CF, and Hirschsprung disease.[1] Except for those with Hirschsprung disease or CF, these infants begin to show spontaneous clinical improvement in 1–2 weeks following a contrast enema. Some infants may find additional benefit with a trans-anal catheter for drainage. In a case series of 105 IDMs, five had NSCS, and all showed resolution of clinical symptoms with contrast enema.[12]

The absence of a transition zone on imaging and during intraoperative examination, presence of ganglion cells that showed normal histomorphology and number, and the reassuring postoperative course have largely excluded the possibility of Hirschsprung disease.[19] Cystic fibrosis was less likely because of ethnic origin and normal screening tests; we will continue to follow and request for genetic tests if needed.[6,7] This case report brings up the dilemma of a clinician who is treating an infant with bowel dysfunction related to a well-documented, long narrow-caliber segment of the intestine, and is not showing clear evidence of recovery; it is difficult to decide between conservative management vs early surgical exploration in these cases.

To summarize, we report an IDM with an unusually severe and extensive NSCS, where signs of nonobstructive bowel dysfunction persisted for 2 weeks. An exploratory laparotomy was then performed, and viscous stool and pellets were seen in the distal small and the entire large intestine. An enterostomy with regular irrigations helped, and the infant began to feed normally after about 10 days. She has now been discharged home and has shown normal tolerance to oral feeds, growth, and development. We plan to close the stoma soon and will follow this infant closely for 3 years.[12,20] If problems recur or if she does not develop normal bladder control, we will request for genetic testing.[21]

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CASE REPORT

Neonatal Hypothyroidism following Prolonged Exposure to Povidone-iodine in a Preterm Infant with Giant Omphalocele: A Case Report and Call for Awareness

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Abstract

Omphalocele is a congenital midline defect into the base of the umbilical cord, which frequently contains herniated abdominal viscera. Giant omphaloceles (GOs) are defined as larger than 5 cm. Management of omphaloceles is usually focused on closing the abdominal wall defect after supportive care to stabilize the patient. Some clinicians prefer a nonoperative "paint and wait" strategy without graft closure; the sac is maintained with topical medications such as silver sulfadiazine or combinations of polyvinylpyrrolidone and iodine (the most frequently used commercial preparation being povidone-iodine®) mixed with topical antibiotic powder sprays. Povidone-iodine can cause thyroid dysfunction, especially in preterm infants. The authors present one such case in the article; the goal is to sensitize the medical care-providers to these adverse effects. A female infant born at 26^{+2} weeks' gestation/birth weight of 830 gm showed a GO with intact membranes. A transparent silicone adhesion wound-contact dressing was used to cover the abdominal herniation, and on the 2nd postnatal day, the surgeon began applying povidone-iodine over the omphalocele followed by nonadherent dressings. Serum thyroid stimulating hormone (TSH), free T4, and iodine levels were followed over time. The iodine levels were monitored but the levels at 35 weeks' corrected gestational age suddenly rose to 33,917 µg/L (normal 40–100 µg/L). The infant was still receiving daily povidone-iodine dressings at this time. These dressings were stopped immediately, and the serum iodine levels dropped to 97 µg/L in 2 months. The authors seek to remind that infants, especially preterm, who are exposed to repeated topical exposure to iodine-containing antiseptic solutions over a large surface area are at risk of developing transient hypothyroidism. There is a need to remain cognizant of these complications and be aware of the need for close monitoring of thyroid function in high-risk infants.

Keywords: Case report, Giant omphalocele, Iatrogenic hypothyroidism, Levothyroxine, Neonatal hypothyroidism, Neonatal screening, Omphalocele, Povidone-iodine, Preterm infants, Thyroid dysfunction, Topical iodine.

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Introduction

Omphalocele is a congenital midline defect into the base of the umbilical cord. Most show a small periumbilical herniation. Giant omphaloceles (GOs) are typically larger than 5 cm in diameter and the peritoneal sac could contain herniated abdominal viscera, such as parts of the gastrointestinal system, uterus, ovaries, or spleen.[1–3] The rates of occurrence in the Middle East can reach 2 in 10,000 newborns.[4,5] The incidence is higher in infants born to mothers younger than 20 or older than 35, and is more common in males and in multiple births.[6]

