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# newborn

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***The Carlo GNS Center for Saving Lives at Birth***
***and The Vishwa Mahesh Parivaar***

***And***

***GNS Down Syndrome Foundation***
***Autism Care Network Foundation***
***Newborn Foundation of Azerbaijan***
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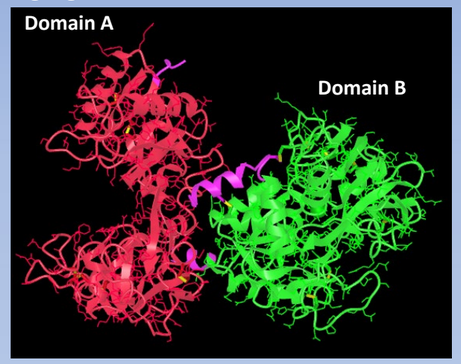
***National Federation of Neonatologists of Mexico***
***College of Neonatologists of the State of Jalisco, Mexico***
***The Skylar Project***
***International Society for Marginalized Lives***
***Friends Aid Africa, Bukedea, Uganda***
***Society of Bacteriophage Research and Therapy***
***GNS Center for Computational Scientific Methodology***
***GNS International Association of Neonatal POCUS***
***SABREE Enrichment Academy: Empowering Ability***

***Highlighted articles***:




**Lactoferrin: A multi-faceted glycoprotein in milk**

**A Bill of Rights for Children Born into Historically-Marginalized Communities**
**Medicine is not the Sole Determinant of Outcomes: Lessons to Learn from Neonatal Tetanus**
**Cryptophthalmos**

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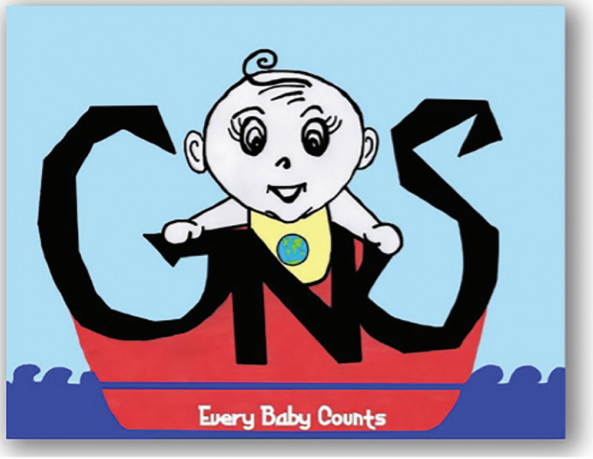
*Bibliographic Listing:*
J-Gate, Scilit, WorldCat,
PORTICO, ICMJE




**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.

## *Issue Information*

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# Contents

EDITORIAL 10.5005/newborn-4-2-iv

## It's time: Let's Erase Racism

Racism begins to affect lives starting *in utero*.[1] Pregnant mothers have noted unequal power dynamics, discrimination, and vulnerability in patient–provider relationships.[2-4] Black women recall the influence of mistreatment by providers in their healthcare decisions.[3] Latinas expressed fears of differential care because of immigration status.[5] There are also religious biases; Muslim ban has bolstered stereotypes in many situations.[6] Asian, Black, and Latina participants have experienced constant racism-related stress during pregnancy and childbirth **(Fig. 1)**.[1]

All administrative applications we fill on a day-to-day basis typically ask for information on race and ethnicity.[7,8] Race is projected as a formal definition of who we are as humans. It looks like a logical next subcategory following kingdom (animalia), phylum (chordata), class (mammalia), and order (primates). Common examples are White, Black or African American, Asian, Native American, and Pacific Islander. It contrasts with ethnicity, which seems to be more of a cultural identity rooted in geographical regions or ancestral roots; the Hispanic/Latino is an example.[9] However, in addition to the lack of need, there are inaccuracies. People with one shared racial identity can have different ethnic backgrounds.[10] Subjects racially categorized as Black may have different ethnic identities as Caribbean, African American, or Afro-Latino. Jews have been viewed in White, Black, and Middle Eastern racial subsets, and the Jewish identity is often tied more to ethnicity.

Racism is an extension of all these assumptions. It is a social/political construct, a belief that one race is inherently superior to another.[11] It can manifest in individual attitudes with beliefs/actions leading to prejudice or discriminatory institutional policies. The bias can be conscious or unconscious, and over time, established racial inequality can lead to structural stereotypes and manifest in laws, norms, financial assets, and social and educational disparities.[12] There can be societal consequences with discrimination in privilege, justice, and access to human/physical resources; we have seen slavery, colonialism, and segregation.[13] In South Africa, there was apartheid—strict racial separation laws gave power only to the white minority until the 1990s.[14] The genocide seen during the holocaust and in Rwanda cannot be forgotten.[15]

In the United States (US), racism has been a difficult problem for several centuries. The first enslaved Africans were brought to English colonies in Virginia in 1619. In the 17th and 18th centuries, millions of Africans were forcibly transported via transatlantic slave trade to work in tobacco, cotton, and sugar farms in the South. Even though some resistance was seen in the Stono rebellion, the practices continued to be justified through racist ideologies. The Civil War began in 1861, where slavery was a key issue. The Emancipation Proclamation of 1863[16] declared the freedom of enslaved people in Confederate territories, and then the 13th Amendment of 1865[17] finally abolished slavery throughout the US. There was a 10-year period of reconstruction but the subsequent Jim Crow law[18] again brought in disenfranchisement, segregation, and racial violence. The next 50 years saw a Great Migration[19] of millions of people towards the North and West to escape racism. A major social movement first led to the desegregation of schools in 1954,[20] and then in 1964, the Civil Rights Act finally banned discrimination.[21] The Voting Rights Act of 1965 then removed barriers to voting.[22] These societal changes were a major landmark; the best-known leaders of this movement include Martin Luther King Jr.,[23] Malcolm X,[24] Rosa Parks,[25] and Fannie Lou Hamer.[26] Unfortunately, even though we have made progress, racism continues to be an important issue even today. The "Black Lives Matter",[27] a political and social movement, was launched to highlight racism and related inequality, discrimination, and violence experienced by black people. We need more such efforts.

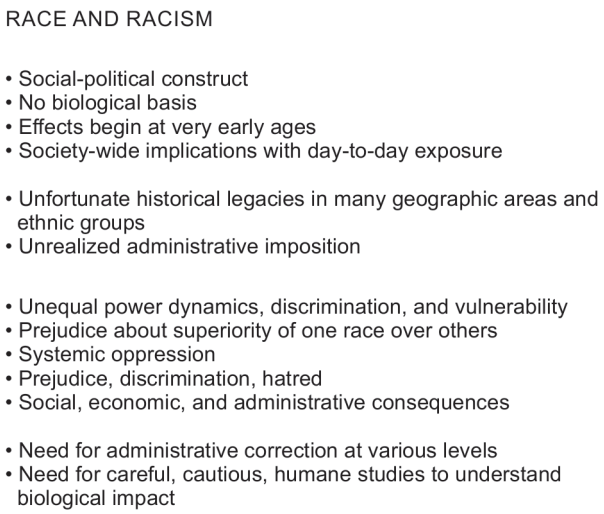


**Fig. 1:** We need to understand, study, and correct the impact of racism at various levels in the society.

Modern scientific research, particularly in genetics and anthropology, has shown race to be more of a social-historical-political construct, not a biological one.[28] However, medicine has a long history of defining race in biological terms whereby races are viewed as genetically distinct populations.[1,28] This racial essentialism, where racial groups are viewed as different due to inherent, biological or genetic characteristics,[29] is scientifically inaccurate and contributes to healthcare disparities. The prevalence of sickle cell disease (SCD), cystic fibrosis, sarcoidosis, and glucose-6-phosphate-dehydrogenase deficiency in different regions have been ascribed to race, not different geographic origins.[30–33] SCD has originated in regions with a high incidence of malaria as it does provide some resistance to these infections.[34] In patients with cystic fibrosis, specific mutations can possibly be associated with different places of origin.[35] Thus, we have been conveniently using race as a proxy for geography and contributing to an incomplete picture of the disease. Many clinical algorithms, equations, and risk assessment tools adjust recommendations by racial categorization.[36] The National Institutes of Health's National Human Genome Research Institute states that more genetic variation exists within, not between, racial groups.[37]

2025 is one year when the United Nations (UN) has continuously focused on lessening the impact of racism in the world. A Forum on People of African Descent was formed in April 2025. The 4th session of the Permanent Forum on People of African Descent took place at the UN Headquarters in New York. The 60th anniversary of the International Convention on the Elimination of All Forms of Racial Discrimination was observed on March 21, 2025. Starting January 1, 2025, a 2nd International Decade for People of African Descent has been recognized (2025–2035). The goal is to advance recognition, justice, and development for people of African descent. In its June 2025 report, the United Nations Children's Fund (UNICEF) has outlined efforts to implement antiracism reforms within its operations. And finally, the Geneva Alliance against Racism, launched in 2023, has continued its work with 16 corporate pledges and annual scorecards to root out racism within UN agencies in Geneva.

As we are all aware, 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. Similar to our previous issues, we present 8 articles here **(Fig. 2)**. In this issue, Harold et al.[38] have proposed a Bill of Rights for children born in historically marginalized communities, aiming to raise awareness about the dignity, equity, and healing during the fetal, perinatal, and neonatal periods, and in early childhood. This declaration responds to the pervasive and persistent disparities that disproportionately affect socially and economically disenfranchised populations.[39] Through 10 explicit rights,[40] the framework outlines the need for humane, effective care. They present a blueprint for clinical practice reform, institutional reflection, and policy reimagination; the goal is to position lived experience, cultural insight, and emotional integrity to promote healing and delivery of care. This Bill of Rights challenges systems to move beyond mere symbolic inclusion towards a structural transformation.

Moving from this line of discussion, we once again remind our readers and ourselves that the Global Newborn Society (GNS) aims for a worldwide social movement for improving neonatal care. The Dr Mozib Newborn Foundation is now fully registered in Bangladesh. A Vishwa Mahesh Parivaar (Global Mahesh Family) and its regulatory committee has been established in India to support the journal and the forthcoming conference in Sweden through intellectual/financial contributions. The American Society for Black Lives has decided to rename itself as the International Society for Marginalized Lives, to be more inclusive. Now our group is comprised of these 4 sponsoring organizations and 45 other organizations. We regularly consult each other and share scientific data, viewpoints, and our experiences relevant for care of newborn infants in various parts of the world.

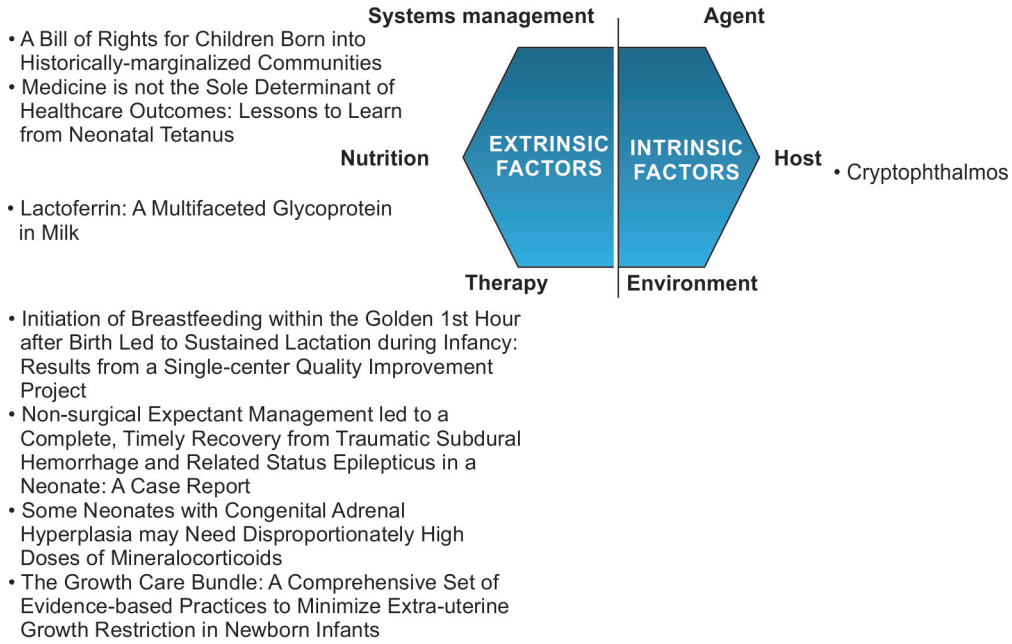


**Fig. 2: Areas of focus in the *newborn,* Volume 4, Issue 2.** We have expanded the traditional agent-host-environment trinodal disease model to a hexagonal system. The three additional foci represent extrinsic factors that can affect health - those originating in therapy, nutrition, and systems management are shown. This issue covers 4 nodes, with articles focused on host factors, therapy/monitoring systems, nutrition, and systems management.

The Global Newborn Society thanks Professor Drs Akhil Maheshwari, Kei Lui, and Mario Motta for their service as the Editors-in-Chief of the journal *newborn* for the period of January 2022 to March 2025. During their period of service, the 121 articles were published in the journal and these have been cited 331 times.[41] We are grateful to have had this chance to serve in their positions and have listed ourselves at the end of this article. As a first goal, we plan to apply to the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) to enlist the journal in medical literature resources such as PubMed.

In each issue of this journal, our editorial team highlights the achievements of one of our partnering members. Here, we present the Hospital Civil de Guadalajara "Dr Juan I Menchaca" located in Guadalajara, Jalisco, Mexico **(Fig. 3)**.[42] The Division of Pediatrics, which is comprised of Neonatology and Infectious Disease Services, is renowned for its research contributions in transient tachypnea of the newborn, hyaline membrane disease, and invasive candidiasis in newborn infants. The neonatal unit has 27 beds committed for intensive care, 32 for intermediate care, and 25 for growing infants. The teaching service for both national and international students is centered at the University of Guadalajara.

Michie et al.[43] have recounted the historical experiences with neonatal tetanus to show medicine is not the sole determinant of healthcare outcomes. Even though the neonatal mortality has decreased over the last 100 years, problems such as neonatal tetanus remain.[44] One challenge has indeed been in quantifying the case burden,[45] but increasingly, we are also realizing that medicine may not be the sole determinant of healthcare outcomes.[46] We need to standardize and focus our practices afresh to engage parents and clinical care-providers.[47] Newer methods using geo-temporal mapping applications[48] can help quantify the number of individuals in a target population who are reachable by existing immunization locations.[49]

Bagga et al.[50] have developed a growth care bundle[51] focused on evidence-based practices[52] to minimize extrauterine growth restriction (EUGR) in infants.[53] EUGR, defined as a discharge weight below the 10th percentile (Z score: –1.28),[54] is associated with increased morbidity/mortality in premature and very-low-birth-weight (VLBW) infants.[55] There are potentially modifiable factors related to nutrition, feeding guidelines, and environmental factors; and other issues such as chronic maternal illnesses, placental abnormalities, genetic conditions, intrauterine growth restriction, and extreme prematurity that can impact an infant's growth in the immediate extrauterine period. There is a need for identification, standardization, implementation, evaluation, and continual monitoring of growth-restricted infants after birth.[56] In this article, the authors have proposed a 5-pronged care bundle comprised of steps to optimize enteral feeding, parenteral nutrition, growth monitoring, metabolic rates, and postdischarge follow-up. They plan to follow these guidelines and evaluate the impact on the rates of EUGR in 3 years.

Sahota et al.[57] have reported a small single-center study to show that the effects of early initiation of breastfeeding within the Golden 1st Hour after birth[58] on lactation were sustained throughout the 1st year. They had low breastfeeding rates at their center despite repeated efforts focused on recruitment of experienced staff and education of mothers. Hence, they developed a quality-improvement project[59] focused on infants born at ≥35 weeks' gestation to increase breastfeeding rates. A multidisciplinary team was developed[60] to promote early initiation of breastfeeding.[61–63] They studied 756 mother-infant dyads over a 1-year period. Early initiation of breastfeeding increased the number of HM-fed infants from 8% to 88% within 3 months. A minor, statistically insignificant drop in breastfeeding rates to 82% was seen at 6 months but reinforced educational efforts restored this success back to 87% within a month. These rates were then maintained throughout the rest of the year. They suggest that early initiation of breastfeeding is more important than hitherto recognized.

Mohammadabadi et al.[64] have described the characteristics of lactoferrin, a multifaceted glycoprotein in milk that carries iron and other trace metals important for infant nutrition.[65] This protein also shows important antibacterial, antiviral, anti-inflammatory, and antioxidant properties.[66] Lactoferrin is present in high concentrations in mammalian milk;[67] it is often the most abundant protein in milk


**Fig. 3:** A-B. Hospital Civil de Guadalajara "Dr. Juan I. Menchaca" located in Guadalajara, Jalisco, Mexico. The hospital is renowned for its Pediatric Neonatology and Infectious Disease Services. C-F. Units for intensive care and for infants with decreasing acuity of illness.

after casein.[68] The current review highlights our understanding of lactoferrin's structure, properties, and possible clinical applications, offering insights for future research and the development of functional products.

Arora et al.[69] have described an infant with cryptophthalmos, a rare congenital disorder characterized by incomplete/total separation of eyelids.[70,71] Here, the authors have described a premature infant with bilateral cryptophthalmos. The lids were completely fused on the right; the left side showed partial fusion but there were no responses to light. Sonographic examination showed aphakia and cryptopthalmos on the right, and a microblepharon on the left side.[72] There was also a peripheral pulmonary stenosis and renal cortical cysts.[73,74] Genetic studies showed known autosomal recessive compound heterozygous variants,[75,76] p.Arg2167Trp,[77,78] in the gene *FREM2* (Fraser syndrome 1-related extracellular matrix protein 2).[79] This article provides a summary of diagnostic approach and management strategies available for these infants.

Nair et al.[80] report their recent experience with a 10-day-old neonate who was admitted with status epilepticus following a head injury. There was a left parietal extradural hemorrhage (EDH) with a midline shift of 3 mm. EDH is not a frequent occurrence in neonates but when it occurs, it is potentially life-threatening.[81,82] If there are seizures, the situation is viewed with even greater concern.[83] Since this infant showed signs of severe injury with continuous seizures,[84] the surgeons had a pessimistic view of the likely outcome. Hence, the medical team counseled the family very cautiously and decided for conservative management without surgical intervention to observe the clinical course. Interestingly, the EDH began to resolve with improvement in the EEG pattens over 48–72 hours. This report shows that all infants with EDH might not need emergency surgical intervention. We need to re-evaluate our protocols for assessment of these patients.

Finally, there is a report[85] about congenital adrenal hyperplasia (CAH)[86] and mineralocorticoids;[87] infants with CAH need hormone replacement beginning in early infancy to avoid abnormal metabolic effects and progression of masculinization.[88,89] The authors describe an infant in whom the diagnosis was established in the early neonatal period and hormone replacement was started immediately. The infant showed increasing needs for fludrocortisone,[90] from an initial 50 mcg/day to 300 mcg/day during the neonatal period. The authors have noted that infants with CAH, particularly those with the salt-wasting form,[91] may require disproportionately higher doses of mineralocorticoids than would be needed in adults who have lost adrenal function. The underlying reasons remain unclear and might reflect an interplay of multiple mechanisms.

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DEDICATION

# A Bill of Rights for Children Born into Historically-marginalized Communities

Sonji Fatima Harold[1–5], Deborah Discenza[1–5], Latoya Blueford[1–5], Waldemar A Carlo[1–7], Akhil Maheshwari[1–18]

## Abstract

This article presents a bill of rights for children born into historically-marginalized communities, aiming to safeguard the dignity, equity, and healing during the fetal, perinatal, and neonatal periods, and in early childhood. This declaration responds to the pervasive and persistent disparities that disproportionately affect Black, Indigenous, Latinx, immigrant, and economically-disenfranchised populations. Drawing from the principles of cultural humility, trauma-informed care, and structural justice, this article reviews the limitations of procedural compliance and advocates for a paradigm of ethical presence and relational accountability. Through 10 explicit rights, the framework outlines the need for humane care that is operational, not merely aspirational. There is a blueprint for clinical practice reform, institutional reflection, and policy reimagination; the goal is to position lived experience, cultural insight, and emotional integrity to promote healing and delivery of care. Finally, this bill of rights challenges systems to move beyond symbolic inclusion toward a structural transformation, to prioritize safety, voice, and wholeness for these individuals and their families, especially those left historically at the margins.

**Keywords:** Black, Blueprint, Cultural insight, Economically-disenfranchised, Emotional integrity, Immigrant, Indigenous, Infant, Latinx, Reform.

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## Key Points

- Whereas, this is agreed upon, we present a bill of rights for children born into historically-marginalized communities, aiming to safeguard the dignity, equity, and healing during the fetal, perinatal, and neonatal periods, and in early childhood.
- Whereas, this is agreed upon, this declaration is a response to the disparities that affect Black, Indigenous, Latinx, immigrant, and economically-disenfranchised populations.
- Whereas, this is agreed upon, we present the limitations of procedural compliance and advocates for a paradigm of ethical presence and relational accountability.
- Whereas, this is agreed upon, this Charter challenges systems to move beyond symbolic inclusion toward a systemic transformation, to prioritize safety, voice, and wholeness for these patients and their families.

## Introduction

The Global Newborn Society aims to study life from the time of conception to the age of 5 years after birth. Despite all the scientific and technological advancements expanding the pivotal crossroads during the fetal, perinatal, neonatal, and early childhood periods, the outcomes remain tragically disparate. The chasm between access and equity remains unacceptably wide for historically-marginalized populations. Black women face much higher maternal mortality rates than in their white counterparts. Latinx, Indigenous, immigrant, and low-income families continue to report institutional neglect, cultural erasure, and trauma in various social settings. These disparities are not aberrations; these are a symptom of a structurally-flawed system that often fails to see, hear, and serve those outside the normative center of power. This article proposes a transformative framework – each component grew in our discussions from being merely a definition of policy to become a moral reckoning, a call for healthcare institutions to interrogate their values and practices.