Many infants with GOs show respiratory insufficiency, pulmonary hypoplasia, and chronic lung disease.[7] Up to 35% have congenital heart defects and 15% may have diaphragmatic hernia.[8] Some patients show clinically significant gastroesophageal reflux disease.[7] Omphaloceles have also been associated with many complex genetic conditions such as the Beckwith–Wiedemann syndrome; trisomy 13, 18, and 21; pentalogy of Cantrell; Shprintzen–Goldberg syndrome; CHARGE syndrome; Marshall–Smith syndrome; Carpenter syndrome; and the Meckel–Gruber syndrome.[6,9–19] Overall, infants with GOs may have mortality as high as 15–25%.[20]

The management of GOs is challenging; some surgeons prefer to close the abdominal wall defect after supportive care to stabilize the patient. Others prefer a nonoperative "paint and wait" strategy; the sac is maintained with topical medications such as silver sulfadiazine or combinations of polyvinylpyrrolidone and iodine (the most frequently used commercial preparation being povidone-iodine®) mixed with topical antibiotic powder sprays (polymyxin B sulfate, bacitracin zinc, and/or neomycin).[21–26] Studies have shown that the combining topical povidone-iodine with powdered antibiotics may accelerate epithelialization of omphaloceles.[10,20] Regular dressings to wrap the infant's torso with an elastic bandage can promote epithelialization and wound contracture to obliterate the abdominal wall defect, and also the closure of the ventral hernia with delayed surgery.[27,28] Both silver sulfadiazine and povidone-iodine have unique advantages and disadvantages; silver sulfadiazine is less expensive over time and facilitates early granulation with good

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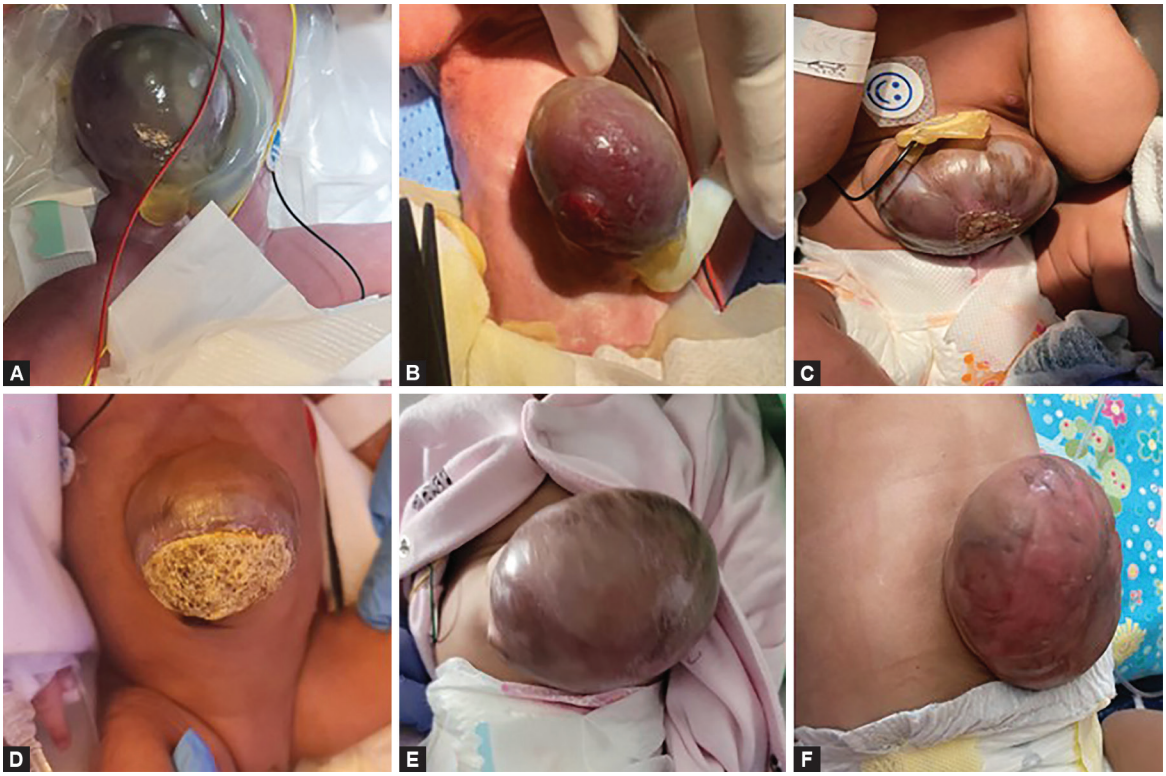


Figs 1A to F: A 26^{+2} weeks' gestation/830 gm female infant was born with a GO. She was managed conservatively: serial photographs show gradual maturation of the lesion at (A) birth; (B) 2 weeks' postnatal age; (C) 1 month; (D) 3 months; (E) 6 months; and (F) 1 year after birth

broad-spectrum antibiotic coverage.[29] However, it might disrupt the granulation tissue in some situations.[27] Povidone-iodine can cause thyroid dysfunction, especially in preterm infants.[30] We present one such case in the article; the goal is to sensitize the medical care-providers to these adverse effects.