[1]S.A.B.R.E.E. Enrichment Academy, Saint Louis, Missouri, United States

[2]The Skylar Project, Estia St. Daphne, Alabama, United States

[3]American Society for Marginalized Lives, Harrison, New York, United States

[4]PreemieWorld Foundation, Springfield, Virginia, United States

[5]Global Newborn Society, Harrison, New York, United States

[6]Pediatrics/Neonatology, University of Alabama at Birmingham, Birmingham, Alabama, United States

[7]Carlo GNS Center for Saving Lives at Birth, Birmingham, Alabama, United States

[8]Pediatrics/Neonatology, Boston Children's Health Physicians Group at the Maria Fareri Children's Hospital, New York Medical College, Valhalla, New York, United States

[9]GNS Forum for Transgenerational Inheritance, New York, United States

[10]Banaras Hindu University Institute of Excellence, Varanasi, Uttar Pradesh, India

[11]Mongolian Association of Obstetrics, Gynecology, and Neonatology, Ulaanbaatar, Mongolia

[12]Bangladesh Neonatal Foundation, Dhaka, Bangladesh

[13]Autism Care Network Foundation, India

[14]Neonatology-Certified Foundation, Brooksville, Texas, United States

[15]GNS Infant Nutrition Education Program, Harrison, New York, United States

[16]Pioneers - looking for sustainable ways to reduce infant mortality, Oslo, Norway

[17]St. Bernards Healthcare, Jonesboro, Arkansas, United States

[18]International Prader-Willi Syndrome Organization, Cambridge, United Kingdom

**Corresponding Author:** Sonji Fatima Harold, S.A.B.R.E.E. Enrichment Academy, Saint Louis, Missouri, United States, Phone: +1 3104918012, e-mail: drsonjifatima@sabreeenrichmentacademy.org

It challenges the notion that procedural adequacy is sufficient in spaces where lives hang in the balance. It asserts that true healing cannot take place in environments that replicate the very harms they claim to redress.[1]

Each right articulated within this document reflects a core tenet of ethical care. These rights are not idealistic abstractions; we view each as a practical and actionable standard drawn from both lived experience and emerging best practices in culturally responsive, trauma-informed, and equity-centered care. They represent the accumulated voices of parents who have stood in neonatal intensive care unit (NICU) corridors without answers, of families who have buried children without being acknowledged, of patients who have advocated through language barriers and cultural misunderstandings, only to be labeled noncompliant. This framework asserts that justice must be structurally embedded, not simply offered as an apology after harm has occurred. Through this bill of rights, the article seeks to reimagine care not as a transaction, but as a relationship; one that affirms the sacredness of life, the wisdom of culture, and the resilience of the human spirit. It is both a diagnostic tool and a roadmap for reparation. At its heart, this work is not only about reducing harm; it is about restoring humanity (Fig. 1).

## Our Rights

In a world that too often minimizes the pain of the unseen, sanitizes the suffering of the unheard, and undervalues the lives of those historically excluded, this declaration rises, not as a polite appeal to power, but as a bold, sacred, and immovable assertion of worth. It is a collective cry for justice wrapped in affirmation, and a reckoning for systems that have grown comfortable with selective compassion. We need to let it stand not merely as words on a page, but as a call to conscience. Here is a reminder that healing spaces must first be equitable and fair spaces; this should stay alive in every waiting room, every exam room, every ward, and wing where decisions are made about lives that matter. Every life deserves dignity. Regardless of race, income, immigration status, language, ability, sexual orientation, or faith tradition.

Every baby counts – each time we lose an infant, we lose an entire life and its potential. Lives are not negotiable. Death, spoken through tears, translated across language barriers, whispered from exhaustion, or thundered with righteous rage, the voice is not optional. Every family deserves to be held fully, compassionately, and without condition. No one should have to explain their pain, prove their worth, nor perform composure in order to receive humane care.

This bill of rights is more than a document. It is a moral imperative, a human proclamation, a generational reckoning. It is born of bloodlines marked by endurance, by ancestors whose

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**Fig. 1:** Beautiful Black and Brown babies from historically-marginalized communities

names may never be recorded in medical journals, but whose sacrifices paved the way for this moment of declaration. It stands in honor of the babies in NICUs who are fighting for breath, as machines beep in rhythm with a mother's prayer. It honors the parents who have carried the ache of unanswered questions home from a hospital, their arms empty, their grief unacknowledged. It speaks for the families who have had to make impossible decisions under fluorescent lights, without cultural understanding, without trauma-informed care, and without the dignity of time.[2]

It is written for the patient who is asked to retell their story five times to five different providers, but never fully heard. For the person whose pain is measured against someone else's comfort. For those whose knowledge of their own body is undermined by institutions that prefer compliance over partnership. It speaks for the child of immigrants who translates medical instructions while still learning how to say "pain" in two languages. For every person whose existence has been considered inconvenient in a space that should have protected them. This bill of rights is for those whose pain was never charted, whose tears fell in silence, whose advocacy was mistaken for agitation, and whose insistence on being seen has always been a radical act. It is for those who walk into hospitals bracing for battle instead of comfort. It is for those who have waited too long for too little and left with more wounds than they brought in. Let it be known that healing must be equitable. Safety must be universal.

Compassion must be unconditional. Let it be declared: questions are not threats. Boundaries are not burdens. Self-advocacy is not disrespect. It is survival. Let it be affirmed: respect, dignity, informed consent, and cultural humility are not "nice-to-haves." They are the baseline. This is not a list of demands. It is a sacred restoration. It is the reclamation of what should have always been. It is the spiritual return of power to those who have had it stolen, and the prophetic refusal to ever be silenced again. In the face of systemic neglect and generational erasure, this bill of rights stands tall as a monument of resilience and a roadmap for reform. It is both a mirror and a mandate. It restores voice to the silenced, value to the devalued, and humanity to the dehumanized. It names the harm, honors the hurt, and insists that *from this moment forward*, we do better, not just in word, but in practice, policy, and presence. This is your right. This is your declaration. You are not invisible. You are not inconvenient. You are not asking for too much. You are asking for what should have always been yours. And this time, the answer must be yes. This is a collective standard. This is a sacred claim. This is a call for justice in every room where life begins, and in every moment that follows. Here are the 10 basic rights:

## 1. The Right to Dignity

Dignity is not a courtesy. It is a covenant. Every individual, no matter their race, ethnicity, primary language, faith tradition, socioeconomic status, immigration background, gender identity, sexual orientation, ability, age, or family structure, possesses an inalienable and sacred right to be treated with dignity in every encounter with the healthcare system. This right is not contingent upon how someone presents, how they speak, nor whether they conform to institutional expectations. It does not require prior approval, eloquent self-expression, nor perceived worthiness. It is not a reward for politeness nor patience. Dignity is inherent. It is irrevocable. It is owed simply because a person exists. To treat someone with dignity is to recognize the entirety of who they are, beyond symptoms, beyond charts, and beyond biases. It is to see a person not as a problem to be solved, but as a life to be honored. Every individual carries a sacred story, woven from struggle, resilience, and lived truth. Dignity is what allows that story to be heard, respected, and held. It requires more than clinical efficiency; it demands presence. It asks healthcare providers to show up not only with skill, but with humility, empathy, and humanity. There is perhaps no time more deserving of this sacred recognition than during moments of birth and bereavement, times when the human spirit is at its most raw and its most vulnerable. These are not just medical events to be monitored and managed. They are rites of passage, thresholds between life and loss, joy and grief, expectation, and eternity. To reduce birth to a medical task or to treat death as a routine procedure is to strip these moments of their sacredness. The birth of a child is a divine encounter. It is not just a clinical outcome; it is a profound transformation that must be approached with reverence, informed consent, and cultural sensitivity. And the loss of a child, or any loved one, is not an inconvenient detail in a shift change; it is an indescribable fracture in the heart that must be held with silence, gentleness, and sacred space.[3]

To deny someone dignity in these moments is not simply a breach of professionalism. It is a violation of moral and spiritual responsibility. When a provider ignores a mother's instincts, dismisses a father's grief, or fails to explain a procedure in terms a family can understand, they do more than overlook protocol. They inflict harm that lingers long after the physical wounds have healed. They deepen generational distrust. They widen the chasm between patient and provider. They plant seeds of trauma that may take years, or lifetimes, to uproot. But when dignity is centered, when care is offered with cultural humility, when every voice is honored without judgment, when presence is offered over performance, healing becomes possible. Trust begins to form. Safety becomes tangible. And the sacredness of life, in all its complexity and fragility, is restored. The right to dignity proclaims that no one should ever have to plead to be respected. No one should ever feel dehumanized while seeking help. No one should be made to feel disposable in spaces created for healing. Every person, regardless of circumstance, deserves to be seen, heard, and valued in their full humanity. They deserve to be treated not only as patients, but as people. As parents. As children. As souls. Because dignity is not an act of charity. It is an act of justice. And justice must begin with how we treat one another at our most vulnerable.

## 2. The Right to Culturally-responsive, Trauma-informed Health Care

Every individual and every family carry a rich and complex narrative that extends far beyond medical records and presenting symptoms. People do not enter healthcare spaces as blank slates; they arrive layered with memory, meaning, and often, pain, much of which is shaped by systemic forces far outside their control. They carry not only their physical ailments, but also the quiet burdens of generational trauma, historical disenfranchisement, cultural dislocation, and the inherited grief of those who came before them. For individuals from historically-marginalized communities, the medical space is not always a place of relief. It can be a place of reactivation, where past wounds are retraumatized, and longstanding fears of being dismissed, disrespected, or harmed are realized again. Culturally responsive, trauma-informed healthcare is not a luxury nor an optional enhancement. It is a fundamental right rooted in justice, humanity, and healing. It requires that providers move beyond the narrow confines of clinical detachment and lean

into a more holistic, contextualized, and compassionate approach to care. To be culturally responsive means to acknowledge and affirm the values, belief systems, communication styles, and ancestral legacies that shape a patient's identity and response to illness. To be trauma-informed is to understand how personal, historical, and intergenerational trauma, especially among communities of color, Indigenous people, immigrants, and survivors of violence, can influence a patient's ability to trust, communicate, and participate in their own healing.

This kind of care does not begin with a diagnosis. It begins with a posture. One of humility, openness, and deep listening. It means recognizing that medical training alone does not make one an expert in someone's lived experience. It calls for an intentional shift from power over patients to partnership with them. It asks the provider to not only ask "What's wrong?" but also "What happened to you?" and more importantly, "How can I honor who you are while I help you heal?" Culturally responsive, trauma-informed care sees the sacred in the stories. It respects the mother who clutches prayer beads while waiting for test results. It hears the father who speaks in proverbs, not prescriptions. It understands the grandmother who insists on burning herbs before surgery, not as superstition, but as a centuries-old act of spiritual preparation. It creates space for language, ritual, emotion, and ancestral knowledge without judgment. And when a patient is silent, withdrawn, or distrusting, it interprets this not as noncompliance, but as possible protection, a shield shaped by experience, not defiance.[4]

This right calls for more than passive tolerance. It demands active accountability. Healthcare systems and institutions must ensure that every member of their staff, from the receptionist to the specialist, is trained in cultural humility and trauma-informed care. This education cannot be a checkbox on a compliance form. It must be an ongoing, intentional, and deeply reflective process. It must include learning about the history of medical racism and reproductive injustice, confronting personal and institutional bias, and creating protocols that elevate respect, choice, and consent as sacred pillars of care. To treat without understanding is to risk wounding the very people one is meant to serve. And while good intentions may soothe the conscience, they do not shield against the real and lasting harm that results from cultural incompetence or clinical indifference. Compassion without context is not enough. Policies without perspective are not enough. True care requires both heart and history. The right to culturally responsive, trauma-informed health care affirms that no one should have to choose between being understood and being treated. No one should be forced to flatten their identity, to decode their grief, nor to justify their traditions in order to receive the care they need. Your culture is not a barrier to health care. It is part of your healing. Your trauma is not an inconvenience. It is a reality that deserves recognition. Your story is not too complicated. It is worth the time it takes to listen. This right insists that healing must be whole. That dignity cannot be divorced from context. That true medicine is not just technical, it is spiritual, emotional, and relational. And until the system sees every person through that full and sacred lens, it cannot call itself just.

## 3. The Right to be seen and Heard

In moments of profound vulnerability, especially in NICUs, emergency settings, and in the sacred space of bereavement, families must be recognized not as passive witnesses to their child's nor loved one's care, but as central figures in the story of their child's or loved one's life. They are not visitors to the clinical experience; they are emotional anchors, spiritual interpreters, and deeply attuned observers whose wisdom extends beyond what a monitor can measure, or a chart can capture. They know their children in ways no training manual ever could. Their voices must not only be invited; they must be honored, centered, and acted upon. The right to be seen and heard is not a courtesy; it is a cornerstone of dignified, ethical, and humanizing care. To see a parent or other individual is not merely to acknowledge their physical presence in the room. It is to understand the emotional weight they carry: the sleepless nights spent by incubators or bedside, the quiet prayers whispered into sterile air, the mental cataloging of every shift in temperature or tone, and the deep spiritual labor of holding hope and fear in the same breath. These families are doing far more than waiting; they are actively watching, interpreting, and protecting. And to truly *hear* them is not to simply allow them space to speak; it is to believe what they say. It is to treat their voice as data, as insight, as truth, not as interference. Neonatal intensive care unit parents, in particular, inhabit a paradoxical world. They are simultaneously invited to bond with their baby while being asked to stand back. They are encouraged to trust medical expertise while being left with unanswered questions. In this liminal space of machines and margins, they become extraordinarily attuned to the language of their baby's body, every pause in breath, every flinch, and every sigh. Their voices are shaped by both love and loss, by hope and hypervigilance. When they speak up, they are not reacting; they are responding to something real. Ignoring them is not only disrespectful; it is dangerous.

The same holds true for grieving families, who are navigating the most devastating rupture of the human spirit. The death, or impending death, of a child is not a clinical event; it is a soul-deep shattering that demands reverence, not routine. These families do not need to be protected from the truth; they need to be protected *within* the truth. And in those moments, their rituals, beliefs, stories, and requests are not distractions; they are sacred acts of meaning-making. Their voices are not to be managed; they are to be held. To silence these families, whether through medical jargon, dismissive gestures, or institutional rigidity, is to inflict further harm in the moments when gentleness is needed most. To override a parent's concern, to minimize their insight, or to label their advocacy as disruptive is not only a breach of care, but also a profound violation of human trust. Every concern, no matter how it is voiced, deserves acknowledgment. Every observation, no matter how emotional, deserves consideration. And every story, no matter how painful, deserves space to be spoken, to be witnessed, and to be honored. Healthcare professionals must move from a paradigm of control to a posture of collaboration. The goal is not to manage families, but to partner with them. That partnership means relinquishing the assumption that clinical expertise is always supreme. It means understanding that when a parent advocates passionately, it is not an attack, it is love in action. When they ask questions, it is not to undermine authority, it is to participate in the care of the person they love most. Emotion is not a liability. It is a form of sacred intelligence. The right to be seen and heard affirms that families, especially in the NICU and during times of loss, deserve more than presence. They deserve presence *with power*. They deserve to be seen as the coauthors of care and the rightful narrators of their own experiences. Their words are not background noise. Their insights are not optional. Their presence is not ornamental. Their perspective is essential. When healthcare systems choose to truly see and hear the families they serve, they begin the real work of healing, not just

the body, but the breach between institutions and those they are called to protect. It is in listening with humility, and responding with empathy, that care becomes sacred again.

## 4. The Right to Self-advocacy without Retaliation

In the intimidating world of health care, where sterile corridors often echo with authority and where patients and families are expected to defer quietly to medical expertise, speaking up is a radical act of self-preservation. It is not easy to find your voice when you are in pain, afraid, or grieving. It is not easy to ask questions when you feel outnumbered, outpaced, or overwhelmed. For many individuals, especially those from historically-marginalized communities, the simple act of self-advocacy can feel like walking a tightrope between survival and silence. To say, "Something does not feel right," or "I need more information," or "I do not agree," requires not only courage, but conviction. It demands a level of internal strength that must rise above exhaustion, cultural barriers, implicit bias, and the historical memory of systems that have not always been safe. Yet when individuals and families do speak up, their voices are too often misinterpreted as defiance. Their questions are viewed as threats. Their emotions are seen as liabilities rather than signals of deep engagement and care. The right to self-advocacy without retaliation asserts that every person has the inalienable right to advocate for their well-being, their loved ones, and their dignity, without fear of dismissal, retribution, or shaming. This right is especially critical in moments of grief, crisis, or injustice, when advocacy is not an option, it is a lifeline. It is the language of survival in a system that too often expects passivity, even when the stakes are life and death.

Self-advocacy is not a disruption. It is a dimension of healing. It is the expression of human intuition, intelligence, and self-awareness. Families that question, clarify, or challenge decisions are not being "difficult"; they are doing what anyone would do when love and responsibility collide. Their advocacy is not a failure to trust; it is a plea to be treated as partners, not pawns. And yet, in too many clinical environments, the emotional labor of self-advocacy is met with resistance, not respect. A mother advocating for her child is labeled "emotional." A father asking for another opinion is seen as "demanding." A patient raising concerns about pain management is dismissed as "drug-seeking." These characterizations are not neutral; they are violent reductions of complex, legitimate human behavior. They strip people of the right to assert control over their own bodies and silence the very voices that most need to be heard. This silencing is more than harmful; it is retraumatizing. It teaches patients and families that asking for respect may cost them care. It reinforces the myth that professionalism requires emotional detachment. And it communicates, whether overtly or subtly, that dignity must be negotiated, earned only by those who ask quietly, express gently, or suffer silently.

But true care, ethical care, does not punish voice. It does not penalize presence. It does not shame people for showing up as their full, feeling selves. Healthcare institutions must do more than tolerate advocacy. They must actively protect it. This includes training providers to respond without defensiveness, listening without assumption, and building systems that create safety for dissent, discussion, and diverse communication styles. It means teaching staff that a raised voice may be the echo of generations who were never allowed to speak. That tears may be truth leaking through exhaustion. That frustration is not resistance to healing; it is often resistance to being erased. The right to self-advocacy without retaliation is not simply a patient-centered value, it is a justice-centered demand. No one should have to choose between being heard and being helped. No one should have to silence their perspectives to preserve their safety. No one should be told, directly nor through tone, policy, nor posture, that their questions are too much, their presence too loud, and their pain too inconvenient. To advocate is not to disrespect care. It is to deepen it. To protect it. To ensure that healing is not a transaction, but a collaboration grounded in mutual trust. Let it be declared with clarity and compassion: Speaking up is not the problem. Silencing those who do is.

## 5. The Right to Equity and Justice in Medical Outcomes

Health care should never be a gamble. It should never be a privilege tied to wealth, proximity, whiteness, nor the ability to navigate complex systems with ease. Health care, real, life-affirming care, should be a guarantee rooted in the inherent worth of every human being. It should protect life not selectively, but universally. Yet for too many individuals, particularly those from Black, Indigenous, Latinx, immigrant, low-income, and historically excluded communities, access to health care has not meant access to outcomes. It has meant surviving *despite the system*, not because of it. The right to equity and justice in medical outcomes is a bold affirmation that families do not deserve merely access, they deserve accountability. It is not enough to say that a patient was "seen" if they were not truly *served*. A warm tone and kind words cannot cover the failure to diagnose, to listen, nor to intervene in time. A clean facility and polite staff cannot erase preventable harm. Respectful bedside manner does not redeem fatal neglect. Being treated with momentary dignity is not the same as being protected across the arc of care.

True justice in health care demands that we look beyond the front door and examine the exit outcomes. Who leaves the hospital whole? Who leaves broken? Who never leaves at all? It is not sufficient to boast about diversity in waiting rooms when the disparities in discharge outcomes, maternal mortality, and infant death remain appallingly unchanged. We cannot talk about healing while willfully ignoring harm. We cannot celebrate compassion while entire communities are grieving what should have been preventable loss. We cannot claim progress while Black mothers die at three to four times the rate of white mothers, regardless of income or education. These disparities are not theoretical. They are not random. They are systemic. They are structural. And they are a direct result of centuries of exclusion, exploitation, and erasure. Indigenous women and Latinx families continue to face heightened risks due to a combination of language barriers, insufficient culturally responsive care, and the lingering impact of colonial trauma. Immigrant families must often navigate healthcare systems that are not only unfamiliar, but unwelcoming, systems that question their right to exist before honoring their right to heal. And it is not just about maternal and infant health. The patterns persist across chronic illness, pain management, cancer screenings, mental health diagnoses, and more. Bias is baked into medical education. Discrimination is embedded in provider attitudes. And funding disparities ensure that the most vulnerable communities continue to receive the fewest resources. To call for equity in outcomes is to confront this painful legacy head-on. It is to say, unapologetically, that intent is not enough. That apologies after harm are not enough. That outcome data must be disaggregated, analyzed,

and addressed, because until we know who is dying and why, we will continue to mistake activity for impact and access for equity.

True equity means that birth is no longer a battlefield for Black and Brown women. It means that immigrant families are not denied care because of documentation status or language barriers. It means that cultural practices are respected, that pain is taken seriously, and that treatment is tailored, not just for disease, but for humanity. It means that justice lives in the numbers, in the patient experiences, in the survival rates, in the quality-of-life outcomes, not just the quality of the facilities. To demand justice in medical outcomes is to ask the hard questions: Whose body is listened to, and whose is dismissed? Whose pain is believed, and whose is minimized? Whose life is prioritized, and whose is quietly grieved as "unfortunate but unavoidable"? And who gets to decide what is "acceptable" in terms of risk, response, and responsibility? The right to equity and justice in medical outcomes insists that we stop applauding effort and start measuring impact. That we stop framing disparities as unfortunate and start naming them as unacceptable. That we stop using "better than before" as a benchmark when lifesaving is the rightful standard. It is a demand for outcome accountability, not just procedural compliance. It is a call for hospitals, providers, institutions, and policymakers to restructure care around those who have been most harmed, not as an act of charity, but as a matter of justice. Because justice in health care is not a metaphor. It is not a buzzword. It is a deliverable. And it must be built, protected, funded, and measured, not once, but every single time care is given.

## 6. The Right to Compassionate Grief Support

The loss of a loved one, or even more devastating, the loss of a child, whether through miscarriage, stillbirth, during delivery, in the NICU, or in the fragile hours and days that follow, is not just a clinical outcome. It is a soul-shattering rupture. It is an unmaking of joy, a redefinition of self, and a quiet yet thunderous dislocation of everything a parent thought they understood about life and love. It is a grief that lives in the deepest chambers of the heart and radiates through every cell, memory, and future moment that will now be lived differently, forever altered by absence. This kind of loss is not merely experienced, it is embodied. It is etched into the spirit. It becomes part of the landscape of a parent's identity. And yet, in too many healthcare systems, it is treated as a footnote. A difficult outcome. A discharge with a follow-up phone number. But grief is not a line item in a medical chart; it is a sacred journey that deserves reverent, continuous care. The right to compassionate grief support affirms that no family should walk through loss unsupported, unseen, nor unacknowledged. It affirms that parents deserve more than polite condolences or quiet avoidance; they deserve to be surrounded by clinicians, chaplains, social workers, and systems that will hold space for their devastation without trying to rush, repair, or reduce it.

They deserve care that continues after the physical body of their child is no longer present. That care must be immediate, but it must also be enduring. It must include structured grief counseling, trauma-informed follow-up, connection to bereavement groups, spiritual guidance, culturally and linguistically appropriate resources, and opportunities to memorialize and honor their child. It must include hospital policies that center compassion over liability, flexibility over formality, and dignity over procedure. Because while discharge may mark the end of a medical stay, it is only the beginning of a lifelong journey with loss. Far too often, the emotional and spiritual needs of bereaved families are abandoned once clinical care has ended. The machines grow quiet. The staff retreat. And families are left to piece together their brokenness in a world that moves too quickly and speaks too little about their kind of grief. Without intentional, ongoing support, the silence becomes deafening. The absence becomes isolating. And the opportunity for healing, through reflection, community, and ritual, slips further from reach. Compassionate grief care demands a new kind of attentiveness, one that does not see grief as a temporary inconvenience, but as a permanent part of the family's story that requires sacred tending. It must be as varied as the people it serves. Some families will need space to be still; others will long to speak. Some will want to return to traditional spiritual practices; others will grieve through activism, art, or solitude. All of it must be welcomed. None of it should be judged. This right also recognizes that grief is deeply cultural. It is racialized. It is shaped by history, access, and power. Black, Indigenous, Latinx, and immigrant families, those already disproportionately affected by maternal and infant loss, must not only be included in conversations around bereavement care; their voices and rituals must shape the model. Grief that is expressed loudly, communally, or spiritually must not be pathologized. Grief that is embodied through tears, silence, prayer, or song must not be dismissed.

To truly support families in the wake of loss, healthcare systems must interrogate their own comfort levels with death, their biases about who deserves extended care, and their tendency to retreat when the outcome is not "successful." They must fund grief-informed programs not as charity, but as equity. They must train staff not just in what to say, but how to *be*, in stillness, in humility, in solidarity with those whose world has collapsed in front of them. The right to compassionate grief support is also a demand for dignity. It says: You do not have to collapse privately to be believed. You do not have to be strong to be supported. You do not have to grieve quietly to be respected. You have the right to fall apart and still be held. You have the right to grieve visibly, culturally, messily, and receive care that meets you there, without judgment nor expiration date. Because to lose a child is not just to lose a heartbeat; it is to lose birthdays, first days of school, lullabies unsung, and stories unfinished. And no family should lose, in addition, the care they were promised. Let it be etched into every corridor of every care facility: Grief is not a disruption to care; it is an extension of it. It is not a side effect; it is a sacred rite of passage. And it is not a private burden, it is a communal invitation for us to show up as healers, listeners, and witnesses to love in its most broken and beautiful form.

## 7. The Right to Healing-centered Spaces

Healing is never one-dimensional. It is not simply the mending of tissue, the regulation of vitals, or the administration of medication. True healing is emotional, spiritual, psychological, and cultural. It is the rebuilding of trust after betrayal, the restoration of dignity after dismissal, the reclaiming of power in places where silence was once survival. But healing cannot flourish in spaces that replicate the very traumas they are meant to relieve. It cannot take root in clinical settings where bodies are seen but souls are ignored. The right to healing-centered spaces affirms that every patient, regardless of race, background, income, gender identity, immigration status, or language, has the right to receive care in

an environment that not only avoids harm, but actively fosters restoration, belonging, and respect. It is not enough for hospitals and clinics to offer services. They must offer sanctuary. For many patients from historically-marginalized communities, walking into a healthcare facility is not a neutral act, it is often one steeped in vigilance, fear, and memory. The space itself can be a trigger. It may call back lived or inherited experiences of racial bias, medical neglect, misdiagnosis, or loss. Cold waiting rooms, indifferent gazes, or tone-deaf interactions are not minor details, they are reminders of historical exclusion and ongoing erasure. These microaggressions are not isolated; they compound. And when experienced during moments of vulnerability, such as illness, childbirth, or grief, they do not just wound; they deepen the harm that healing is meant to undo. Healing-centered spaces must be intentionally cultivated on three levels: environmental, relational, and institutional.

- Environmentally, these spaces should be warm, welcoming, inclusive, and trauma-informed. Waiting areas should reflect the culture and community they serve, not as decoration, but as declaration. Signage, imagery, and even architectural flow should communicate: *You are seen. You are safe. You are not an outsider here.*
- Relationally, providers must be trained not only in the science of care but in the sacred art of connection. They must understand that tone matters, that silence can either soothe or sever, and that presence is sometimes more healing than prescription. They must be taught to *honor narrative as much as they honor lab results*, and to listen with both clinical clarity and cultural humility.
- Institutionally, healing-centered care demands accountability, not abstraction. It demands that systems dismantle any policies, practices, or attitudes that prioritize efficiency over empathy, or compliance over compassion. It means questioning whose voices shape protocol, whose pain is deemed "valid," and whose behaviors are labeled as "noncompliant" when they are, in fact, cultural expressions of distress.

A healing-centered space does not expect families to check their emotions, culture, or grief at the door. It does not demand composure to earn credibility. It does not pathologize emotion, nor penalize passion. Instead, it creates room for full expression. It says, "Your feelings are not too loud here. Your fear is not inconvenient. Your advocacy is not a threat. You are already enough." And when it comes to perinatal and infant loss, NICU trauma, or maternal complications, this right becomes even more sacred. A healing-centered space does not simply offer a room to deliver or recover. It becomes a vessel for sacred transitions, a space where life begins, where grief is held, and where families are allowed to cry, question, rage, rest, or remember without shame. It is a space where ritual is invited, where storytelling is welcomed, and where silence is understood as a holy act, not an absence of need. To build healing-centered spaces is to make justice tangible. It is to stop asking families to adapt to systems that were never designed with them in mind, and to instead reshape those systems until they honor every voice, every culture, and every kind of healing. It means acknowledging that physical safety is just the starting point. Emotional safety, spiritual alignment, and cultural integrity are just as critical, and must be treated with equal urgency. Let it be said without apology: Sterile is not the same as safe. Neutrality is not the same as justice. Quiet is not the same as comfort. And presence without empathy is not healing. The right to healing-centered spaces demands that institutions commit, not only to avoiding harm, but to cultivating conditions where every person can reclaim their breath, their voice, and their wholeness. It requires healthcare leaders to continuously ask themselves: *Does this space protect? Does it empower? Does it see the people who walk through it, or only treat their charts?* Because healing begins long before a procedure and continues long after a prescription. It begins with how people are welcomed, how their stories are heard, and whether they leave not only treated, but transformed.

## 8. The Right to Informed Participation in Care Decisions

In health care, especially when it involves the life of a child, information is not a courtesy. It is not a privilege to be granted at the discretion of medical professionals. It is a right. A moral obligation. A matter of justice. Parents and guardians must not only be informed; they must be involved. And not just when it is convenient or when the outcome is certain, but always, especially when the stakes are high, the path is unclear, or the prognosis is complex. The right to informed participation in care decisions declares that every parent, guardian, and caregiver has the sacred right to fully understand, question, and contribute to every decision made regarding their child's or loved one's care. This includes, but is not limited to, being briefed in clear, jargon-free language; receiving regular and proactive updates about their child's or loved one's condition; being included in discussions of treatment options, risks, and alternatives; and being offered interpretation and translation services without delay, shame, nor resistance. Medical expertise is essential. But it must never be used to obscure, override, nor silence the voices of those who are entrusted with the life of a child. Parents bring a kind of wisdom that no textbook can teach. They are attuned to subtle shifts in their child's behavior, they understand cultural and familial context, and they often carry deep spiritual insight or intuition about what their child needs. This knowledge must not be sidelined in clinical conversations; it must be centered as part of an integrated care approach.

When information is withheld, whether intentionally, passively, or through inaccessibility, it sends a clear and harmful message: *You do not need to know. You do not get to decide.* But to withhold information is to withhold power. And when families are stripped of the power to make informed choices, they are not only disrespected, but they are also disempowered. That is not just poor communication. It is a violation of ethical care. Informed participation means more than consent, it means collaboration. True consent is not a signature on a form. It is an ongoing process of understanding, questioning, reflection, and choice. It requires time. It requires space. It requires trust. Families must never feel rushed into decisions they do not understand, nor pressured to accept a plan that does not align with their values or beliefs. They must feel safe enough to ask, *Why this? Why now? What are the alternatives?*, and know that these questions will be met with respect, not resistance. This right also includes access to second opinions, transparency about possible side effects or outcomes, and the ability to decline or delay certain interventions without fear of retaliation or judgment. When providers default to technical explanations that alienate rather than empower, or when care is administered without full and understandable disclosure, families

are no longer participants in their own narrative; they become spectators of decisions being made for them rather than with them.

Historically-marginalized families, particularly those who speak languages other than English, who come from low-income backgrounds, or who carry generational trauma from medical systems, face compounded barriers to informed participation. It is the responsibility of the healthcare system to remove these barriers, not the responsibility of the family to work around them. Language access, cultural sensitivity, and trauma-informed dialog are not optional; they are fundamental to building trust and ensuring ethical transparency. Informed participation is about honoring both agency and ancestry. It is about ensuring that families do not have to relinquish their voice, culture, nor autonomy in order to receive competent care. It is about building relationships between providers and families that are based not on hierarchy, but on shared humanity. Let it be known expertise does not equal authority over another's story. And clinical power must never become a substitute for ethical partnership. When parents and guardians are informed, respected, and invited to participate, care becomes more effective; trust becomes more possible; and outcomes become not only more equitable, but more humane. Because the goal of healthcare is not just to treat illness. It is to build relationships grounded in honesty, mutual respect, and shared decision-making. That is where healing begins.

## 9. The Right to grieve without Guilt or Erasure

Grief is not weakness. It is not inappropriate. It is not an interruption to care. It is care. Grief is a sacred language. It is the heart's cry when words fail. It is the body's trembling response to absence, the spirit's resistance to forgetting. It is not something to be solved, silenced, nor hidden. It is love with nowhere to go, and it must be allowed to exist, to be expressed, and to be seen. The right to grieve without guilt or erasure affirms that every family, especially those navigating the trauma of child loss, perinatal complications, systemic negligence, or cultural disenfranchisement, has the fundamental right to grieve without shame, without censorship, and without having to shrink their pain to fit the comfort levels of others. Grief is not a disruption to the medical process; it is an integral part of the healing journey. And yet, in too many healthcare settings, grief is treated as a problem to manage. Families are offered condolences in hushed tones, and then quickly ushered toward paperwork and discharge. The sterile language of "unfortunate outcomes" replaces the name of a child. Staff members shift awkwardly, unsure of what to say or do. And the deep, raw sorrow of parents, especially those from historically-marginalized communities, is often met not with reverence, but with resistance. This is not compassion. It is erasure.

To expect composure in the face of devastating loss is to confuse professionalism with humanity. To dismiss visible grief as "too much" is to miss the truth: that mourning is not a performance, it is a right. It is a form of protest against the silence that often follows tragedy. And it is an act of honoring the child whose life, however brief, mattered deeply. Let us be unequivocally clear: To cry is not to collapse. To ask questions is not to accuse. To express anger is not to be dangerous. To remember out loud is not to dwell in the past. It is to love. It is to survive. It is to reclaim space in a system that too often expects silence from the wounded. Grieving families must never be expected to suppress their sorrow in order to remain "respectable." They must not be asked to package their heartbreak into tidy narratives. They must not be told that time will heal all wounds, nor that their child is in a "better place," nor that they must be strong for others. These phrases, though often well-meaning, deny people the right to be fully present in their pain. Especially for families who are Black, Indigenous, Latinx, immigrant, low-income, or differently abled; whose voices have long been marginalized in medical settings, the right to grieve is not merely emotional. It is political. It is cultural. It is ancestral. These communities have developed their own languages of mourning: drumbeats, prayers, wails, silence, dance, candlelight, storytelling, and song. None of these expressions should be labeled "too emotional," "too spiritual," "too loud," nor "too dramatic." They are not deviations from the norm; they are sacred truths embodied in grief. Grief is not private pain. It is public witness.

Healthcare institutions must create systems that acknowledge this right, not as an afterthought, but as a built-in component of care. This includes grief-informed protocols, the presence of trained bereavement staff, space for memorialization, and institutional practices that make room for cultural and spiritual mourning rituals. It means providers must learn how to hold space; how to say *I am here* without trying to fix, how to be silent without retreating, how to let the moment be heavy without rushing toward closure. It also means giving families permission to speak the name of their child. Their loved one. To light candles. To ask hard questions. To express rage without being labeled difficult. To fall apart without being expected to hold others together. To take their time. Because grief does not follow a schedule. It does not respect institutional timelines. It does not end at discharge. It lingers. It shapes. It transforms. Let it be known: Grief is not a disruption. Grief is a declaration. It is a reminder that love was real. That life was present. That something sacred was lost. And that something sacred must still be honored. To grieve without guilt is to be seen. To grieve without erasure is to be free. And to be free is to heal, on one's own terms.

## 10. The Right to be Remembered

Every child matters. Every life, no matter how brief, deserves to be named, honored, and remembered. Whether a child lived for a few minutes, a few days, or never took a breath outside the womb, their presence was real. Their story is sacred. Their impact is immeasurable. Their existence does not vanish with their final heartbeat, it echoes. In memory. In legacy. In the breath and bravery of the families who carry that love forward every single day. The right to be remembered affirms that families who have endured pregnancy loss, stillbirth, neonatal death, or early infant loss are entitled not merely to clinical closure, but to sacred continuity. Their child is not a footnote in a medical record, not a procedural statistic, not a "loss" to be filed away. Their child is *theirs*, forever part of their lineage, their family tree, and their love story. In too many care environments, death is met with quiet retreat. The room that once held prayers, joy, and anticipation is quickly cleared. Monitors are silenced. Staff avert their eyes. What was holy becomes hurried. What should be tender becomes transactional. What should be reverent becomes routine. But grief must never be met with silence. And loss must never be compounded by erasure.

To remember a child is not to dwell in sorrow; it is to declare that *this life mattered*. That this love continues. That though death may have interrupted the physical presence, it did not break the spiritual bond. Memory is not clinging to pain; it is clinging to truth. It is honoring what was real. It is a resistance to the cultural

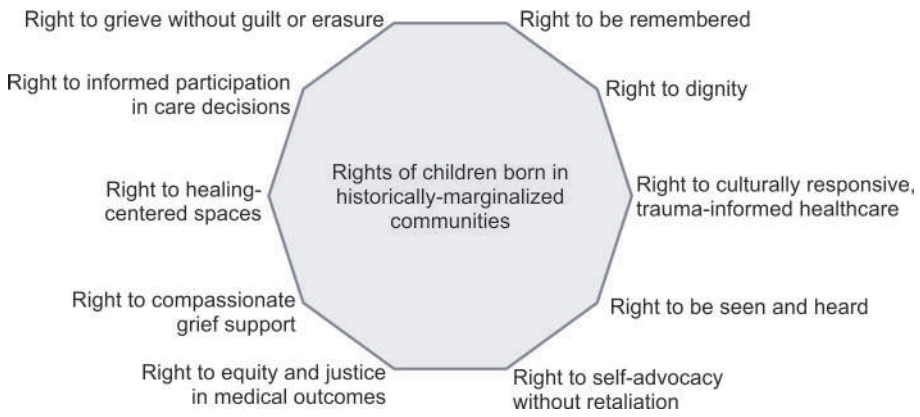


**Fig. 2:** Rights of children born in historically-marginalized communities

impulse to look away from what is difficult, and an insistence that the sacred be seen. Families have the right to remember *out loud*, without guilt, apology, nor performance. They have the right to say their baby's name, their loved one's name, and hear others say it too. To hold photos, footprints, and locks of hair. To light candles. To celebrate anniversaries and mourn missed milestones. To find joy in remembrance and refuse the lie that healing requires forgetting.

Families have the right to:

- Be offered gentle, inclusive, and proactive opportunities for memory-making in the clinical setting, not only if they ask, but because it is owed.
- See their child's name reflected with reverence in medical records and conversations, not replaced with sterile terminology.
- Participate in culturally aligned, spiritually grounded rituals of closure, transition, and continued connection.
- Be invited to institutional and community-based memorial events, not as afterthoughts, but as honored participants in a sacred collective.
- Share their story, in their words, in their time, in their truth, and be met with compassion, not correction.
- Know that their child will not be forgotten, by them, by their care team, nor by the systems that once held their hope.

These are not symbolic gestures. These are acts of justice. These are not extras. They are sacred essentials. They are not sentimental. They are structural. For families from Black, Indigenous, Latinx, immigrant, and other historically-excluded communities, this right is even more critical. These communities carry generations of silencing, where lives have been deemed invisible in birth and in death. To be forgotten in life is injustice. To be erased in death is trauma layered upon trauma. Ancestral memory, cultural ritual, communal lament, and spiritual continuity are not embellishments; they are inheritances. They are survival. Remembrance is not a privilege; it is a birthright. Hospitals, clinics, and care institutions must do more than accommodate grief. They must structure for remembrance. This means building it into policy, not just bedside manner. It means creating physical and emotional spaces for memory-making. It means staff are not only trained to respond, but to *revere*. It means rituals are not improvised; they are anticipated, planned, and protected. It means families are not guests in remembrance practices, they are architects of how their child will be remembered.

Because the end of life is not the end of relationship. And healing does not require forgetting, it requires being allowed to remember. To be remembered is to be affirmed. To be affirmed is to be dignified. And to be dignified, even in death, is the beginning of restoration. We will not shrink for comfort. We will not whisper where clarity is needed. We will not wait silently for the care we deserve. We will speak. We will rise. We will reclaim. We will honor our grief. We will protect our memory. We will demand dignity, not only for the living, but for the lives we hold sacred. Because their lives mattered. And so do ours (Fig. 2).

## Conclusion

A Bill of Rights for Children Born into Historically-marginalized Communities is not a rhetorical device; it is a reorientation of what it means to care. It is an invocation to reframe healing as an act of justice, not merely a function of treatment. In the face of generational trauma, institutional indifference, and systemic bias, this declaration stands as a testimony to what health care must become if it is to be worthy of trust.

Each of the 10 rights laid out in this article challenges the status quo and offers a vision for health care that is not only safer but more sacred. From dignity to remembrance, from self-advocacy to grief support, these rights are designed to center those who have long been ignored or dehumanized. They are not aspirational, they are actionable. And their implementation must be treated as urgent.

For clinicians, this framework calls for the cultivation of presence over performance, empathy over efficiency, and partnership over paternalism. For healthcare institutions, it demands the dismantling of policies and cultures that privilege some lives over others. For policymakers, it offers a blueprint for crafting systems that are not only technically proficient but spiritually and ethically sound.

This bill of rights invites us into a new clinical ethic, one where healing is not measured solely in vital signs, but in trust restored, dignity upheld, and justice made tangible. It is a declaration that every life matters, not just in birth, but in every moment of care, in every voice that speaks, and in every memory that remains. Let this be the beginning of a movement in which care becomes a covenant, systems become sanctuaries, and the most marginalized are not merely included but centered as the standard by which excellence is defined.

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COMMENTARY

# Medicine is not the Sole Determinant of Healthcare Outcomes: Lessons to Learn from Neonatal Tetanus

Colin Michie[1,2], Angela Hoyos[2,3], Enrique G Pomar[2,4,5], Kei Lui[2,6], Maryam Ebrahimpour[2,7], Ashok Kumar[2,8], Akhil Maheshwari[2,9–18]

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## Abstract

Improved survival of newborn infants has been a great global achievement of the last century. However, medical problems, such as neonatal tetanus, continue to be important healthcare concerns. One challenge has been in quantifying the case burden; actuarial measures of these disorders are not accurate. But increasingly, we are also realizing that medicine is not the sole determinant of healthcare outcomes. There is a need to study how differences of neonatal practice that could increase infant deaths may have persisted, despite access to affordable, effective, and efficient interventions. Free exchange of information could have changed history. We need to standardize and focus our practices afresh and then develop/apply diverse skill-sets to engage parents and other practitioners. Newer methods using geo-temporal mapping applications can help quantify the number of individuals in a target population who are reachable by existing immunization locations.

**Keywords:** *Clostridium tetani,* Eighth-day disease, Four–six wind, Ginklofi, Hippocratic aphorism, Maternal and neonatal tetanus elimination, Neonate, Pasmo, Quechohuara, Toxemia.

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## Key Points

- Even though neonatal mortality has decreased significantly in the past few decades, some medical problems have persisted. Neonatal tetanus is one example.
- Quantifying the case burden of neonatal tetanus can be challenging, as actuarial measures of infant tetanus are rarely accurate.
- There is a need to study how differences of neonatal clinical practice, that could reduce infant deaths, may have persisted. Efficient exchange of information could have changed history.
- We need to standardize and focus our practices and then develop/apply the diverse skill-sets to engage parents and other practitioners. Newer methods using geo-temporal mapping applications can help quantify the number of individuals in a target population who are reachable by existing immunization locations.

## Introduction: Some Medical Problems Have Persisted Despite Medical and Scientific Advances

Improved survival of newborn infants has been a great global achievement of the last century. However, medical problems, such as neonatal tetanus, have affected us for eternity. In many populations/regions, infant tetanus used to be a leading cause of infant deaths in nearly half of all live births in the first 2 weeks after birth.[1,2] Today, even though most perinatologists will never treat a case of infant tetanus, the challenges faced in its elimination can provide critical insights to improving neonatal care (Fig. 1). This paper outlines many of these challenges.

[1]Population, Policy, and Practice Research and Teaching Department, Institute of Child Health, University College, London, United Kingdom

[2]Global Newborn Society, Harrison, New York, United States of America

[3]Department of Pediatrics, El Bosque University, Bogota, Capital District, Colombia

[4]Department of Pediatrics, Division of Neonatology, University of Kentucky, Lexington, Kentucky, United States of America

[5]Department of Neonatology, St. Bernards Regional Medical Center, Jonesboro, Arkansas, United States of America

[6]Newborn Care Level 1, Royal Hospital for Women, Randwick, New South Wales, Australia

[7]Perinatal Medicine and Neonatology, Afzalipour Hospital, Kerman, Iran

[8]Neonatology/Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

[9]Boston Children's Health Physicians, New York Medical College/Maria Fareri Children's Hospital, Valhalla, New York, United States of America

[10]Banaras Hindu University Institute of Eminence, Varanasi, Uttar Pradesh, India

[11]Mongolian Association of Obstetrics, Gynecology, and Neonatology, Ulaanbaatar, Mongolia

[12]Bangladesh Neonatal Society, Dhaka, Bangladesh

[13]Autism Care Network Foundation, Chandigarh, India

[14]PreemieWorld Foundation, Springfield, Virginia, United States of America

[15]International Prader-Willi Syndrome Organization, Cambridge, United Kingdom

[16]The Skylar Project, Daphne, Alabama, United States of America

[17]American Society for Black Lives, Harrison, New York, United States of America


**Fig. 1:** The success of a seemingly-essential medical intervention often depends on many nonmedical factors. Affordability, efficacy (achievement of desired results under controlled conditions), effectiveness (achievement of desired results in clinical conditions), efficiency (proportion of subjects with the desired results with minimal wastage), social acceptance, information (raw, unprocessed facts), knowledge (understanding and application of information), and the magnitude of disease (incidence, prevalence, and severity) are important factors in the achievement of solutions

## A Historical Perspective about Neonatal Tetanus

During the late 18th and 19th centuries, the North Atlantic islands of Iceland and St Kilda were depopulated due to "ginklofi" and the "eighth-day disease" (infant tetanus). Over a few generations, 60% of all infants died from contamination of their umbilical wound by soiled dressings or swaddling materials.[1,2] In 1775, a large number of infant deaths in Puerto Rico and Buenos Aires were ascribed to "Quechohuara," the native American term for the same disease. These events led to the adoption of strict preventive measures, such as the deferral of baptism of newborn infants for 10 days.[3] *Clostridium tetanus* spores are ubiquitous, and so tetanus cannot be eradicated – a more achievable goal may be one of elimination. Maternal and neonatal tetanus elimination (MNTE) has been defined as an incidence of less than one case per 1,000 live births. As of December 2024, data from the World Health Organization (WHO) showed that neonatal tetanus continued to be a public health problem in 10 countries, namely, Afghanistan, Angola, Central African Republic, Nigeria, Pakistan, Papua New Guinea, Somalia, Sudan, South Sudan, and Yemen.[4] From ancient times, this toxemia meant a certain gruesome death, preceded by horrific convulsions and spasms. A Hippocratic aphorism is particularly expressive… "The spasm that follows a wound is fatal."