Case Description

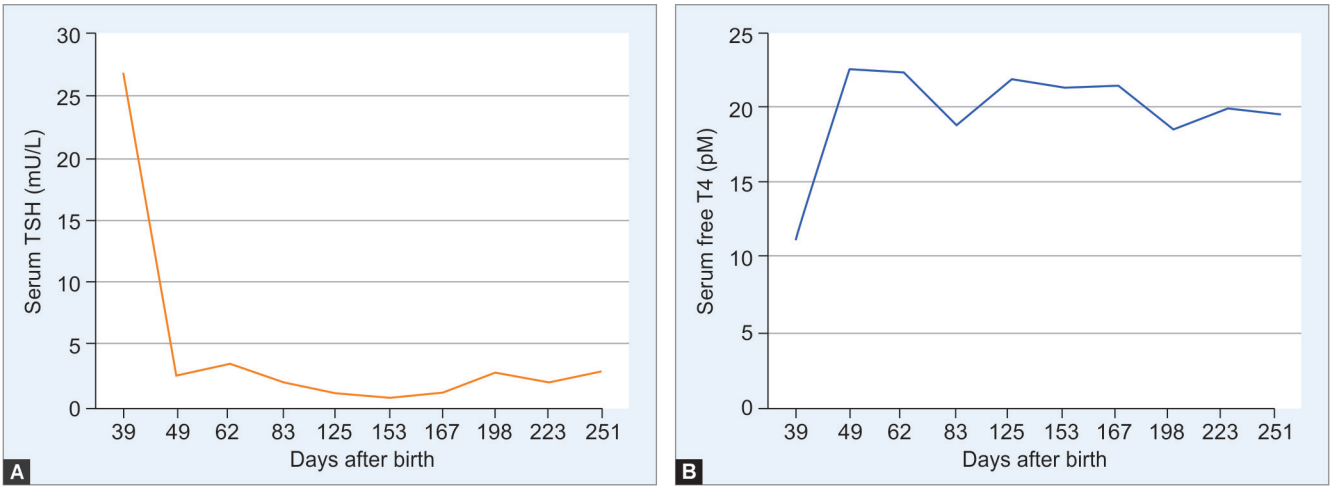
A 27-year-old primigravida mother with an *in-vitro* fertilization pregnancy was diagnosed to have an omphalocele on sonography at 23 weeks' gestation. Except for an unicornuate uterus, the pregnancy was otherwise uneventful. The fetus did not show any other congenital anomalies. She was transferred to our hospital for premature labor and vaginal bleeding. On arrival, a prenatal ultrasound scan showed an omphalocele (3.9×3.9 cm^2). She was admitted and given one dose of betamethasone 7 hours before delivery per protocol for prematurity and one dose of magnesium sulfate for neuroprotection.

A female infant was born at 26^{+2} weeks' gestation with a birth weight of 830 gm by an emergency cesarean section in view of premature labor, antepartum hemorrhage, and breech presentation. At birth, the baby was resuscitated per protocol using a plastic bag, head covering, and the American Academy of Pediatrics neonatal resuscitation protocol. She was dusky in color and had irregular breathing with heart rate less than 100 beats/minute. Apgar scores were 4, 7, and 9 at 1, 5, and 10 minutes, respectively. The baby was intubated and treated with supplemental oxygen as needed per saturations/blood gas evaluations. A GO was noted; the membranes were intact and parts of the liver could be seen inside it. A right microtia was noted.[31] Echocardiography showed a patent foramen ovale and an apical ventricular septal defect, all are known associations.[31]

The abdominal herniation was covered with a transparent perforated silicone adhesion wound-contact dressing. The perforated design of these dressings allows the drainage of exudates. Per the manufacturers' guidelines, we can keep these dressings in place for up to 14 days. On the 2nd postnatal day, the surgeon began applying povidone-iodine over the omphalocele followed by nonadherent dressings. The peripheral edges of the dressing were supported using dry gauze. Similar protocols have been previously described from other neonatal units.[32] The baby received assisted ventilation for respiratory support and intravenous fluids per our protocol at 80 mL/kg/day through a peripheral line. On the 2nd postnatal day, the surgeon began applying povidone-iodine over the omphalocele followed by a nonadherent dressing. The infant remained intubated for 2.5 months and was then weaned gradually to nasal cannula.