## Quantifying the Case Burden of Neonatal Tetanus can be Challenging

Actuarial measures of infant tetanus are rarely accurate. Making this diagnosis in the community is not simple. Distinguishing it from sepsis or asphyxia is difficult if no trained personnel are present. Because infants suffering tetanus die before they are formally named, blessed, or introduced to their communities, formal registrations are rarely possible. Infant tetanus also has many local names, for instance "four–six wind" in China; "pasmo" in Puerto Rico; "eighth-day disease" in the Scottish islands; "trismus neonatorum" in the Caribbean and Southern States, and "dhanurvat" in India.[5] Even contemporary reports from Pakistan and the Philippines have been shown to be incomplete.[6,7] Accurate counts rely on the availability of health systems with high fidelity records that are used by all mothers.

## Traditional Practices Persist Despite There Being Knowledge about Safer Clinical Practices

Umbilical cord care is most frequently delivered by mothers and their birth-assistants using traditional techniques to cut and dress the navel string.[8,9] These pluralist approaches can increase the risk of contaminating the umbilical wound with *Clostridium tetani* spores.[10] These spores are capable of producing a potent neurotoxin, against which humans have no genetic defences.[11] Pastoral cultures maintain that substances such as cow dung are safe as a dressing because of its perceived beneficial medicinal properties.[12,13] Medical excrements continue to be used on the neonatal umbilicus, for instance in Zimbabwe and Zambia.[14,15] Potentially contaminated substances, including turmeric, mustard oil, and ash, have historically been applied to the umbilical stump too, in the belief that these have protective properties.[16]

## Family and Cultural Triage may Determine Which Infants are Presented for Medical Care

Tetanus affects males and females equally, whether one is a veterinary surgeon working with horses, or a clinician caring for infants in a rural Hospital. However, patients brought to hospitals are often selected by their families or family head for such treatment. Cultural preferences supporting male infants are evidenced by skews in recently published hospital case series from several countries.[17,18]

## Socioeconomic Factors can Influence Outcomes

Income, education, and occupation are key determinants of health outcomes.[19] Higher socioeconomic status (SES) brings better access

[18]S.A.B.R.E.E. Enrichment Academy, St Louis, Missouri, United States of America

**Corresponding Author:** Colin Michie, Population, Policy, and Practice Research and Teaching Department, Institute of Child Health, University College, London, United Kingdom; Global Newborn Society, Harrison, New York, United States of America, Phone: +44 7590620293, e-mail: c.michie@ucl.ac.uk

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to healthcare, nutritious food, safe housing, and healthier lifestyles, while lower SES can increase morbidity and mortality.[20–22] Women from high-income sections of the society are more likely to have received adequate tetanus vaccination during pregnancy, which can then protect their infants against neonatal tetanus.[23,24] Tetanus protection at birth, a measure of maternal immunization coverage, has been shown to be lower among poorer wealth quintiles.[25,26] Increased income levels and access to resources rapidly facilitates access to better healthcare and vaccination.[27]

Mothers with higher levels of education are more likely to have received adequate vaccination against tetanus too.[28] This extends further – communities with higher levels of women in education show a lower incidence of neonatal tetanus.[29]

Distance to health facilities can limit access to individuals with lower incomes and fewer resources, impacting their ability to receive vaccinations.[30] Women with limited or no ante- and postnatal follow-up are less likely to have births protected against neonatal tetanus.[31]

Geo-temporal mapping applications can help quantify the number of individuals in a target population who are reachable by existing immunization locations.[32]

## Sharing of Information about Best Practices can be Delayed

Chinese physicians recorded in the 7th century that the lethal "four–six wind" was prevented by methods we now recognize as hygienic umbilical care. They further noted that this illness resembled the disorder they described as tetanus in older individuals.[33] However, these observations, recommendations, and practices were not shared or disseminated.[34] Infant tetanus remained a challenge in rural China even after 2000 perhaps because of a shortage of training for birth assistants, who protected the secrecies and deep-rooted practices of the birth chamber.[35]

Prior to the 14th century, trades across oceans and land witnessed a constant exchange of information and innovations between China and Europe, relating, for instance, to the use of the compass, printing on paper, or the invention of gunpowder.[36] However, even in the late 18th century, the Spanish puzzled as to the cause and prevention of the "jaw disease of the newborn."[37] How could these differences of neonatal practice, that could reduce infant deaths, persisted?[38] Here, efficient exchange of information could have changed history.

## Cultural Impediments: Vaccination is Not Always Accepted

The WHO recommends that at least 80% of pregnant women should be vaccinated with tetanus toxoid during pregnancy.[39] However, current rates still remain between 50 and 60% in many developing countries.[23,40,41] In 1988, an estimated 787,000 newborns died of neonatal tetanus.[42] The WHO has proposed global strategies to work toward the goal of eliminating neonatal tetanus; the 2021 estimates were ambitiously aimed to be at 24,000 deaths.[3] The WHO currently targets 59 countries in its MNTE campaign.[43]

Improved antenatal vaccination is challenged by logistics and a wealth of local socioeconomic factors that are distinct, for instance, in Turkey, Benin, and Zambia.[41,44,45] A lens of intersectionality may prove helpful in understanding and overcoming these challenges.[13,46] Mapping "hotspots" where vaccination levels are poor using artificial intelligence methods may prove helpful.[47]

## Conclusions

We need to standardize our practices and then develop/apply diverse skill-sets to engage parents and other practitioners. In these efforts, the science of medicine alone will not suffice. Worldwide platforms, such as the Global Newborn Society, are the need of the day to promote dialog and agreement on how to achieve these goals. Poliovirus vaccination is another example – we have a safe medical intervention available to us that is both highly effective and affordable, but it still has not succeeded in eradicating this disease.[48] As individuals, we can educate young people about the importance of vaccination and safe neonatal care. In our organizations, we can build trust with healthcare teams and advocate for policies prioritizing maternal and neonatal well-being. On a wider front, we can engage in outreach programs to address hesitation in accepting vaccination. Through all, we can question and research with the aid of tools using artificial intelligence. As the example of infant tetanus continues to show, we are likely to face many barriers. Perinatology involves wider audiences than individual parents: Sometimes the whole village needs to embrace change. In the end, it is always the team that wins![49]

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*Akhil Maheshwari* https://orcid.org/0000-0003-3613-4054

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ORIGINAL RESEARCH

# The Growth Care Bundle: A Comprehensive Set of Evidence-based Practices to Minimize Extra-uterine Growth Restriction in Newborn Infants

The *LAYA** Group of the Global Newborn Society
**L*ooking *A*t *Y*our practices in *A*pplication

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## Abstract

Advances in neonatology have significantly improved the survival of premature and very low birth weight (VLBW) infants, but concerns remain about optimal growth for these infants. Extra-uterine growth restriction (EUGR), defined as a discharge weight below the 10th percentile (*z*-score: −1.28), poses significant morbidity risks for both premature and VLBW infants. Approximately half of all VLBW infants face this preventable condition, which is indirectly linked to an increased risk of necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and long-term neurodevelopmental challenges. There are potentially-modifiable factors such as inadequate nutrition, lack of standard feeding guidelines, frequent stoppage of feeds, and cold stress; and many non-modifiable conditions such as chronic maternal illnesses, placental abnormalities, genetic conditions, intrauterine growth restriction, and extreme prematurity that can impact an infant's growth in the immediate extrauterine period. There is a need for identification, standardization, implementation, evaluation, and continual monitoring of growth-restricted infants after birth. In this article, we focused on a 5-pronged care bundle comprised of steps to optimize enteral feeding, parenteral nutrition, growth monitoring, metabolic rates, and post-discharge follow-up. We will follow these guidelines and evaluate the impact on the rates of EUGR in 3 years.

**Keywords:** Adjusted risk ratio, Assessment, Body mass index, Development, European Society for Pediatric Gastroenterology, Evaluation, Family-centered care, Golden hour management, Grades of recommendation, Hepatology, Institute for healthcare improvement, Intergrowth-21, Intrauterine growth restriction, Kangaroo mother care, Light-emitting diode, Neonate, Newborn, Nutrition, Reference growth charts, Relative risk, Secretory IGA, Secretory IGM, Somatometric, Speed of increasing milk feed trial, Standard growth charts, Trans-epidermal heat and water loss, *z*-scores.

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## Keypoints

- Extra-uterine growth restriction (EUGR), defined as a discharge weight below the 10th percentile (*z*-score: −1.28), poses significant morbidity risks for premature and very low birth weight (VLBW) infants.
- Modifiable factors such as inadequate nutrition, lack of standard feeding guidelines, frequent stoppage of feeds, and cold stress; and other non-modifiable conditions such as chronic maternal illnesses, placental abnormalities, genetic conditions, intrauterine growth restriction, and extreme prematurity can impact an infant's growth in the immediate extrauterine period.
- There is a need for identification, standardization, implementation, evaluation, and continual monitoring of growth-restricted infants after birth.
- In this article, we describe our recently-finalized 5-pronged care bundle comprised of steps to optimize enteral feeding, parenteral nutrition, growth monitoring, metabolic rate, and post-discharge follow-up.
- We will follow these growth bundle guidelines and evaluate the impact on the rates of EUGR in 3 years.

## Introduction

Advances in neonatology have significantly improved the survival of premature and VLBW infants, but concerns remain about optimal growth for these infants.[1–3] Extra-uterine growth restriction, defined as a discharge weight below the 10th percentile (*z*-score: –1.28), poses significant morbidity risks for these infants.[4] Approximately half of VLBW infants face this preventable condition, which is indirectly linked to an increased risk of necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and long-term neurodevelopmental challenges.[5–8] Multiple factors can impact an infant's growth in the immediate extrauterine period: Some are modifiable, such as inadequate enteral and parenteral nutrition, lack of standard feeding guidelines, frequent and non-protocolized stoppage of feeds, improper growth monitoring, and cold stress;[9] others are non-modifiable chronic maternal illnesses, placental issues, genetic conditions, intrauterine growth restriction, and extreme

**Corresponding Author:** Nitasha Bagga, Department of Neonatology, Rainbow Children's Hospital, Hyderabad, Telangana, India; Global Newborn Society, Clarksville, Maryland, United States of America, Phone: +91 9000764206, e-mail: nitashabagga@gmail.com

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**Fig. 1:** We have designed a growth bundle to minimize extrauterine growth restriction in preterm infants. There are five areas of focus: Enteral feeding, parenteral nutrition, growth monitoring, metabolic rate, and post-discharge follow-up

prematurity.[9] There is a need for identification, standardization, implementation, evaluation, and continual monitoring of growth-restricted infants after birth. Many potentially better, evidence-based practices can help.[10,11] Use of nutrition care standards, enteral and parenteral nutrition guidelines, and interdisciplinary growth monitoring, either singularly or as combined quality-improvement toolkits can improve growth outcomes.[10,12–14] This article presents a five-pronged approach: Early enteral and parenteral nutrition, growth monitoring, minimizing metabolic rates, and postdischarge follow-up to establish a preterm growth care bundle—a comprehensive set of evidence-based practices designed to promote growth in preterm infants and prevent the modifiable risk factors associated with EUGR (Fig. 1).

## Defining a Care Bundle

Care bundles are collections of evidence-based interventions associated with a specific disease or care process that, when implemented together, result in better outcomes than when applied separately. The Institute for Healthcare Improvement (IHI) developed the care-bundle concept to enhance medical practice and adhere to evidence-based guidelines in intensive care units (ICUs). Care bundles are comprised of 3–5 evidence-based or traditionally accepted interventions that are applied to all patients in a unit/multi-unit cohort unless contraindicated. Numerous studies have shown that growth and nutrition bundles can potentially improve the consistency of care and nutrition in preterm infants.[15]

Our multi-center group has reviewed existing information on various interventions that aim to improve postnatal growth of infants. We have defined and adopted a multidisciplinary care bundle comprised of 5 interventions, and aim to analyze and report any changes in our growth outcomes in 3 years:

1. **Enteral nutrition:** Early and exclusive human milk (HM) feeding can reduce several complications in the neonatal period, including late-onset sepsis (LOS), NEC, mortality, and BPD.[16–21] In addition, it has improved neurodevelopmental outcomes.[22,23] Human milk is considered the best source of nutrition for these infants. However, HM may require additional supplementation to meet the needs of growing premature infants for energy, protein, and other nutrients. Various approaches have been studied for optimizing the delivery of adequate nutrition; early initiation of enteral feeds, higher feed volumes, and fortification of HM are the most well-studied.
   (i) **Early vs late enteral nutrition:** Early feeding as soon as possible after birth can promote the crypt-villous development with enhanced total absorptive mucosal area, strengthen the gut mucosal barrier, and optimize

the intestinal microbiome.[24,25] Early enteral feeding (EEF) can reduce the risk of NEC, ROP, BPD, and LOS.[26] A meta-analysis of randomized controlled trials (RCTs) to establish complete enteral nutrition during the first 2 weeks after birth has shown that early feeding (before or on postnatal day 4) is associated with increased growth velocity from birth until hospital discharge with increased weight-for-age *z*-scores for term equivalent.[27] Preterm neonates at low-to-moderate risk may benefit from introducing enteral feeding within the first 24 hours of life, while high-risk neonates may benefit within the first 72 hours.[28]

(ii) **Rate of advancement of feeding volumes:** The pace of enteral feeding progression has been questioned primarily due to fears of enhanced NEC and mortality. However, well-structured studies have not shown any evidence of such harm. Oddie et al.[29] found that slowly advancing enteral feeding volumes actually increased the risk of invasive infection. A meta-analysis conducted by Morgan et al.[27,30] found no statistically significant impact on the risk of NEC among very preterm neonates [relative risk (RR): 0.97, 95% confidence interval (CI): 0.54–1.74] or mortality (RR: 1.41, 95% CI: 0.81–2.74). Furthermore, the authors observed that neonates with a slow progression of feed volume took significantly longer to reach full enteral feeding and to regain their birth weight. Another well-noted study, the speed of increasing milk feed trial (SIFT), compared slow, 18 mL/kg/day vs faster, 30 mL/kg/day increases in feeding volumes; there was no significant difference in survival without moderate-to-severe neurodevelopmental disability at 24 months of age [adjusted risk ratio (aRR) 0.96; 95% CI: 0.92–1.01; $p = 0.16$], NEC (aRR 0.88; 95% CI: 0.68–1.16), and LOS (aRR: 0.96; 95% CI: 0.86–1.07).[31] Other similar studies have also found any impact of delayed introduction of progressive enteral feeding beyond 96 hours after birth on the incidence of NEC in VLBW infants (RR: 0.81; 95% CI: 0.58–1.14; RD: 0.02, 95% CI: −0.04 to 0.01; low-certainty evidence) or mortality.[29] Although the slow progression of enteral feeding may lower the risk of developing feeding intolerance (RR: 0.81; 95% CI: 0.68 to 0.97; RD: −0.09, 95% CI: −0.17 to 0.02; low-certainty evidence), it could increase the risk of infection (RR: 1.44; moderate-certainty evidence). The World Health Organization (2023) recommends increasing feed volumes by daily increments of up to 30 mL/kg for preterm neonates who are not breastfeeding.

(iii) **High-volume vs low-volume feed:** Preterm neonates with lower gestational age and birth weight have a higher extracellular fluid loss in the first days of life because of the high surface area to body mass ratio and water-permeable immature skin. In addition, many may have factors such as respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), NEC, BPD, and interventions [radiant warmers, older non-light-emitting diode (LED) phototherapy] that can alter the fluid needs in neonates. The high- and low-volume feeding strategies have been analyzed in many trials. High-volume feeding can address potential fluid and nutrient needs for growth and neurodevelopmental outcomes. At the same time, concerns about feeding intolerance, NEC, BPD, or a persistent PDA have not completely been shed despite extensive evidence to the contrary. Several trials assessed the effect on growth and safety of high enteral feed intake (>180 mL/kg/day) vs standard intake (≤180 mL/kg/day) in preterm neonates. A meta-analysis conducted by Abiramalatha et al.[32] assessed the effect on growth and safety of high vs standard volume enteral feeding with fortified human milk or preterm milk formula in preterm neonates born at ≤32 weeks of gestation. High-volume feeding may probably improve weight gain [mean difference (MD) 2.58 gm/kg/day, 95% CI: 1.41–3.76] but not change head growth (MD: 0.02 cm/week, 95% CI: −0.04 to 0.09) or linear growth (MD: 0.05 cm/week, 95% CI: −0.02 to 0.13). There was no significant increase in the risk of NEC (RR: 0.74, 95% CI: 0.12–4.51). A similar effect of result in improving weight gain, but not head/linear growth or risk of NEC, was reported with high-volume feeding with term formula or unfortified HM. High intake volume may have to be used cautiously in neonates with a large, hemodynamically-significant PDA and BPD.[32]

(iv) **Monitoring gastric residuals:** One of the standard practices for withholding enteral feeding in preterm neonates is high pre-feed gastric residual. The term "gastric residuals" means the amount of aspirated gastric content before feeding. Gastric residuals can be an early sign of NEC or delayed gastric maturity.[33] However, without standardized guidelines, routine monitoring of gastric residuals may predispose to unnecessary delays in beginning and advancement of feeding, and consequently, prolong the dependence on nutritionally-inadequate parenteral nutrition. This increases the risk of EUGR, neurodevelopmental impairment, and metabolic complications.[34,35] Routine evaluation of gastric residual volumes may disrupt the natural secretion of acid secretion in the stomach, and thereby promote altered/increased bacterial colonization in the gastrointestinal system.[36]

Additionally, routine assessment of gastric residuals may also injure the immature gut mucosa due to repeated application of negative pressure. Furthermore, removing gastric residuals may lead to the loss of gastric enzymes like pepsin, which digest milk proteins, thereby increasing the likelihood of feeding intolerance.[37] Several RCTs have linked not checking gastric volume residuals with a lower risk of feeding intolerance and NEC.[38,39] Rysavy et al.[40] reported more advanced enteral feeding volumes in neonates randomized to no routine gastric residual monitoring ($p = 0.02$) and higher feeding volumes at 5 and 6 weeks postnatal age compared to the group monitored for gastric residuals ($p = 0.03$). A recent moderate-certainty meta-analysis by Abiramalatha et al.[41] indicates that routine evaluation of gastric residuals has no significant effect on the incidence of NEC.

Enteral feeding can be continued by removal of gastric residual volumes and feeding only fresh human milk/milk formula or by re-feeding residual volumes. There is no strong agreement on whether to discard or re-feed the stomach aspirates. Re-feeding the aspirated volume may replace the partially digested milk and gut hormones essential for the gut's maturity. However, re-feeding abnormal aspirates may predispose to infection, feeding intolerance, and NEC. Limited evidence suggests that re-feeding gastric residual volume in extremely preterm neonates is considered as safe as fresh feeding as it does

not reduce the time to attain full enteral feeding. It has little or no effect on feeding intolerance or incidence of NEC. Salas et al.[42] found no difference in the time taken to reach full enteral feeding volumes in re-feeding vs fresh feeding groups (95% CI: −2.9, 0.3; $p = 0.11$). Furthermore, there were no significant differences in the outcomes like NEC, death, or spontaneous intestinal perforation (SIP) in both groups ($p = 0.26$). A more recent systematic review also did not find any significant difference in the duration of enteral feeding, weight gain, incidence of NEC, or mortality with re-feeding residual volumes. This is compared to feeding only with fresh milk or formula based on the low-evidence data.[43] The available evidence is insufficient to assess the possible risks or potential benefits of re-feeding of stomach aspirates.

(v) **Oropharyngeal colostrum (OPC):** Colostrum is rich in immunoglobulins like secretory IgA (sIgA) and secretory IgM (sIgM), along with lysozymes, lactoferrin, leukocytes, cytokines, and other growth factors.[44,45] These components enhance innate immunity in the gut, support intestinal growth, repair, and development, possess anti-inflammatory properties, and aid in establishing a healthy gut microbiome.[46–48] However, when Panchal et al.[49] studied 6 RCTs ($n = 269$) and 4 non-RCTs ($n = 737$), the meta-analysis using the random effects model did not find a reduction in ≥ stage 2 NEC (RR: 0.83; 95% CI: 0.39, 1.75; $p = 0.62$) or time to full feeds (MD: −2.86 days; 95% CI: −6.49, 0.77; $p = 0.12$). Meta-analysis of data from non-RCTs also showed no benefit for any of these outcomes. Oropharyngeal colostrum increased secretory IgA and lactoferrin concentrations (4 RCTs) but had only a transient effect on the oral microbiome (1 RCT). There were definitely no adverse effects, such as aspiration, of OPC. The overall quality of evidence (grades of recommendation, assessment, development, and evaluation analysis) was very low. They concluded that adequately powered RCTs were needed to confirm OPC's nutritional and immunomodulatory benefits in preterm infants.

Recently, Anne et al.[50] included 21 studies ($n = 2,393$). They showed that OPC administration significantly reduced the incidence of NEC (17 studies, 1,692 neonates, RR: 0.59, 95% CI: 0.43, 0.82), feeding intolerance (4 studies, 445 neonates, RR: 0.59, 95% CI: 0.38, 0.92), and the time to full enteral feeding (TFEF) (19 studies, 2,142 neonates, MD: −2 to 21 days, 95% CI: −3.44, −0.99 days). Certainty of Evidence (CoE) was high for culture-positive sepsis and mortality, moderate for NEC, low for TFEF, and low for feeding intolerance. Kumar et al.[51] concluded that CoE was low for NEC, sepsis, and TFEF and recommended routine OPC administration given the low cost and minimal risk of harm. Fu et al.[52] actually detected less NEC and shorter TFEF in 4 hourly OPC group, and a more robust impact with duration (TFEF shorter in 1–3 days and 4–7 days groups; NEC lower in 8–10 days group) of OPC. Huo et al.[53] reported reduced NEC (RR: 0.51; 95% CI: 0.31–0.84; $p = 0.009$) and TFEF (MD: −3.4; 95% CI: −3.87 to −2.92; $p < 0.00001$) in addition to increased weight gain (kg/day: MD: 2.63; 95% CI: 2.10–3.16; $p < 0.00001$) from 11 RCTs ($n = 1173$). Ramos et al.[54] reported shorter TFEF in the OPC group (MD: −4.26 days; 95% CI: −7.44 to −1.08). Similar to these reports, Lamsehchi et al.[55] showed that very premature infants receiving OPC had shorter TFEF and lower rates of NEC (11.1% vs 28.6%; $p = 0.01$). However, Aggarwal et al.[56] did not find any reduction in the primary composite outcome of death, NEC, or sepsis in 260 very premature infants.

*Physiological Effects*

In their pilot RCT with cross-over design, Mohammed et al.[57] showed that OPC administration before gavage feeding was associated with higher levels of motilin (median, 233; interquartile range [IQR], 196–296 vs median, 196; IQR, 128–233; $p < 0.01$), secretin (median, 401; IQR, 353–458 vs median, 370; IQR, 331–407; $p = 0.04$), and cholecystokinin (median, 21.4; IQR, 16–27.1 vs median, 14.9; IQR, 11–20.5; $p < 0.01$) but not gastrin (median, 202; IQR, 125–238 vs median, 175; IQR, 128–227; $p = .7$), compared with regular gavage-feeding practice in 40 very premature infants. Oropharyngeal colostrum administration also improves breastfeeding rates, although more evidence from adequately-powered randomized control studies and meta-analysis is needed.[58,59]

(vi) **Fortification:** Exclusive feeding with unfortified breast milk may not provide nutrients to preterm VLBW infants fed standard volumes (150–180 mL/kg/day), considering fetal growth targets.[60–63] Pasteurization also modifies HM's biological and nutritional properties.[64] Hence, fortification of HM is a widely-used strategy to optimize the nutritional outcomes of preterm infants. Human milk fortifiers were developed and commercially introduced in the 1980s, most commonly being multi-component bovine preparations; others include HM-based fortifiers or single-component preparations of carbohydrates, fats, or proteins.[65] Fortification with an exclusive HM diet did not result in statistically-significant differences in body composition compared to a diet containing bovine milk products.[66] Kumar et al.[67] have recommended fortifying with a formula compared to bovine fortifiers. The optimal timing of fortification is uncertain, with the common practice being the introduction of a fortifier once an enteral volume of 100 mL/kg/day has been reached. Thanigainathan and Abiramalatha[68] assessed the safety and effects of following early (enteral feeds <100 mL/kg/day or <7 days of age) vs late fortification (enteral feeds ≥100 mL/kg/day or ≥7 days postnatal age) on growth in preterm infants. Two RCTs ($n = 237$) were included. Early fortification was started at 20 mL/kg/day enteral feeds in one study and 40 mL/kg/day in the other study. Late fortification was started at 100 mL/kg/day feeds in both studies. One study used a bovine milk-based fortifier, and the other used an HM one. Meta-analysis did not show a significant effect of early fortification on growth outcomes, including time to regain birth weight (MD: −0.06 days; 95% CI: −1.32 to 1.20 days), linear growth (MD: 0.10 cm/week; 95% CI: −0.03 to 0.22 cm/week), or head growth (MD: −0.01 cm/week; 95% CI: −0.07 to 0.06 cm/week) during the initial hospitalization period. Early fortification may have little or no effect on the risk of NEC (MD: −0.01, 95% CI: −0.07 to 0.06). The CoE was low for these outcomes due to the risk of bias (lack of blinding) and imprecision (small sample size). Early fortification did not reduce the incidence of EUGR or the incidence of surgical NEC, TFEF, proportion of infants with episodes of feed interruption, duration of total parenteral nutrition (TPN), incidence of invasive infections, all-cause mortality, and duration of hospital stay. The CoE was low for these outcomes due to the risk of bias (lack of blinding) and imprecision (small sample size). There were no data for other outcomes, such as subsequent weight gain after regaining birth weight, parenteral nutrition-associated liver disease, post-discharge growth, and neurodevelopmental outcomes.

The influence of HM fortification on gut microbiota seems controversial. Asbury et al.[69] reported lower microbial diversity

and higher proteobacteria and *Enterobacteriaceae* following fortified feeds with human-derived fortifiers. Kumbhare et al.[70] showed a better microbial profile with mothers' own milk vs donated milk than fortification with human or bovine origin fortifier, which had a minimal impact. Moreira-Monteagudo et al.[71] reported the multifactorial influence of pasteurization of donor milk on microbial development. Embleton et al.[71] analyzed differences in the microbiota between preterm infants fed exclusive human nutrition (donated ± breast milk and fortifiers derived from HM) and breast milk ± formula and fortifiers of bovine origin without appreciating differences in microbiota patterns. They concluded that the impact of HM on the reduction of comorbidities does not appear to be related to the microbiome. Some systemic reviews have reported significantly improved growth with high-protein fortification. Accumulation of fat-free mass increased, and growth was optimized without excessive body fat accumulation by achieving 4–5 gm/kg/day protein intake.[72,73] Gao et al.[74] supported this result while highlighting adverse effects. Agakidou reported increased serum IGF-1 levels, resulting in decreased fat mass and improved initial growth of preterm infants. Kadioglu et al.[75,76] reported improved weight, length, and head circumference growth in VLBW infants supplemented with adjusted and targeted fortification compared to those who received standard fortification. Rochow et al.[77,78] reported improved macronutrient intake, better lean mass percentage, and improved anthropometry following targeted fortification. Fabrizio et al.[79] included seven RCTs ($n$ = 521) and showed that individual (targeted or adjustable) fortification increased weight gain (typical MD: 1.88 gm/kg/d; 95% CI: 1.26–2.50; 6 studies, 345 participants; CoE: low to moderate), may have increased length gain (typical MD: 0.43 mm/d; 95% CI: 0.32–0.53; 5 studies, 242 participants; CoE: low to moderate), and may have increased head circumference gain (typical MD: 0.14 mm/d, 95% CI: 0.06–0.23; 5 studies, 242 participants; CoE: low to moderate) compared to standard non-individualized fortification. Evidence from post-discharge clinical outcomes was sparse and of very low certainty, thus limiting inference regarding benefits beyond short-term growth and safety. Khorana et al.[80] reported significantly higher weight and length gains with adjustable fortification protocol than standard guidelines but no correlation between energy intake, volume intake, and growth outcomes. Salas et al.[81] showed increased length gain velocity and reduced decline in head circumference-for-age $z$ scores from birth to 36 weeks postmenstrual age (PMA) following early fortification (on day 2 of life) with HM-based fortifier in 150 extremely preterm infants. Fat-free mass-for-age $z$-scores were comparable. In 52 VLBW infants, Wynter et al.[82] reported that immediate fortification with bovine milk-derived fortifier was safe and well tolerated, although growth was comparable.

Chova et al.[65] reported that fortifying HM is a recommended nutritional strategy for preterm infants. High protein intake (4–5 gm/kg/day) in fortification seems beneficial for the growth and neurodevelopment of preterm infants without increasing the risk of comorbidities. Human milk-based fortification reduces the incidence of NEC, with no improvement in somatometric or neurodevelopmental parameters. Individualized fortification, especially the "directed" modality, has shown better results than standard fortification.

2. **Parenteral Nutrition (PN):** Parenteral nutrition is provided to preterm neonates and infants when their estimated energy and nutrient requirements cannot be adequately and safely provided via the enteral route immediately after birth. Parenteral nutrition includes intravenous amino acids, dextrose, and injectable lipid emulsion (ILE). PN should be started as soon as vascular access is established after birth. Early initiation of PN improves the growth outcomes.[83]

   **Proteins:** *In utero*, a fetus receives amino acids from the mother at an estimated rate of 3–4 grams/kilogram of body weight per day, an amount that can promote fetal growth and brain development.[84] However, insufficient transfer of these proteins can lead to a negative nitrogen balance. Even though there is some controversy about the most appropriate protein intake to support the growth and development of VLBW infants in the immediate postnatal period. Observational studies have correlated relatively high levels of protein intake with improved growth and neurodevelopment.[85–87] Hence, several guidelines have been proposed to promote earlier and higher amino acid intake for these infants.[88,89] A recent Cochrane review in 2024 by Trivedi et al.[90] looking at the impact of early vs late amino acid intake on the discharge weight for neonates born at <37 weeks of gestation suggests that even though this is an understudied subject, early administration of amino acids may result in a significant increase in positive nitrogen balance. However, it did not significantly change the crown-heel length, head circumference, and neurodevelopmental index at 2 years after birth (evidence of certainty low). They also showed that standardized PN has several benefits over individualized PN in infants without specific nutritional requirements as it reduces errors in prescription, preparation, and administration of PN. It also reduced the risk of infections and made it more cost-effective. Further work can definitely help in refining/defining the details of the best solutions tailored for individual needs.[91–93]

   According to recent recommendations from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), fluid intakes of 70–80 mL/kg/day are suggested at birth. These volumes can, and if possible, should be progressively increased to 150 mL/kg/day by the end of the 1st week. The caloric intake of 120 kcal/kg/day and a minimum protein intake of 2.5–3 gm/kg/day. Regarding glucose intake, an infusion rate of 3–5 mg/kg/min is recommended, but VLBW and ELBW preterm neonates may require up to 12 mg/kg/min in preterm infants.[91] The American Society for Parenteral and Enteral Nutrition committee reviewed 2,460 citations published between 2001 and 2023 and evaluated 57 clinical trials. They examined 12 questions and guidelines. They recommended starting AA within 24 hours of life at <3 gm/kg/day and not exceeding >3.5 gm/kg/day. The protein levels should not be routinely decreased to prevent PN-related liver injury.[94] Notably, the composition of ILEs is important to avoid essential fatty acid deficiency.

   **Lipids:** To improve growth outcomes, daily advancement to higher doses of ILEs to a maximum of 3 gm/kg/day; soyabean oil (SO-ILE) or multi-component ILE is recommended.[94] Several studies compared lower (0.5 gm/kg/day) vs higher (2 gm/kg/day) doses of ILE at initiation with the same maximum doses.[95,96] Other studies have compared lower vs higher doses with the

higher maximum doses (3.8 gm/kg/day). All studies utilized ILE with the same composition.

The weight near the time of discharge was similar between groups, although fewer infants in the higher-dose group weighed <10th percentile for age at discharge. Head size was more significant with the higher dose than the lower dose.[95] The particular goal of providing ILE is EFAD prevention.[97] Specific dose reductions of any ILE may result in EFAD for preterm infants.[98,99] Therefore, the strong recommendation considers the very low-quality evidence and an awareness of the EFAD risks. Additionally, caution and close attention are advised to ensure adequate fatty acid provision to prevent EFAD if a dose reduction of ILE is ever considered. It is crucial to remember that the risk of EFAD is influenced by the oil source(s) and dose of the ILE.

**Micronutrients:** Providing micronutrients in PN enhances growth outcomes and reduces morbidities. Micronutrients, such as calcium and phosphorus, are recommended in the ASPEN and ESPGHAN consensus guidelines.[100–102] Clinical trials investigated 5 parenteral nutrients: Acetate, carnitine, glutamine, manganese, and iron.[103–112] Prematurity-related morbidities that were examined included BPD, osteopenia of prematurity, and sepsis. None of the studies assessed osteopenia as a distinct outcome related to specific micronutrients, mineral supplementation, or dosage variation. Providing carnitine was not associated with the risk of BPD.[105,106] The outcome of sepsis was evaluated in single trials of carnitine, glutamine, and manganese.[104,107,109] There was no difference in the BPD outcomes in one of the trials with manganese.[109] The use of acetate and chloride with sodium showed no outcome variability. Days to regain birth weight were fewer in one of the trials with carnitine.[104] However, another trial did not show a difference in growth measurements near discharge with the usage of carnitine.[105,113] Due to heterogeneity in intervention and outcomes, a combined analysis of the usage of iron with or without erythropoietin could not be done.[110–112] Finally, the clinical trials could not suggest any specific dose of the micronutrients that affect the change in the outcome.

**Customized vs standard PN:** Customized PN solutions are prepared per the individual and specific needs of infants, unlike standard solutions that contain the same set of nutrients without regard to clinical circumstances. No clinical trial met the standards and definitions to address this question. Standardized PN solutions may reduce prescribing and administration errors and ensure that preterm infants receive the recommended doses of parenteral and micronutrients. Additional clinical trials are warranted to determine if different PN solutions standardized for specific periods show safety and efficacy while ensuring that the preterm infants' metabolic needs are met. The current lack of evidence through clinical trials does not recommend standardized solutions. However, pre-made PN, also referred to as starter or stock PN, which is used for the first 24 hours, can still be used, always given its availability.

3. **Growth Monitoring**

Growth monitoring is an indispensable part of preterm care. Its importance lies in its utility as a diagnostic tool for identifying neonates with nutritional problems before it is seriously compromised and instigating appropriate actions. Several quality improvement studies[2,114] have shown that a protocolized growth monitoring system can help in early identification of at-risk infants and, thereby, timely-initiation of appropriate actions. Such systems can also help review the reasons for poor growth.

Growth curves can help in early identification and longitudinal monitoring of infants at risk of EUGR. There might be two broad groups: (a) Infants with IUGR who are at higher risk; and (b) critically-ill infants with multi-system illnesses, who might respond to timely, appropriate care and nutritional intervention. We still need a consensus for the best growth charts and methods/indices to monitor the growth of preterm neonates. There are nearly 61 growth charts available at present; most have limitations arising from gestational age assessment, skeletal vs other soft-tissue indices used to assess growth, duration of follow-up, and various concomitant morbidities.[115] These differences may result in overdiagnosis of EUGR, and to match fetal standards, have led to excessive caloric/protein supplementation leading to being overweight vis-à-vis skeletal parameters. There is a risk of long-term consequences such as obesity and cardiometabolic syndrome.

There are two broad types of preterm growth charts: (a) Reference growth charts, which are based on cross-sectional data of anthropometric indices at birth. As the health status of the subjects is not included in these charts, these are usually perceived as providing descriptive information.[116–119] Furthermore, the postnatal growth of preterm infants seldom matches a fetal growth trajectory due to multiple factors, which further limits the utility of reference charts; (b) standard growth charts, which are based on growth targets of a healthy preterm infant rather than a fetus, and have been seen as prescriptive tools. INTERGROWTH-21 charts (acronym for International Fetal and Newborn Growth Consortium for the 21st Century) describe the new standards for the growth of a preterm infant.[120] These curves were constructed based on prospective serial monitoring of 'healthy' preterms born between 26 and 37 weeks of gestation. Strikingly, the curves of preterm postnatal growth charts are lower than the intrauterine growth curves; this discrepancy increases further with lower gestational ages.[121] A recent study demonstrated that the diagnosis of EUGR decreased when using INTERGROWTH-21 for monitoring growth compared to Fenton and Kim's 2013 fetal-infant growth curves.[122] The only limitation of INTERGROWTH-21 curves is the limited number of infants born <33 weeks ($n = 12$), which limits its validity for this subgroup.

Apart from anthropometric parameters of growth, the composition of the growth has equal importance, as highlighted by the American Academy of Pediatrics.[123,124] Body mass index (BMI) and body composition at term-equivalent age in preterm have been used. Despite advances in preterm care and nutrition, evidence suggests that preterm neonates have substantially less lean body mass and a higher fat mass percentage at term-equivalent age.[123] The potential associated factors include body composition at birth (IUGR), inflammation, inotropes, and post-natal steroids leading to hormonal imbalances, inadequate nutrition postnatally, concurrent illness like surgery, infection, lung disease, etc. Although not routinely used in the NICU, body composition can be measured through dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging, or air displacement plethysmography.[125]

Body mass index curves for preterm infants are available to identify disproportionate growth.[126,127] However, this approach

is limited because it becomes less reliable if both parameters (weight and length) are affected in the same direction. Also, BMI is a poor surrogate of adiposity. Nonetheless, assessing body proportionality gives additional information about growth and enables earlier intervention to identify any deviation in growth.

**Recommendations:** Serial, appropriate, and accurate growth assessment is required in preterm neonates to prevent growth failure and long-term consequences of overfeeding. Currently, preterm postnatal growth reference curves are the most widely used growth charts. Besides monitoring the "quantity" of growth, tracking the 'quality' of growth through BMI and body composition can provide more information on adjusting preterm nutritional interventions.

4. **Minimize Metabolic Rate**
   (i) **Trans-epidermal heat and water loss (TEHWL):** In preterm neonates, inadequate skin keratinization results in high evaporative heat and water losses.[128] This permeability decreases within the first 7–10 days after birth, and it is critical to monitor and provide high ambient humidity to minimize evaporative heat losses and lower the metabolic rate.[129] High TEHWL is associated with not only heat and water loss but also with consequent temperature instability and hypernatremic dehydration.[130,131] There is a significant caloric drain, which can result in considerable growth failure.[132,133] Devices such as incubators can create a high degree of ambient humidity and thereby reduce TEHWL.[134,135] We still need a consensus about the choice of the most effective methods for increasing ambient humidity in the care of these neonates.[136]
   (ii) **Kangaroo mother care (KMC):** Kangaroo mother care is a straightforward, cost-effective intervention that enhances growth and also reduces neonatal mortality in preterm neonates.[137] Neonates exhibit minimal or absent non-shivering thermogenesis and muscular activity, and consequently can benefit from external support to maintain their body temperature.[138] Placement on the upper maternal body provides the infant with warmth, prevents heat loss, and aids in maintaining metabolic rate.[139] KMC has been shown to positively influence short- and long-term infant health outcomes. Sharma et al. have shown that KMC significantly enhances the growth of VLBW neonates.[140] A recent Cochrane review by Conde-Agudelo, and Diaz-Rossello[141] compared KMC with conventional neonatal care for preterm infants and showed improved infant growth; there was also a reduction in the risk of mortality, LOS, hypothermia, and length of hospital stay. Other studies have shown similar results.[142]
   (iii) **Family-centered care (FCC):** Family involvement in healthcare settings has now been emphasized for more than 60 years.[143] Notably, FCC emphasizes the participation of family members in patient care and emphasizes the patient's emotional, social, and developmental needs.[144] While FCC is universally recognized in pediatric settings, the medical setup in many countries still restricts family access to NICUs and limits their involvement in their baby's care.[145,146] However, the data supporting FCC over standard care and its impact on outcomes of preterm infants are scant. Yu et al.[147] assessed the feeding and growth of preterm infants. The study demonstrated earlier achievement of full enteral feeding volumes in preterm infants in the FCC group, but no significant difference was observed in weight at term age between the two groups. A recent meta-analysis by Yu et al.[148] showed that FCC reduced the total length of stay in the NICU and in the hospital compared to standard care. However, there was insufficient evidence to show any effect of FCC on infant morbidity, feeding, growth, or neurobehavioral performance.
   (iv) **Golden hour management to decrease the metabolic rate:** Premature neonates, defined by birth weight (VLBW and extremely low birth weight, ELBW), or gestational age (extremely low gestational age, ELGAN) are more prone to hypothermia as there is a rapid loss of heat after delivery. Hypothermia is a dangerous problem in newborns as it alters the basal metabolic rate and can alter weight accretion during early infancy. The golden hour management aims to prevent hypothermia by keeping the delivery room temperature at 26–28 °C, using pre-warmed linen sheets to receive the newborn just after birth, re-warming surfaces, and eliminating drafts. Interventions during delivery and transportation, including plastic wrap or bags, plastic caps, cling wrap, radiant warmers, thermal mattresses, pre-warmed single/double walled incubators, warm humidified gases, and skin-to-skin contact can help.[149–153] A Cochrane meta-analysis has supported the use of plastic wraps or bags, plastic caps, skin-to-skin care (SSC), and trans-warmer mattresses to minimize heat losses and hypothermia to optimize the basal metabolic rate.[154]

5. **Postdischarge follow-up:** Postnatal growth and bone accretion in preterm neonates lags behind that of fetuses at the same gestational age. The primary nutritional goal for preterm infants in postnatal care is to achieve a growth rate that mimics intrauterine growth, ensuring appropriate weight gain without causing nutritional deficiencies, metabolic imbalances, toxicities, or excessive dietary intake.[155] At discharge, 40–80% of preterm neonates weigh the 10th percentile, and approximately 50% develop osteopenia.[156,157] In preterm and low birth weight infants, each *z*-score increase in weight gain from term to 12 months is associated with a 1.9-point improvement in cognitive scores at 8 years, as measured by the WISC-III scale. There is only a minor increase in systolic blood pressure (0.7 mm Hg).[158] However, faster linear growth in the early postnatal period is linked to a higher risk of obesity at 8 and 18 years, although it significantly reduces the odds of an IQ below 85.[158] After NICU discharge, these infants require individualized nutritional plans and follow-up, considering factors such as gestational age, birth and discharge weights, coexisting comorbidities, and family feeding preferences influenced by socioeconomic and socio-emotional factors.[159] A multidisciplinary team, including physicians, dieticians, lactation nurses, and speech therapists, can provide better monitoring and assessment to support growth and development.

   **Recommended post-discharge nutrition:** Healthy preterm infants require 110–130 kcal/kg/day to support adequate growth.[160,161] This requirement can increase to 150 kcal/kg/day in complex health conditions and remains elevated until consistent catch-up growth is achieved or until they reach 12 months of corrected age. The recommended protein-to-energy ratio is 2.5–3 gm per 100 kcal.[11,162] Human milk is universally recommended for its benefits in enhancing host defense and supporting cognitive development in preterm infants.[161,163,164]

(i) **Human milk composition and post-discharge fortification:** Fortification has been associated with improved growth outcomes, particularly in head circumference, and better neurodevelopmental outcomes, though its long-term effects remain unclear.[165] A small RCT ($n$ = 39) comparing fortified vs non-fortified mother's milk over 12 weeks showed improved growth parameters and bone mineral content in the fortified group.[166] In contrast, another larger RCT did not find a significant growth benefit of fortification in very preterm infants.[167] Neither of these studies provided neurodevelopmental data for review.

Fortification can pose challenges for breastfeeding, and hence many alternative approaches have been evaluated. McCormick et al.[168] suggested using HM concentrate (3–4 mL), prepared from small amounts of expressed milk as a more practical option. The optimal duration of fortification post-discharge still needs further investigation.[165] Expert recommendations suggest continuing fortification for 3 months corrected age to achieve catch-up growth or 6–12 months corrected age in high-risk infants (birth weight <1,250 gm, gestational age <28 weeks, high alkaline phosphatase, or poor bone mineralization).[169] Fortification with HMF to 24 kcal/oz or 22 kcal/oz is commonly used but is not routinely recommended beyond 3 months of corrected age. It is suggested that personalized postdischarge feeding plans be provided based on the infant's nutritional and growth status, maternal breastfeeding goals, and logistical challenges of fortifying milk at home.