Serum thyroid stimulating hormone (TSH) and free T4 levels were followed over time (Figs 1 and 2). The first and second thyroid screens were normal, but the third screen showed a high TSH at 17 mU/L. The repeat TSH level was 26.9 mU/L and free T4 levels of 11.1 pM. Daily levothyroxine supplementations were initiated, and repeat tests in 10 days showed a good response with TSH levels of 2.45 mU/L and free T4 of 22.5 pM. The infant had feeding intolerance, and an upper gastrointestinal contrast study showed a hiatal hernia with gastroesophageal reflux.

The iodine levels were also monitored. The levels at 35 weeks' corrected gestational age suddenly rose to 33,917 µg/L (normal 40–100 µg/L). The infant was still receiving daily povidone-iodine



Figs 2A and B: Serial serum levels of (A) TSH and (B) free T4 from postnatal days 39 until 251

dressings at this time. These dressings were stopped immediately, and the serum iodine levels dropped to 97 µg/L in 2 months.

Discussion

Thyroid dysfunction, commonly with hypothyroidism, can occur when infants with giant hemangioma, umbilical stump, or complex open wounds are exposed to exogenous povidone-iodine.[33] This issue needs to be considered, and TSH should be monitored carefully in these patients.[34,35] Exposure to exogenous iodine can cause transient suppression of endogenous thyroid hormone production; this is a well-recognized autoregulatory protective mechanism known as the Wolff–Chaikoff effect (WCE).[36,37]

The WCE is a safety mechanism that prevents thyroid overactivity following exposure to high levels of circulating iodine and typically resolves in 48 hours.[37,38] However, this normalization of thyroid function may take longer in premature infants, ranging from several days to weeks.[39,40] Such delays in thyroid recovery can also be seen in infants with GOs who are treated with topical povidone-iodine solutions that can prevent infections and also promote epithelialization.[23] Repeated exposures over days to weeks can alter thyroid function, particularly in premature neonates; these patients may be at higher risk, as the thin epidermal layer might predispose them to higher iodine absorption and their thyroid axis may be more sensitive to inhibitory effects of iodine overload.[30,41] Term neonates also share this risk, but possibly to a lesser extent and have relatively more transient hypothyroidism.[42]

Thaker et al.[43] reported a rise in TSH in infants following cardiac catheterization and surgical repair for congenital heart defects following exposure to a large amount of iodine from intravenous iodinated contrast studies and topical applications of iodine-containing antiseptic formulations. Many of these infants needed treatment with levothyroxine for up to 10 months.[43] We still do not have sufficient information about the lowest amounts/duration of topical iodine that will likely suppress thyroid function. In addition, the impact of gestational age/birth weight/genetics/ethnicities/geographical origins needs to be explored.[39] Based on the available literature, close monitoring of thyroid function during and shortly after frequent topical use of povidone-iodine is recommended for early detection of secondary thyroid suppression to prevent developmental sequelae from undiagnosed hypothyroidism.[39,44,45]

Our infant was treated with povidone-iodine for a GO and was noted to have developed hypothyroidism during a routine 3-week newborn screening. These findings are important because even though hypothyroidism secondary to exposure to topical povidone-iodine has been reported in the literature, our own center (and most in our region, as evident in a telephonic survey) has not routinely monitored thyroid levels in these patients. Giant omphalocele is not a very frequently-seen condition and so (a) our experience with/anticipation of iatrogenic transient hypothyroidism is limited; (b) premature infants might be at an enhanced risk of suppression of thyroid function due to developmental factors, and possibly of consequent neurodevelopmental delays; (c) there is a need to establish screening protocols in high-risk infants; and (d) there is a need to study the amount and duration of exposure to iodine in infants.[39,46–48] We were fortunate that our patient was diagnosed in routine newborn screens. This might not have been the case in every patient/unit/region.

We conclude that infants, especially preterm, who are exposed to repeated topical exposure to iodine-containing antiseptic solutions over a large surface area may be at risk of developing transient hypothyroidism. There is a need to remain cognizant of these complications and be aware of the need for close monitoring of thyroid function in high-risk infants. Early detection, timely treatment, and possibly, prevention of hypothyroidism can be helpful.[49] Once thyroid hormone supplementation is established, close coordination with endocrinologists will be needed for close monitoring.[50] We also need to evaluate alternatives for iodine-containing topical cleansing solutions in these infants.[51]

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