(ii) **Postdischarge formula:** Post-discharge feeding of preterm infants presents a unique challenge. Preterm neonates without access to breast milk are typically discharged on formula feeds**,** initially receiving preterm formula until 35–36 weeks PMA before transitioning to term formula. While preterm formula provides higher calories and protein, prolonged use may lead to excessive catch-up growth, increasing the risk of obesity and long-term cardiovascular complications. Postdischarge formulas (PDFs) were developed to mitigate this, which would provide a total caloric/protein intake somewhere between a preterm and a term formula; the goal was to balance growth support without excessive weight gain**.** These infants often self-regulate their intake based on calories, potentially consuming less volume with calorie-dense formulas, which can negatively impact overall nutrient intake. Consequently, current research emphasizes isocaloric formulas. These formulas maintain a standard caloric density while carefully optimizing protein and micronutrient levels to promote healthy growth after hospital discharge. Various formulas and approximate calorie, protein, and micronutrient compositions are detailed below.

| *Type of formula* | *Term formula (Per 100 mL)* | *Postdischarge formula (Per 100 mL)* | *Preterm formula (Per 100 mL)* | *Nutrient dense postdischarge formula (Per 100 mL)* |
|---|---|---|---|---|
| Calories (kcal) | 66–67 | 67–75 | 80–90 | 100 |
| Protein (gm) | 1.4–1.6 | 1.7–2 | 2.2–2.4 | 2.6 |
| Fat (gm) | 3.2–3.8 | 3.5–4.09 | 4.1–4.4 | 5.4 |
| Calcium (mg) | 35–54 | 65–94 | 100–128 | 101 |
| Phosphorus (mg) | 27–40 | 35–50 | 50–55 | 57 |
| Magnesium (mg) | 4–6 | 5.2–6.5 | 8–9 | NA |
| Sodium (mg) | 18–19 | 22–26 | 34–41 | NA |
| Potassium (mg) | 60–65 | 73 | 93 | NA |
| Iron (mg) | 0.3–0.5 | 0.65–1.3 | 0.6–0.9 | 1 |
| Zinc (mg) | 0.34–0.5 | 0.6–0.8 | 0.7 | 0.9 |
| Vitamin D (microg) | 1–1.2 | 1.2–1.5 | 2.4 | 2 |
| Folate (microg) | 13 | NA | 291 | NA |
| Osmolality (mOsm/L) | 260–300 | 291 | 280–320 | 340 |

(iii) **Duration of PDF or fortification:** The optimal duration of PDF or fortification in preterm infants remains controversial. Some clinical guidelines recommend preventing PDF or fortification at 48–52 weeks PMA (8–12 weeks corrected age). Evidence from other studies suggests no significant benefit of nutrient-enriched formulas compared to standard infant formula, particularly beyond 6 months of corrected age, with respect to growth, bone mineralization, or neurodevelopmental outcomes.[163,170,171] Catch-up growth is typically characterized by weight attainment between the 5th and 10th percentile on standardized growth charts.[161] Recommended weight gain targets vary with corrected age: 25–35 gm/day (≤3 months), 15–21 gm/day (3–6 months), and 10–13 gm/day (6–12 months). Linear and head circumference growth targets are typically 0.8–1 cm/week.[172] While adequate growth is essential for optimal neurodevelopment, excessive and rapid weight gain should be discouraged due to its increased risk of metabolic syndrome, cardiovascular disease, and reduced bone mineral density in later life.[163,166] Conversely, suboptimal weight gain (<20 gm/day in infants ≤3 months corrected age) may warrant increasing the caloric density of feedings from 22–24 kcal/oz to 24–27 kcal/oz. Maintaining current caloric intake is recommended in instances of adequate weight gain but insufficient linear growth. For infants >3 months corrected age exhibiting excessive weight gain (>30 gm/day) coupled with inadequate linear growth, a reduction in caloric intake may be considered. Further research is required to establish definitive

guidelines for the optimal duration of PDF or fortification in preterm infants, considering individual growth trajectories and long-term health outcomes.

(iv) **Growth monitoring post-discharge:** Standard growth assessments include weight, length, head circumference, and body composition. Advanced methods such as dual-energy DEXA scans or air displacement plethysmography (PeaPod) can provide detailed body composition analysis, including fat mass, lean mass, bone mineral content, and bone mineral density. Additionally, metabolic assessments are crucial in evaluating overall nutritional and endocrine status. Key parameters include:

- Glucose metabolism: Glucose, insulin, insulin-like growth factor I (IGF-I).
- Lipid profile: Triglycerides, total cholesterol, LDL cholesterol.
- Endocrine markers: Cortisol, leptin, free thyroxine (FT4), thyroid-stimulating hormone (TSH), ACTH, IGF-binding protein 3.
- Bone and mineral metabolism: Calcium, phosphate, magnesium, 25-hydroxycholecalciferol (Vitamin D).

These assessments provide critical insights into preterm infants' post-discharge nutritional, metabolic, and endocrine adaptations, guiding personalized nutrition and growth interventions.[173]

## Recommendations/Statements
## Postdischarge Nutrition

- Very preterm neonates on exclusive breastmilk or breastfeeding at discharge.
  - Human milk is superior to formula in promoting better body composition (increased fat-free lean mass) and improved neurodevelopmental outcomes in preterm infants postdischarge (Grade B, moderate CoE).[174]
  - *Fortification and micronutrient supplementation*
    Since HM alone may not fully meet the nutritional needs of preterm infants, fortification with breastmilk fortifiers is recommended over fortification with term or preterm formula (Grade B, moderate CoE).
  - *Tailored fortification strategies*
    Multinutrient fortification can be customized based on the infant's needs and the mother's breastfeeding preferences, such as fortifying half of the feeds or using breastmilk concentrate (Grade C, low CoE).[166,168] Adding micronutrient fortification once daily can increase caloric content by 6.5% and protein by 20%.[175]
  - *Micronutrient supplementation*[176]
    - *Iron*: Iron storage levels should be assessed at discharge and at the start of complementary feeding (CF). Tailored supplementation is recommended (Grade C, low CoE).[176,177]
    - *Zinc*: Routine serial zinc measurements and supplementation are unnecessary unless the clinical deficiency is suspected (e.g., delayed wound healing, poor growth) (Grade D, very low CoE).
    - *Vitamin D*: Supplementation is recommended until 1 year; however, serial vitamin D measurements are not necessary unless deficiency is suspected (Grade C, low CoE).
    - *Long-chain polyunsaturated fatty acids (LC-PUFA)*: Routine serial measurements are not recommended. Docosahexaenoic acid (DHA) supplementation may be beneficial, but optimal dose and timing remain unclear.
    - *Calcium and phosphorus*: Baseline assessments of calcium, phosphorus, alkaline phosphatase (ALP), and parathyroid hormone (PTH) should be done before discharge. Serial measurements are not required unless deficiency is present and supplementation is initiated.
- Very preterm neonates discharged on formula feeds
  - *Nutrient-rich isocaloric postdischarge formula*
    Nutrient-rich, isocaloric PDF has been shown to promote faster catch-up growth, particularly in male infants, while improving lung function and bone mineral content in the short term. However, long-term studies have found no significant impact on bone mineral content or body composition (Grade B, moderate CoE).[170,178–181]
  - *Nutrient-enriched formula in chronic lung disease of prematurity*
    Preterm infants with chronic lung disease fed nutrient-enriched formula post-discharge exhibit more significant linear growth, increased lean mass, and improved bone mineral content compared to those receiving standard formula (Grade C, low CoE).[182]
  - *Extended use of preterm formula*
    Preterm infants fed preterm formula for extended periods (2–6 months corrected age) show better growth, improved bone mineral content, increased head circumference, and higher fat-free lean mass compared to those fed term formula, particularly in appropriate-for-gestational-age (AGA) infants (Grade C, low CoE).[157,183]

    In small-for-gestational-age (SGA) infants, extended preterm formula feeding does not significantly impact body composition at 6 months, though it is associated with higher fat mass. Neurodevelopmental outcomes remain similar between infants fed preterm vs standard term formula.[184]

    For preterm neonates with extrauterine growth restriction, nutrient-dense formula (100 kcal/100 mL; protein 2.6 gm/100 mL) during the first 6 months post-discharge resulted in similar *z*-scores compared to standard pre-discharge formula (74 kcal/100 mL; protein 1.95 gm/100 mL).[185]
  - *Targeted postdischarge nutrition programs*
    Structured post-discharge nutrition intervention programs facilitate faster catch-up growth, allowing preterm infants to reach standard birth centiles by 4–6 months corrected age (Grade C, low CoE).[186]
- *Late preterm (> 34 weeks gestational age)*
  - No difference in body weight gain between late preterm neonates fed with standard vs nutrient enriched formula compared to breastfeeding group (Grade D, very low CoE, premature stoppage of RCT).[187]
- *Complementary feeding in preterm infants*[188–190]
  - *Timing of complementary feeding*
    Complementary feeding should be initiated between 5 and 8 months chronological age and at least 3 months corrected age to ensure adequate developmental readiness for swallowing solid foods (Grade A, moderate CoE).
  - *Complementary feeding in preterm infants with oral dysfunction or comorbidities*
    Preterm infants with oral dysfunction and/or medical comorbidities may require a multidisciplinary assessment

to determine the appropriate timing and method for introducing complementary feeds (Grade C, low CoE).

- *Type and sequence of foods*.
  Current recommendations for food choices, sequence, and speed of introduction in preterm infants align with those for term infants. A varied diet including all major macronutrients (carbohydrates, proteins, plant-based fats) is advised, with special attention to iron and vitamin D intake (Grade C, low CoE).
- *Complementary feeding timing and obesity risk*
  The timing of CF initiation is not linked to an increased risk of overweight or obesity and should not be delayed due to such concerns (Grade A, moderate CoE).
- *Introduction of allergenic foods*
  The introduction of allergenic foods (e.g., nuts, eggs, fish, tomatoes) should not be delayed. However, limiting gluten intake is recommended especially during initial days after CF initiation. (Grade D, very low CoE).
- *Complementary feeding in vegetarian and vegan families*
  For infants in vegetarian or vegan families, nutritional guidance from experts is essential. Monitoring for nutritional deficiencies is recommended, with vitamin B12 and vitamin D supplementation as necessary (Grade D, very low CoE).

### The LAYA* Group of the Global Newborn Society – Authors

Nitasha Bagga[1,2], Akhil Maheshwari[2–18], Gayatri Athalye-Jape[2,19], Jenisha Jain[2,20], Aimen E Ben Ayad[2,21], Pradeep Reddy[1], Roya Huseynova[2,22], Nusrat Khan[21], Manal Mouhssine[21], Gangajal Kasniya[23]

[1]Department of Neonatology, Rainbow Children's Hospital, Hyderabad, Telangana, India
[2]Global Newborn Society, New York, United States of America
[3]Department of Pediatrics/Neonatology, Boston Children's Health Physicians Group at the Maria Fareri Children's Hospital, New York Medical College, Valhalla, New York, United States of America
[4]The Skylar Project, Estia St. Daphne, Alabama, United States of America
[5]International Society for Marginalized Lives, Harrison, New York, United States of America
[6]PreemieWorld Foundation, Springfield, Virginia, United States of America
[7]Department of Pediatrics/Neonatology, University of Alabama at Birmingham, Birmingham, Alabama, United States of America
[8]Carlo GNS Center for Saving Lives at Birth, Birmingham, Alabama, United States of America
[9]GNS Forum for Transgenerational Inheritance, New York, United States of America
[10]Banaras Hindu University Institute of Excellence, Varanasi, Uttar Pradesh, India
[11]Mongolian Association of Obstetrics, Gynecology, and Neonatology, UlaanBaatar, Mongolia
[12]Bangladesh Neonatal Foundation, Dhaka, Bangladesh
[13]Autism Care Network Foundation, India
[14]Neonatology-Certified Foundation, Brooksville, Texas, United States of America
[15]GNS Infant Nutrition Education Program, Harrison, New York, United States of America
[16]Pioneers - Looking for Sustainable Ways to Reduce Infant Mortality, Oslo, Norway
[17]International Prader-Willi Syndrome Organization, Cambridge, United Kingdom
[18]S.A.B.R.E.E. Enrichment Academy, Saint Louis, Missouri, United States of America
[19]Department of Neonatology, King Edward Memorial Hospital, Perth, Western Australia School of Medicine, University of Western Australia
[20]Department of Neonatology, Choithram Hospital and Research Centre, Indore, Madhya Pradesh, India
[21]Department of Pediatrics/Neonatology, Tawam Hospital, Al Ain, Abu Dhabi, United Arab Amirates
[22]Department of Neonatology, King Saud Medical City, Saudia Arabia
[23]Department of Pediatrics, Division of Neonatal-Perinatal Medicine, Ochsner Children's Hospital, Ochsner Health, New Orleans, Los Angeles, United States of America

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ORIGINAL RESEARCH

# Initiation of Breastfeeding within the Golden 1st Hour after Birth Led to Sustained Lactation during Infancy: Results from a Single-center Quality Improvement Project

Ravi Sahota[1], Navpreet Sahota[2], Bharti Gahtori[3], Veena Joshi[4], Vikram Bedi[5], Abhay Mahindre[6]

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## Abstract

**Background:** At our center in Northern India, we have had low breastfeeding rates despite repeated efforts focused on recruitment of experienced staff and providing information about the benefits of human milk (HM) to mothers and families.

**Methodology:** A QI project was conducted in infants born at ≥35 weeks' gestation over 1 year, with an aim to increase breastfeeding rates. A multidisciplinary team focused on the early initiation of breastfeeding (EIBF), in addition to other ongoing measures such as skin-to-skin contact, staff training, and maternal education.

**Results:** We studied 756 mother–infant dyads over a 1-year period. Early initiation of breastfeeding increased the number of HM-fed infants from 8 to 88% within 3 months. A minor, statistically insignificant drop in breastfeeding rates to 82% was seen at 6 months, but reinforced educational efforts restored this success back to 87% within a month. These rates were then maintained throughout the rest of the year.

**Conclusion:** In our center, initiation of breastfeeds in the golden 1st hour after birth has helped not only in initiation but also in maintaining high rates of maternal feeding throughout infancy. Focused education of staff and families can promote a sustained increase in breastfeeding rates.

**Keywords:** Breastfeeding support, Delayed cord clamping, Early initiation of breastfeeding, Maternal education, Neonatal care, Quality improvement, Skin-to-skin contact, Staff training.

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## Key Points

- At our center in Northern India, breastfeeding rates had been low despite repeated efforts focused on recruitment of experienced staff and providing information about the benefits of human milk (HM) to mothers and families.
- Early initiation of breastfeeding (EIBF) within the 1st hour after birth is a widely recognized measure of healthcare quality of neonatal care. Hence, we designed a new quality improvement project with maternal and staff education focused on early, Golden Hour initiation of breastfeeding.
- In this effort, EIBF increased the number of HM-fed infants from 8 to 88% within the first 3 months. This approach has helped us not only with initiation but, surprisingly, also in maintaining high rates of maternal feeding throughout infancy.

## Introduction

Early initiation of breastfeeding within the 1st Golden Hour after birth has been linked with a significant reduction in neonatal mortality. The protective components of colostrum, such as immunoglobulins and lymphocytes, enhance the newborn's immune system, while avoiding pre-lacteal feeds reduces exposure to potential infections.[1,2] Additionally, EIBF is also know to prevent hypothermia and infant diarrhea. For mothers, early breastfeeding stimulates the release of oxytocin, thereby reducing the risk of postpartum hemorrhage.[3] Despite these clear benefits, many mothers face numerous challenges that prevent them from initiating breastfeeding within the 1st hour after giving birth. Early initiation of breastfeeding rates range from 17.7 to 57.6%, with many developing nations reporting rates around 50%.

[1]Department of Pediatrics and Neonatology, Sahota Superspeciality Hospital, Kashipur, Uttarakhand, India

[2]Department of Obstetrics and Gynecology, Sahota Superspeciality Hospital, Kashipur, Uttarakhand, India

[3]Department of Fetal Medicine and OBG and Gynec, Gahtori Hospital, Kashipur, Uttarakhand, India

[4]Department of Obstetrics and Gynecology, Veena Joshi Hospital, Kashipur, Uttarakhand, India

[5]Department of Pediatrics and Neonatology, Bedi Hospital, Chandigarh, India

[6]Department of Neonatology, Noble Hospital, Pune, India

**Corresponding Author:** Ravi Sahota, Department of Pediatrics and Neonatology, Sahota Superspeciality Hospital, Kashipur, Uttarakhand, India, Phone: +91 7055020002, e-mail: sahota24@yahoo.com

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**Conflict of interest:** None

In India, the National Family Health Survey (NFHS-4) indicates that only 41.6% of newborns were breastfed within the 1st hour.[4] It is estimated that over one million neonatal deaths could be prevented annually if breastfeeding is initiated within this critical window. While exclusive breastfeeding during the first 6 months has been widely promoted, the importance of timely initiation is only beginning to gain attention.[1] Recent assessments of maternal

and neonatal care services have highlighted significant gaps in newborn care practices, particularly regarding skin-to-skin contact and EIBF.[5]

At our center in Northern India, we had struggled with low breastfeeding rates despite repeated efforts focused on recruitment of experienced staff and providing information about the benefits of HM to mothers and families. From a global perspective, our state continues to have a relatively high infant mortality rate of 27 deaths per 1,000 live births. Hence, we designed a quality improvement (QI) project with staff and maternal education focused on early, golden hour initiation of breastfeeding. Early breastfeeding initiation within 30 min of delivery is one of the 10 steps promoted by the WHO/UNICEF Baby-friendly Hospital Initiative.[6] This approach has helped us not only with initiation but, surprisingly, also in maintaining high rates of maternal feeding throughout infancy.

## Methodology

This QI study was conducted at our hospital in Kashipur, Uttarakhand, over a 1-year period from June 2023 to June 2024. The goal was to improve breastfeeding initiation rate within the 1st hour of life. We studied 756 deliveries, which included 352 vaginal deliveries and 404 lower segment cesarean sections.

### Study Population

The target population included all newborns ≥35 weeks' gestation delivered vaginally or via cesarean section. Newborns admitted to the Neonatal Intensive Care Unit (NICU) for prematurity, hemodynamic instability, or respiratory distress were excluded. The goal was to improve breastfeeding rates from our baseline 8 to ≥80%.

### QI Team and Data Collection

A multidisciplinary QI team was formed, including obstetricians, pediatricians, nurses, nursing students, lactation consultants, public volunteers ("breastfeeding champions"), and members of the anesthesiology and surgical teams. The faculty members and student nurses directly observed and recorded data on breastfeeding initiation. The study strictly adhered to accepted evidence-based practice guidelines from the WHO/UNICEF Baby-Friendly Hospital Initiative and did not involve any medical treatments or investigation changes.[5]

### Steps in the QI Process

- *Baseline measurement*: Baseline data on the breastfeeding initiation rate within the 1st hour were collected through direct observation, with an initial rate of 8%.
- *Team formation:* A multidisciplinary team – including obstetricians, nursing staff, nursing students, breastfeeding champions or lactation consultants, and members of the anesthesiology and surgical teams – was formed to conduct the project.
- *Root cause analysis*: The team conducted a fishbone analysis to identify possible causes of delays in breastfeeding initiation. The study focused on policy, procedure, people (mothers and nursing staff), and place (hospital environment).
- *Implementation of interventions*: To promote early breastfeeding initiation, we ensured immediate skin-to-skin contact between mother and newborn for at least 60 min after birth, using protocols to minimize delays for all delivery types. We retrained all staff members and mothers on breastfeeding support during the critical 1st golden hour.[7–10] Checklists were used to track initiation times and review data. We also implemented delayed cord clamping whenever possible by waiting 1–3 min at delivery to enhance newborn outcomes.[5,6]

### Intervention Strategies

#### *Promotion of Skin-to-skin Contact (Kangaroo Care)*

We revisited conscious efforts to facilitate immediate and continuous skin-to-skin contact between the mother and her newborn for at least 60 min following delivery. This involves placing the baby after drying and placing a diaper directly on the mother's bare chest, covering both with a warm blanket to maintain temperatures. Skin-to-skin contact is known to enhance thermoregulation, hemodynamic stability, breathing, and promote bonding and early breastfeeding initiation.[6]

#### *Delayed Cord Clamping*

Delayed cord clamping (DCC) for 1–3 min after delivery was incorporated as a standard procedure. It is known to promote additional blood flow from the placenta to the newborn, and thereby enhance iron stores and improve developmental outcomes.[9] Clinical protocols were updated, and staff were retrained to ensure that they understood the benefits and followed standardized procedures for DCC.[10]

#### *Staff Education and Training about EIBF*

We retrained all delivery and postpartum staff, including midwives, nurses, and doctors, on EIBF. The educational points included breastfeeding techniques, ways to assist mothers with latching, and identification of early initiation challenges, such as those following cesarean sections.[7] We emphasized each team member's role in supporting EIBF.[8]

#### *Parental Education*

All expectant mothers were educated about the significance of EIBF using informational hand-outs, visual aids, and interactive discussions during antenatal visits.[7] In the delivery room, this education was continued by offering one-on-one breastfeeding counseling. Mothers were encouraged to ask questions and express their concerns, providing reassurance and practical guidance to boost their confidence in breastfeeding.[9]

#### *Establish Data Tracking and Feedback*

A standardized checklist or form was introduced to record breastfeeding initiation times for all births. This tool captured essential information such as the time of birth, the time breastfeeding was initiated, and any factors that delayed initiation. The data were regularly reviewed with the healthcare team on a weekly basis to monitor performance and identify trends or recurring issues.[7] These insights provided constructive feedback to staff, celebrate successes, and develop action plans for improvement. Sharing this data promoted accountability and fostered a culture of continuous quality improvement (Table 1 and Figs 1 and 2).[5]

## Results

In this cohort, the average maternal age was 27 years. Nearly half underwent cesarean sections (53.4%). In terms of education, 86.9% had not moved beyond senior high school (12th grade). A baseline

survey at our center over a 15-day period showed that only 8% of neonates were breastfed within the 1st hour of birth. The course of breastfeeding rates throughout the intervention over the period of 1 year are demonstrated in Table 2 and Figure 3.

Early initiation of breastfeeding within 1 h improved significantly after the intervention, rising from 8% before the intervention to 88% at 3 months. There was a slight, statistically insignificant drop to 82% at 6 months. Re-strengthening of efforts again raised these numbers to 87%, and these stayed at comparable proportions at the end of the year. The remaining 13% who did not receive EIBF efforts included 7% due to NICU admissions and 6% due to maternal conditions.

**Table 1:** Clinicodemographic characteristics of delivering mothers

| *Clinicodemographic variables* | *Number of mothers (%)* |
|---|---|
| Maternal age (years; mean ± standard deviation) | 27 ± 2.9 |
| Vaginal deliveries (number, percentage) | 404 (53.4) |
| Cesarean sections (number, percentage) | 352 (46.6) |
| Maternal education (number, percentage) | |
| No education | 164 (21.7) |
| Less than senior high school (12th grade) | 492 (65.2) |
| Beyond senior high school | 100 (13.1) |

## Discussion

In this study, we found that EIBF was the most important QI measure to maintain breastfeeding rates during the 1st year. We had previously implemented other strategies, such as skin-to-skin contact (kangaroo care), delayed cord clamping, staff education, and parental counseling, in disparate efforts but could not demonstrate high rates of success. Here, a renewed emphasis on a "bundled" approach possibly helped.[11] These interventions are aligned with global healthcare strategies and recommendations from organizations such as the World Health Organization and the United Nations Children's Emergency Fund, which emphasize the critical role of timely breastfeeding in improving neonatal survival and overall health outcomes.[12]

Early initiation of breastfeeding is likely a key component of early postnatal stabilization of neonatal physiological parameters, such as temperature, heart rate, and respiratory function.[13,14] The close contact with the mother, affectionate handling, and the natural maternal observation of normal responses of the infant likely helped. The success of this approach was reflected in the present study, where breastfeeding initiation rates surged from 8% before the intervention to 87% by the end of the study period. Although NICU admissions and maternal health conditions impacted a small

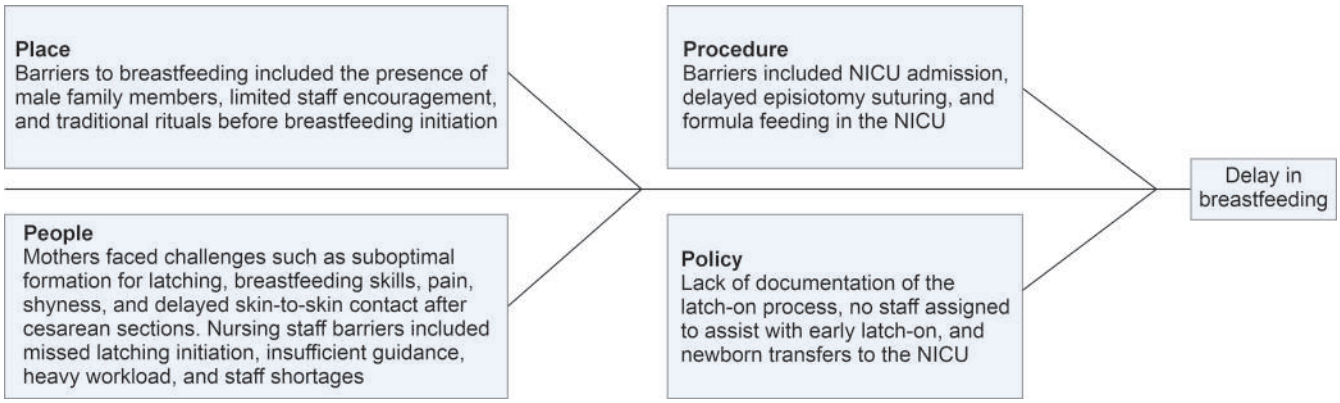


**Fig. 1:** Fishbone analysis of breastfeeding practices

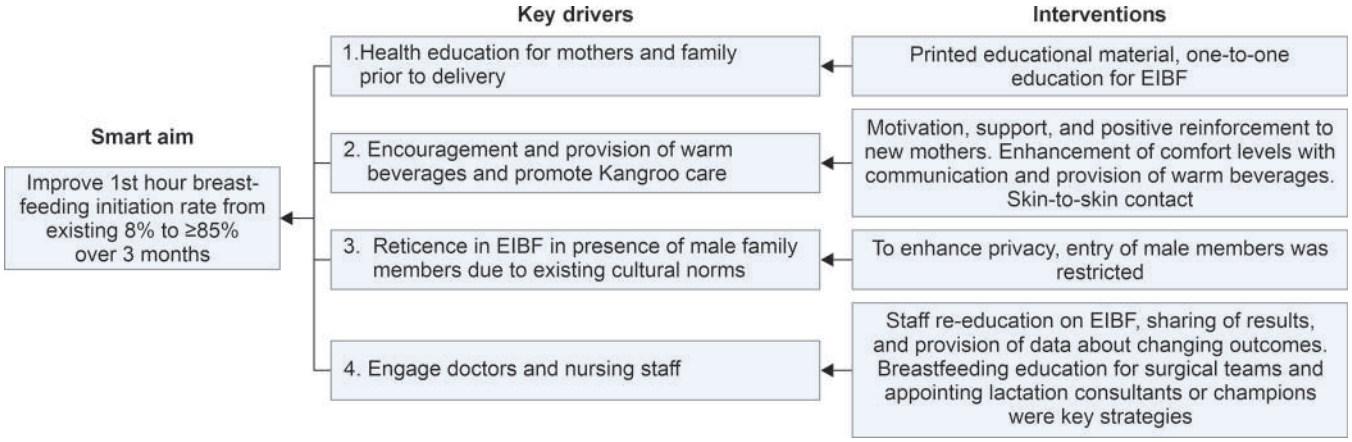


**Fig. 2:** Key driver diagram of quality improvement change ideas and intervention

**Table 2:** Breastfeeding initiation before and after intervention (over 1 year timeframe)

| *Timeframe (1 year)* | *Breastfeeding initiation (%)* |
|---|---|
| Before intervention | 8% of neonates breastfed within 1 h |
| At 3 months | 88% of neonates breastfed within 1 h |
| At 6 months | 82% of neonates breastfed within 1 h |
| At the end of 1 year | 87% of neonates breastfed within 1 h |
| Remaining (13%) | 7% NICU admissions, 6% due to maternal conditions |

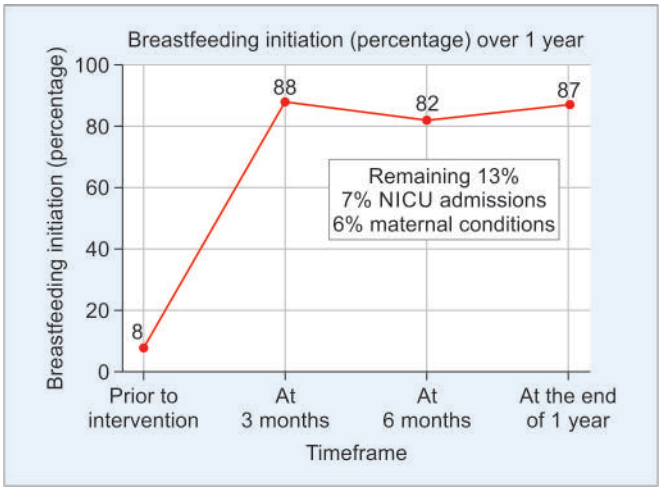


**Fig. 3:** Run chart showing the breastfeeding initiation rate within 1 h of birth

proportion of cases, the overall trend showed a substantial and sustained improvement.

The comprehensive education and training efforts clearly helped in this QI project. Empowering midwives, nurses, and physicians with evidence-based knowledge and practical skills addressed key barriers to EIBF. This approach is consistent with other reports in the literature, where enhanced staff training improved maternal and neonatal outcomes by fostering more effective breastfeeding support.[15] In our QI project, regular performance reviews and data tracking allowed the team to monitor progress and quickly address any emerging challenges, reinforcing the overall success of the interventions.[11]

A slight numerical decline in breastfeeding rates, which was not statistically significant, was observed at the 6-month assessment point. Reinforcement of the interventions led to recovery, highlighting that there is a need for continuous educational support in newborn care units. Such fluctuations have been noted in nearly all QI initiatives, and periodic reinforcement of strategies has helped maintain long-term gains.[14,15] The adaptive and responsive nature of the study's implementation process underscores the importance of flexibility and ongoing evaluation in healthcare interventions.[13]

### Limitations and Future Scope of Research

This study does have some limitations. It was a single-center study, so its findings may not apply to other settings. The exclusion of high-risk infants, such as those admitted to the NICU, limits its relevance to vulnerable populations. Additionally, there is a need to determine whether possible delays in introduction of solid foods with continued breastfeeding at 1 year might have negative implications on growth parameters. The reliance on direct observation for data collection introduces the potential for observer bias, and the study did not thoroughly analyze maternal conditions that could affect breastfeeding. Furthermore, socio-economic and cultural factors were not explored, and the study focused on quantitative outcomes without assessing maternal satisfaction or breastfeeding confidence. Future studies could address these gaps by expanding the study to multiple healthcare settings, including rural and resource-limited environments, for broader generalizability.

## Conclusion

This study emphasizes the importance of EIBF in efforts to increase and maintain breastfeeding in infants ≥35 weeks' gestation. A bundled approach, including skin-to-skin contact, enhanced staff training, parental education, and systematic data tracking, can help.

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REVIEW ARTICLE

# Lactoferrin: A Multifaceted Glycoprotein in Milk

Taherah Mohammadabadi[1,2], Gunjana Kumar[2,3], Akhil Maheshwari[2,4–16]

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## Abstract

Lactoferrin, a multifaceted glycoprotein, is a key milk-borne carrier for iron and other trace metals important for infant nutrition. It also plays an important role in innate immunity with antibacterial and antiviral properties, as an anti-inflammatory agent, and an antioxidant. Lactoferrin is present in high concentrations in mammalian milk; it is often the most abundant protein in milk after casein. The highest concentrations are seen in colostrum at nearly 5 gm/L and then at 2–3 gm/L in mature milk. The current review highlights our understanding of lactoferrin's structure, properties, and possible clinical applications, offering insights for future research and the development of functional products. There are also possible uses in food, pharmaceuticals, and biotechnology industries. There is a need for serious, focused work.

**Keywords:** Antibacterial, Anti-inflammatory, Antioxidant, Antiviral, Casein, Infant nutrition, Innate immunity, Iron, Mammalian milk, Transferrin.

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## Key Points

- Lactoferrin, a multifaceted glycoprotein, is a key milk-borne carrier for iron and other trace metals.
- It plays an important role in innate immunity with antibacterial and antiviral properties, as an anti-inflammatory agent, and an antioxidant.
- Lactoferrin interacts directly with microbial surfaces, where it shows an important static effect against a variety of pathogens by damaging the outer membranes, surface proteins, and other virulence factors.
- In the intestinal mucosa, lactoferrin releases iron to ferroportin, which then delivers the iron to circulating apo-transferrin. Bacteria have hijacked these processes and produce lactoferrin-binding protein-A (LbpA), LbpB, and transferrin-binding protein B to capture the iron cargo on these proteins.

## Introduction

Lactoferrin is a globular, single-chain 80 kDa nonheme iron-binding glycoprotein.[1,2] It is a well-noted member of the transferrin family that is known for its roles in innate immunological defenses and in enteral uptake of iron.[3–5] It is the second most abundant protein in mammalian milk and colostrum after casein and is also detectable in many other body fluids, such as tears, saliva, vaginal fluid, semen, and respiratory and gastrointestinal secretions.[5–8]

Most of our current information about lactoferrin centers on its iron-free apo-lactoferrin and the iron-saturated holo-lactoferrin forms.[1] As shown in Figure 1, apo-lactoferrin is an important mediator in diverse physiological functions, including innate immune responses against microbial infections, its antioxidant and anti-inflammatory properties, regulation of iron absorption in the bowel, and possibly, for its regulatory effects on the cell cycle.[5] It is a highly conserved protein of about 600–700 amino acids; there is a 19-amino acid α-helix signal peptide at the *N*-end and two major domains at the *N*- and the *C*- ends; these lobes are also linked by a α-helix peptide.[9–11] Milk-borne apo-lactoferrin has two major roles: The first as an innate immune mediator, where it interacts directly with microbial surfaces.[12,13] It shows an important static effect against a variety of pathogens by damaging the outer membranes, surface proteins, and other virulence factors.[14,15] In gram-negative

[1]Faculty of Animal Science and Food Technology, Agricultural Sciences and Natural Resources University, Iran

[2]Global Newborn Society, Harrison, New York, United States of America

[3]Department of Neonatology, National Institute of Medical Sciences and Research, Jaipur, Rajasthan, India

[4]Global Newborn Society Forum for Transgenerational Inheritance, Harrison, New York, United States of America

[5]Pediatrics/Neonatology, Boston Children's Health Physicians Group at the Maria Fareri Children's Hospital, New York Medical College, Valhalla, New York, United States of America

[6]Banaras Hindu University Institute of Excellence, Varanasi, Uttar Pradesh, India

[7]Mongolian Association of Obstetrics, Gynecology, and Neonatology, Ulaanbaatar, Mongolia

[8]Bangladesh Neonatal Foundation, Dhaka, Bangladesh

[9]Autism Care Network Foundation, Chandigarh, India

[10]PreemieWorld Foundation, Springfield, Virginia, United States of America

[11]Neonatology-Certified Foundation, Brooksville, Texas, United States of America

[12]Global Newborn Society Infant Nutrition Education Program, Clarksville, Maryland, United States of America

[13]Pioneers – Looking for Sustainable Ways to reduce Infant Mortality, Oslo, Norway

[14]International Prader–Willi Syndrome Organization, Cambridge, United Kingdom

[15]The Skylar Project, Daphne, Alabama, United States of America

[16]American Society for Marginalized Lives, Harrison, New York, United States of America

**Corresponding Author:** Taherah Mohammadabadi, Faculty of Animal Science and Food Technology, Agricultural Sciences and Natural Resources University, Iran; Global Newborn Society, Harrison, New York, United States of America, Phone: +98 6341773637, e-mail: t.mohammadabadi.t@gmail.com

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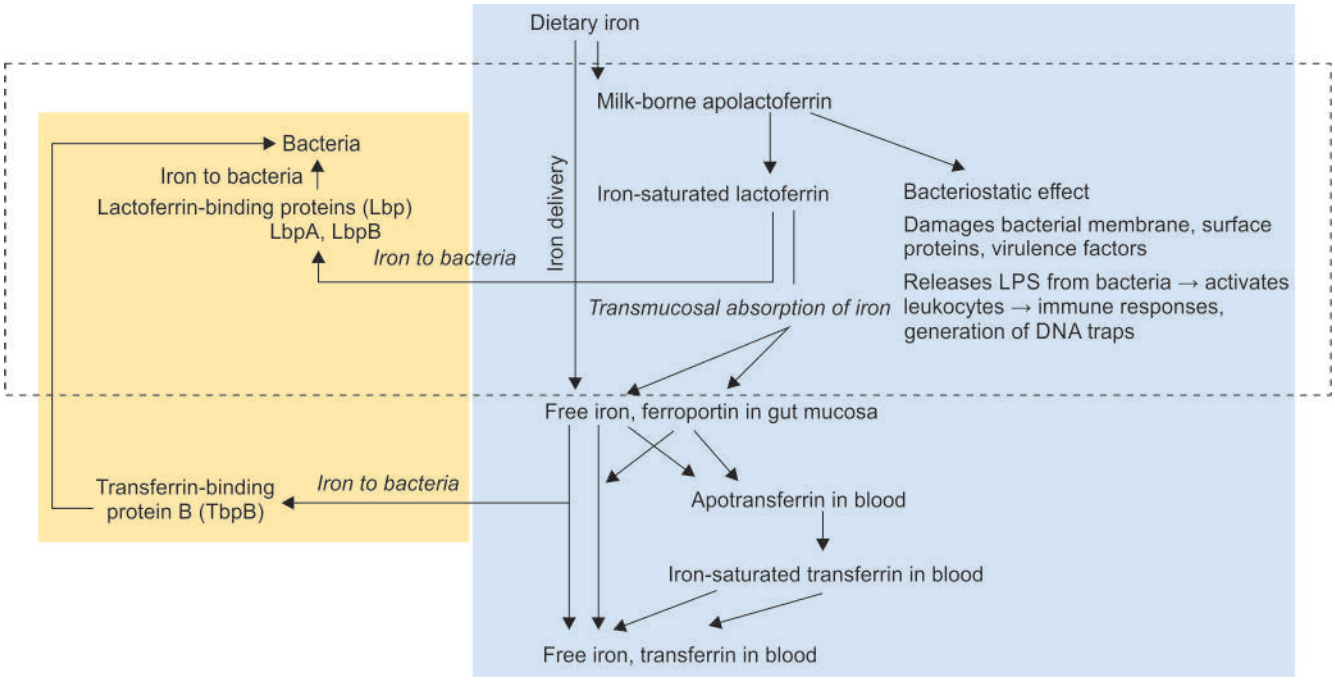



**Fig. 1:** Lactoferrin is an important mediator in innate immunity and in iron absorption in the intestine. In the human body, dietary iron is absorbed across the intestinal mucosa in its elemental form and in lactoferrin (blue). Bacteria have hijacked this process by binding lactoferrin with lactoferrin-binding proteins A and B. These bacterial processes are shown shaded in yellow. The overall role of lactoferrin is highlighted in the rectangle with broken lines. Downstream, ferroportin protein complex and apotransferrin carry iron through the mucosa into the bloodstream. These host processes are shown shaded in blue. Iron-saturated transferrin can bind to transferrin-binding protein B

bacteria, lactoferrin binds and disrupts the outer membrane close to the lipopolysaccharide sites; this interaction promotes bacteriolysis either through direct effects or by synergizing with other antimicrobial agents.[16–18]

The role of lactoferrin as an iron carrier has received considerable attention.[1] Binding to iron optimizes the three-dimensional structure of this protein and enhances its function as a carrier of dietary iron across the gut mucosa.[19] In the mucosa, lactoferrin releases iron to ferroportin, which then delivers the iron to circulating apo-transferrin.[20,21] Bacteria have hijacked these processes and produce lactoferrin-binding protein-A (LbpA), LbpB, and transferrin-binding protein B to capture the iron cargo on these proteins.[22,23] Overall, there is considerable interest in understanding the physiological role of lactoferrin.[24] Given possible pharmaceutical and nutritional applications, it is also now also being recognized as a potential nutraceutical.[25] In this review, we aimed to provide a consolidated source of information about this protein. We have combined some data from our own preliminary studies with an extensive literature search in Embase, PubMed, and Scopus.[26,27] To avoid bias in identification of studies, keywords were short-listed *a priori* from PubMed's Medical Subject Heading thesaurus.[28]

## Major Structural Elements of Lactoferrin

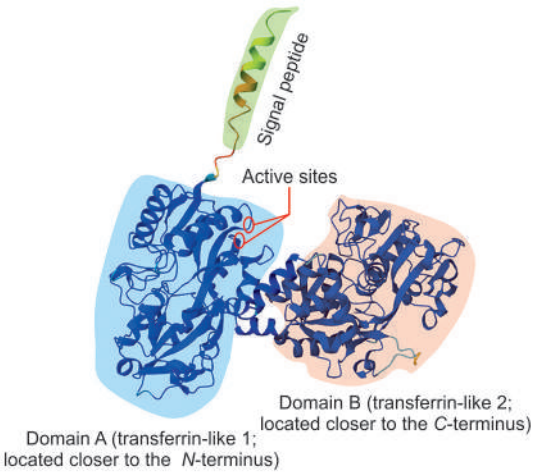
The lactoferrin protein molecule is composed of a signal peptide and two lobes, one near the *N*- and the other at the *C*-terminus (Fig. 2).[29] It is a well-characterized protein with a high degree of certainty about its three-dimensional structure, side-chains, and the molecular surface (Fig. 3A).[30] There are two ~40-kDa lobes linked by a small alpha-helix segment, which provides additional flexibility to the molecule (Fig. 3B).[31–33] Each of these lobes are composed of two sub-domains, *N1* and *N2*, and *C1* and *C2* (Fig. 3C).[29] Figure 3D shows the amino acid composition.[34]

Both lobes contain iron ($Fe^{2+}$/$Fe^{3+}$)-binding sites composed of several negatively-charged residues (Fig. 4).[31,32] Several other metallic ions, such as manganese ($Mn^{2+}$), copper ($Cu^{2+}$), and zinc ($Zn^{2+}$), can also bind in these zones.[3,35] In addition to the known role in nutrition, some of these cationic residues in lactoferrin can bind electrostatically with the anions on the membranes of various pathogens, such as bacteria, viruses, fungi, and parasites to eliminate these.[36–39]

Metal ion binding can stabilize the apo- form and reduce its susceptibility to proteolysis.[9,40] Still, even though iron-binding may stabilize the protein, it does not directly alter/enhance the immune effects of lactoferrin.[41] However, the sequestration of iron at sites of infection may limit its bioavailability to invading pathogens with a secondary bacteriostatic effect.[9]

These two lobes show some homology with each other (33–41%).[9] However, the lactoferrin protein in iron-deficient apo- (iron saturation <5%) and the iron-saturated holo-lactoferrin (saturation ≥85%) forms show important three-dimensional differences in structure.[42] The iron-deficient apo- form appears much more open in configuration than the closed iron-saturated lactoferrin.[43] The iron saturation of lactoferrin defines its physicochemical properties; the iron-free apo-form shows stronger antibacterial and antioxidant activities than the iron-saturated lactoferrin.[42] The osteogenic activity of apo-lactoferrin decreases with the increasing iron saturation.[44]

With an exceptionally high affinity for ferric ions, nearly 250–300 times greater than transferrin, lactoferrin regulates iron-redox homeostasis.[45] This iron chelation reduces free radical




**KEY STRUCTURAL ELEMENTS**

**Major domains**
1-19 signal peptide
20-710 lactoferrin

The *N*-lobe of lactoferrin binds PBP2 (Penicillin-binding protein 2) and Lactoferrin binding protein B (LbpB) on bacteria. Bacteria, particularly the Gram-negative rods, use LbpB to acquire iron. Lbp2 resembles the transferrin binding protein B (TbpB), which is involved in iron acquisition from transferrin. LbpB and TbpB bind the iron-loaded (holo) form of lactoferrin to promote its delivery to the outer membrane transporter, LbpA. The *C*-lobe binds transferrin and bacterial TbpB to promote iron acquisition.

**Iron cation sites**
Positions 79, 111, 211, 272: Iron cation 1
Positions 414, 452, 545, 614: Iron cation 2

**Hydrogencarbonate**
Position 136, 140, 142, 143: Hydrogencarbonate 1
Position 478, 482, 484, 485: Hydrogencarbonate 2

**Specific domains with antimicrobial activity**
Position 20-67: Lactoferricin H
Position 171-201: Kaliocin 1
Position 338-343: Lactoferricin A
Position 543-547: Lactoferricin B
Position 680-686: Lactoferricin C

**Positions known to serve key roles**
Position 23: interacts with pneumococcal surface protein A (PspA)
Position 32: Interacts with PspA
Position 20-24: critical for glycosaminoglycan, lipid A, lysozyme, and DNA binding;
Position 20-29 bactericidal and antifungal activities
Position 39-49: shows anti-lipopolysaccharide, bactericidal, and antifungal activity; interacts with PspA
Position 57-58: interacts with PspA
Position 46-51: involved in glycosaminoglycan binding

**Active site**
Position 92 and position 278

**Cross-links**
Position 379: glycyl lysine isopeptide (interchain with G-Cter in ubiquitin)
Position 391: glycyl lysine isopeptide (interchain with G-Cter in ubiquitin)

*(Contd...)*

**ALTERED STRUCTURE**

**Sequence splicing**
VSP_044308: position 1-44; Isoform DeltaLf (intracellular isoform with a truncated *N*-terminus different from that in the secreted isoform; produced via alternative splicing or promoter usage).

**Modified residue position**
Position10: phosphoserine; alternative

**Glycosylation with altered structure**
Position 10: O-linked (GlcNac) serine; alternative
Position 156: N-linked (GlcNac) leucine; alter
Position 497: N-linked (GlcNac) asparagine; alternative
Position 642: N-linked (GlcNac) asparagine; alternative

**Variants**
Var_ 069298 position 22 dbSNP:rs10662431 associated with lower plasma Lactoferrin conc
Var_ 013504 position 29 dbSNP:rs1126477
Var_013505 position 47: decreased antibacterial activity against Gram-positive bacteria; may reduce susceptibility to localized juvenile periodontitis
Var_013506 position 148 dbSNP:1126479
Var_013507 position 422 dbSNP:1042055
Var_013508 position 579 dbSNP:2073495

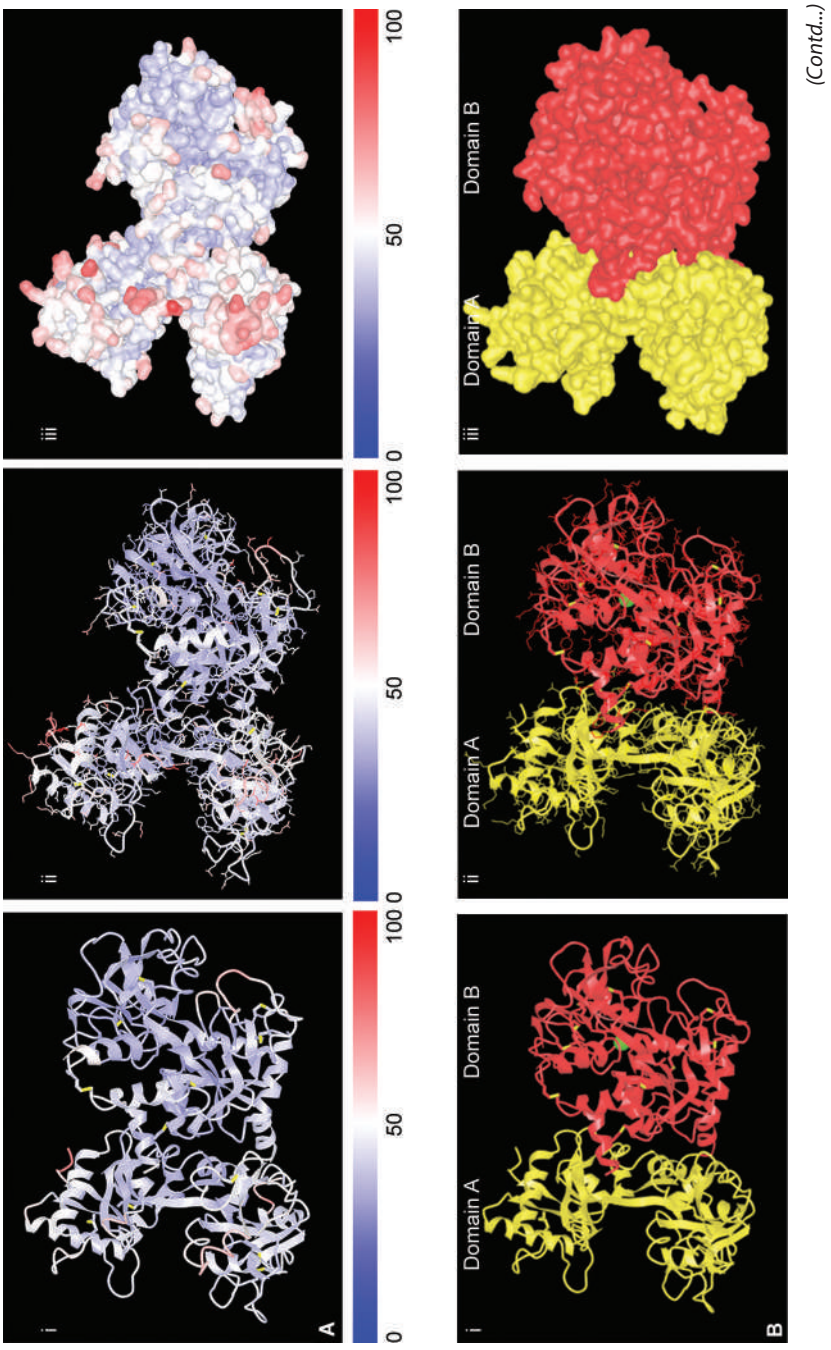
**Altered Lactoferrin amino acid sequence due to mutations**
Position 20-23: abolishes binding to heparin, lipid A, lysozyme, and lipid A
Position 79: abolishes Fe binding and changes domain closure
Position 92: abolishes protease activity
Position 140: disrupts anion binding site and destabilizes Fe binding
Position 229: abolishes Fe binding
Position 272: abolishes protease activity
Position 278: abolishes protease activity

**Fig. 2:** Structure of lactoferrin. The protein comprised a signal peptide and two structural A and B domains connected by a short alpha-helix. The information summarized in this figure was obtained using data/tools provided on the web portal of the Research Collaboratory for Structural Bioinformatics (RCSB) protein data bank, National Center for Biotechnology Information (NCBI) protein data bank (PDB), NIH genetic sequence database (GenBank), Molecular Modeling Database (MMDB), Reference Sequence (RefSeq), Third Party Annotation (TPA), UniProtKB/Swiss-Prot database, Protein Information Resource (PIR), Protein Research Foundation (PRF), and depicted using Microsoft PowerPoint, Microsoft Illustrator, and/or Adobe Photoshop. Some of the information in the box on the right was based on the details depicted at https://www.rcsb.org/groups/3d-sequence/polymer_entity/P02788, and further details were added as highlighted in the text

injury, suppressing oxidative stress, and enhancing the host defense mechanism.[46] It also plays a vital role in iron absorption in the intestines; there is a negative feedback loop in the cellular uptake where dropping intracellular iron levels upregulate the expression of lactoferrin receptors and consequently, boost the iron intake.[47]

## Sources of Lactoferrin

The lactoferrin molecule has been fairly well-conserved through evolution.[29] Figure 5A shows the percent identity matrix of the protein in frequently-encountered mammals.[48] Figure 5B supports these data; the tertiary structure of human, bovine, and camelid lactoferrin show broad similarities.[49] Human and bovine




**Figs 3A to D:** (A, B; continued in C, D on page 5). A to D: Lactoferrin is a well-characterized protein

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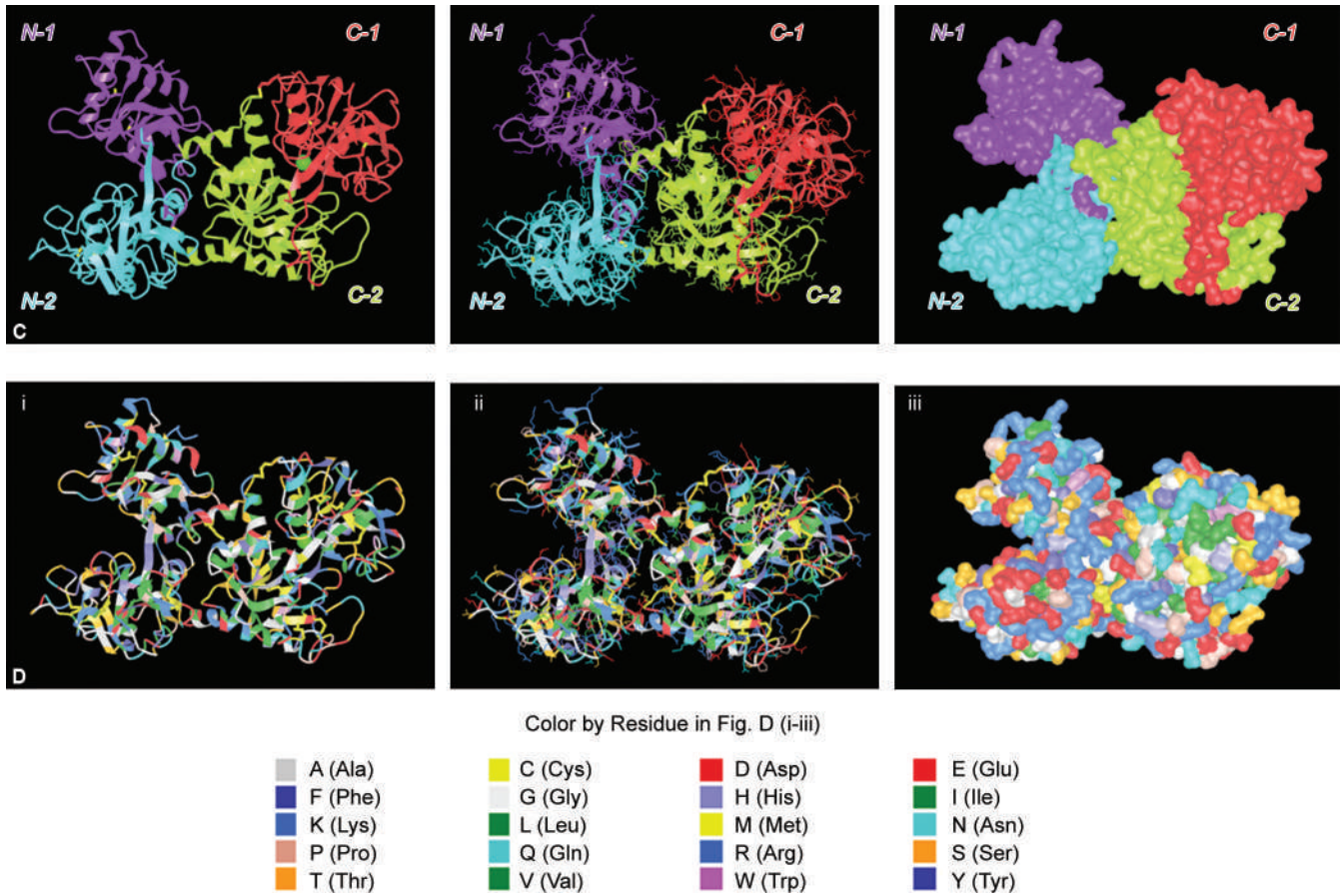
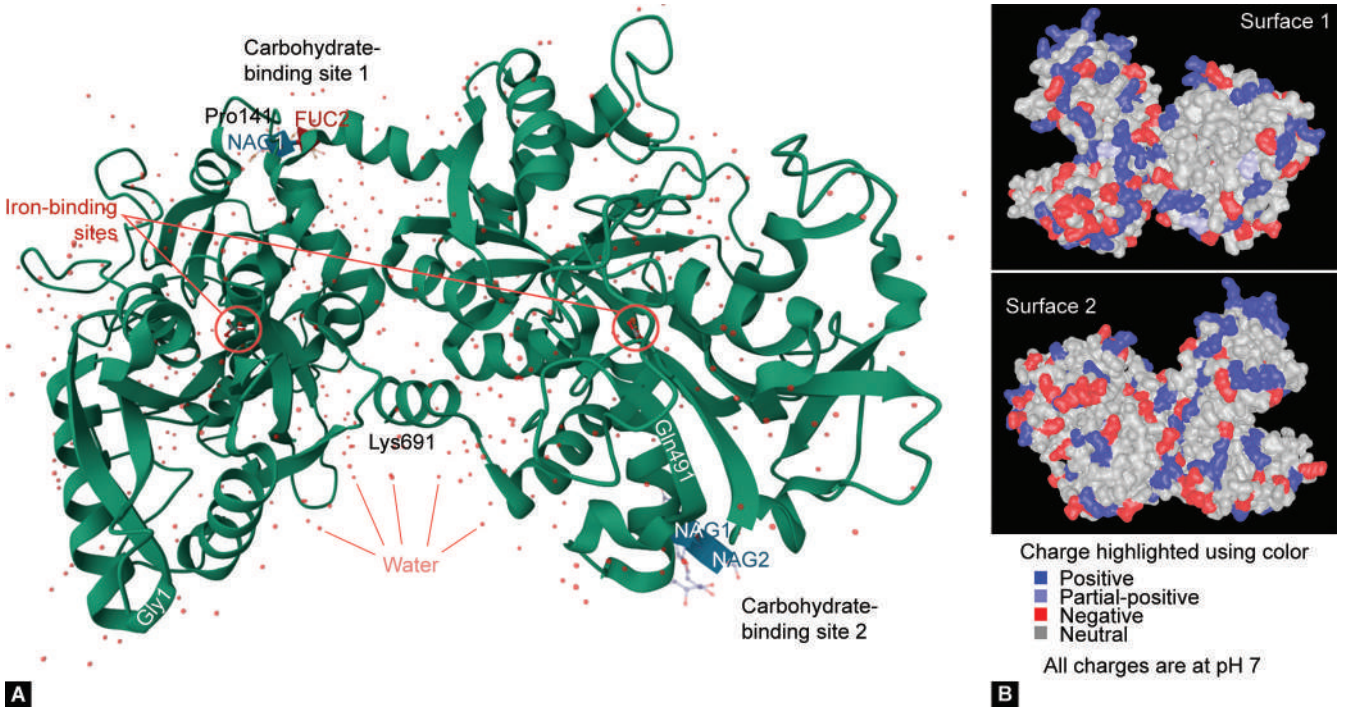
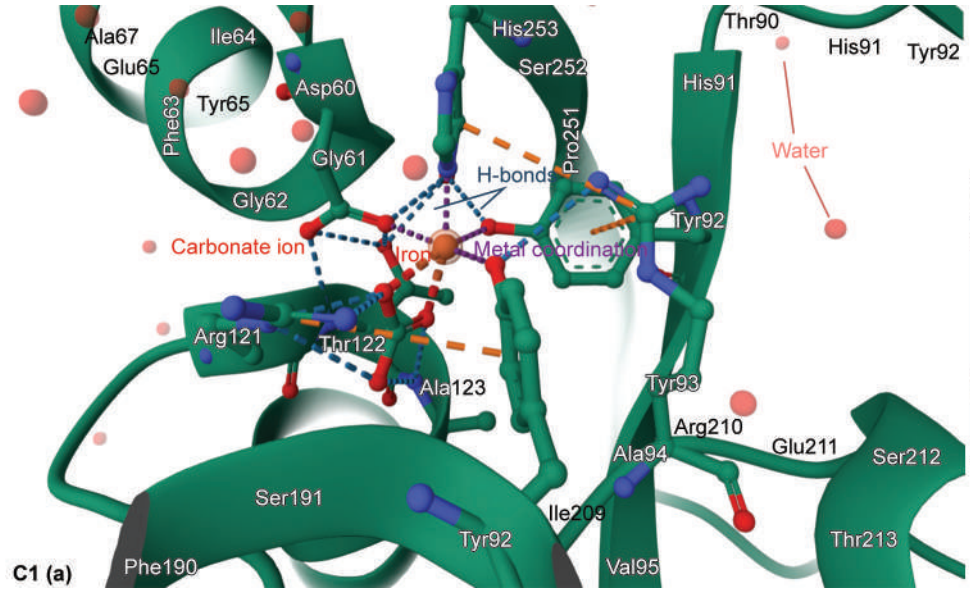
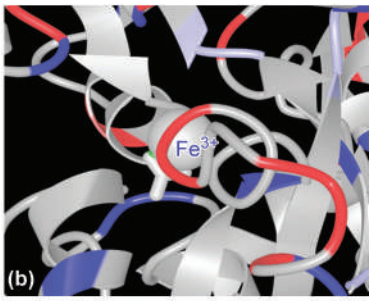


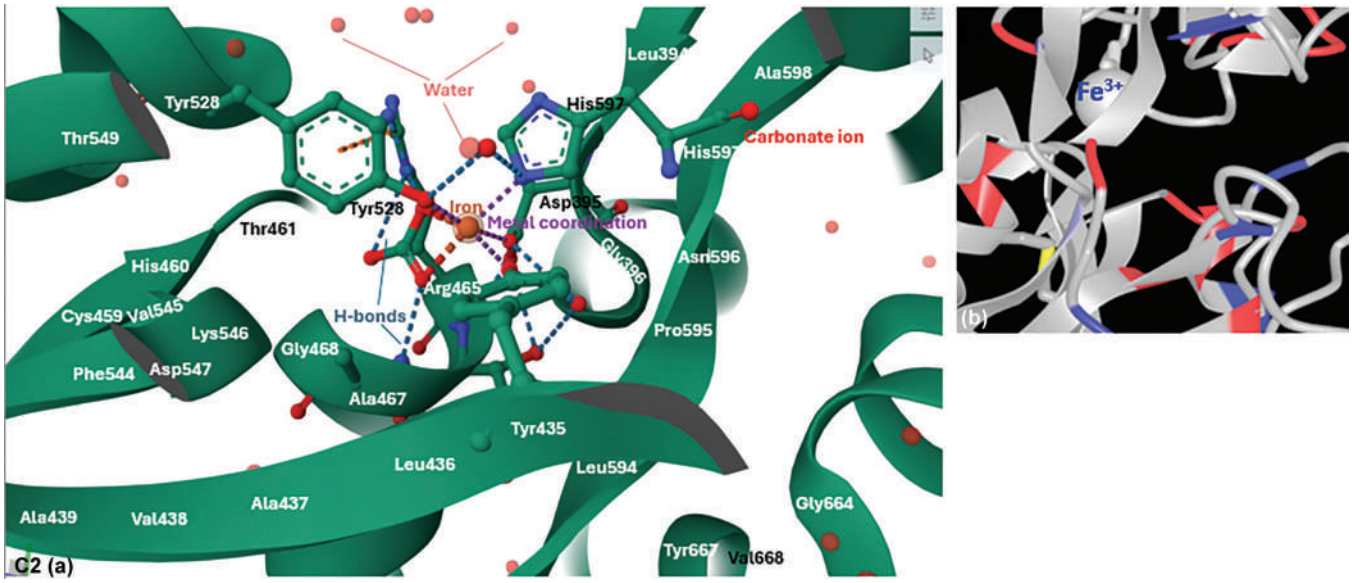

**Figs 3A to D:** (C, D): Lactoferrin is a well-characterized protein (continued from page 4)... protein. In all illustrations (A–D), there are three sequential figures in all rows: (i) primary ribbon structures showing the three-dimensional (3D) schematic representations of protein structure. These show the overall folds and organization of the protein backbone; alpha-helices are shown as coiled ribbons and beta-sheets as arrows. This is a simplified depiction of the 3D structure of proteins without the need to visualize every single atom; (ii) structure with side chains: the central alpha carbon of all amino acids carries unique aliphatic/aromatic side chains, the "R" groups, along with constituent amino, carboxyl, and hydrogen groups. These are not directly involved in the formation of peptide bonds between amino acid, but the size, shape, charge, and reactivity of R groups determines the polarity (hydrophilic/hydrophobic), acidity, basicity, and reactivity. Nonpolar amino acids carry hydrophobic R groups that are primarily made of carbon and hydrogen. R groups in polar amino acids contain polar hydroxyls, thiols, or amides. Charged amino acids contain positively/negatively charged R groups; (iii) molecular surface. These illustrations can be moved and manipulated within interactive 3D viewing programs such as iCn3D (details below). (A) This figure shows the B-factor (Debye–Waller factor), an indicator of the certainty for each atom in the protein; the predominance of blue-white residues indicates a high level of confidence in the position of most atoms. (i–iii) Primary ribbon structures, structures with side chains, and the molecular surface are shown from left to right; (B). This illustration shows the *N*-terminal (yellow) and the *C*-terminal domain (red). (i–iii) Primary ribbon structures, structures with side chains, and the molecular surface are shown from left to right; (C) Domain A, located at the *N*-terminus, has two subdomains (*N*-1 and *N*-2). Similarly, domain B near the *C*-terminus is comprised of *C*-1 and *C*-2. (D) The amino acid composition of the entire lactoferrin molecule. (i–iii) Primary ribbon structures, structures with side chains, and the molecular surface are shown from left to right. The base structure was adopted from the website https://www.ncbi.nlm.nih.gov/Structure/icn3d/full.html?showanno=1&mmdbid=56717. We modified the base structure derived from the iCn3D (short for "I see in 3D") format. This is a web-based interactive tool for analysis of 3D macromolecular structures; was developed using the Web Graphics Library, a JavaScript Application Programming Interface to render 3D graphics in web browsers without requiring plugins. A JavaScript control and a shader code has been executed on the graphics processing unit for high-performance interactive graphics. These illustrations were prepared using data/tools provided on the web portals of the RCSB and NCBI PDBs, MMDB, GenBank, RefSeq, TPA, UniProtKB/Swiss-Prot database, PIR, PRF, and Microsoft PowerPoint, Microsoft Illustrator, and/or Adobe Photoshop


Carbohydrate-binding site 1
Pro141
FUC2
NAG1
Iron-binding sites
Lys691
Gln491
NAG1
NAG2
Water
Gly1
Carbohydrate-binding site 2
A
Surface 1
Surface 2
Charge highlighted using color
Positive
Partial-positive
Negative
Neutral
All charges are at pH 7
B


Ala67
Ile64
Glu65
Asp60
Phe63
Tyr65
Gly61
Gly62
His253
Ser252
Pro251
H-bonds
Carbonate ion
Iron
Metal coordination
Thr90
His91
Tyr92
Water
Arg121
Thr122
Ala123
Tyr93
Arg210
Ala94
Glu211
Ser212
Ser191
Ile209
Tyr92
Thr213
Phe190
Val95
C1 (a)


Fe3+
(b)

*(Contd...)*




**Figs 4A to C:** Lactoferrin contains two iron-binding sites, one in each lobe. (A) Tertiary structure shows the position of the two ferric ions (red circles); (B) The two surfaces show a net positive charge, as reflected in the dominant blue color. NAG1 = *N*-acetyl-beta-d-glucosaminidase; NAG2 = *N*-acetylglucosamine-6-phosphate deacetylase; FUC2 = alpha-l-fucosyltransferase 2. (C1) Predicted ferric-binding site in lobe 1 shown in (a) detailed structural and (b) simplified colored schematic to emphasize the charged niche. The positively-charged ferric ions ($Fe^{3+}$) are enclosed in negatively-charged niches enriched in Asp, Glu, Ala, Arg, and Gly (red) inside the two domains. The presence of carbonate ($CO_3^{2-}$) at these binding sites further stabilizes the iron–lactoferrin complex. (C2) Similar depiction of lobe 2 in (a) structural and (b) colored schematics. Standard amino acid abbreviated names are used. H-bonds = hydrogen bonds. The base structure was adopted from the website https://www.ncbi.nlm.nih.gov/Structure/icn3d/full.html?showanno=1&mmdbid=56717. These illustrations were prepared using data/tools provided on the web portals of RCSB and NCBI PDBs, GenBank, RefSeq, TPA, UniProtKB/Swiss-Prot database, PIR, PRF, and Microsoft PowerPoint, Microsoft Illustrator, and/or Adobe Photoshop

lactoferrin have strong antibacterial effects, particularly at the *N*-terminus.[50] These disrupt gram-negative bacteria by binding lipopolysaccharides and altering their cellular permeability. The tertiary structure of lactoferrin is an important determination of its antibacterial properties; camelid and bovine lactoferrin resemble each other at key functional residues and show comparable bacteriostatic activity.[51] The lactoferrin molecules seem to have evolved from a common molecular ancestor (Fig. 5C).[52,53]

Despite the structural similarities noted above, the concentrations of lactoferrin in colostrum and mature milk show considerable differences in expression across species.[54–56] Human colostrum show lactoferrin levels as high as 5.3 ± 1.9 mg/mL, gradually declining to approximately 1 mg/mL after the first month of lactation.[27] Donkey milk contains low concentrations of only 0.07 mg/mL.[57] Bovine milk may show 1.5–485.3 µg/mL, compared with the higher 1–5 mg/mL in colostrum.[58,59] Camel colostrum and milk contain 1.75–3.33 times higher lactoferrin content than in cow, buffalo, goat, sheep, and donkey milk.[57] This enhanced activity of lactoferrin could be due to lower citrate levels in camel milk, which lowers the competition for iron binding.[57,60,61] There is some variability among the different breeds of camels.[62] This difference in the camel and bovine lactoferrin could be due to variability in the physiochemical properties and the concentration of *N*-linked glycans.[63]

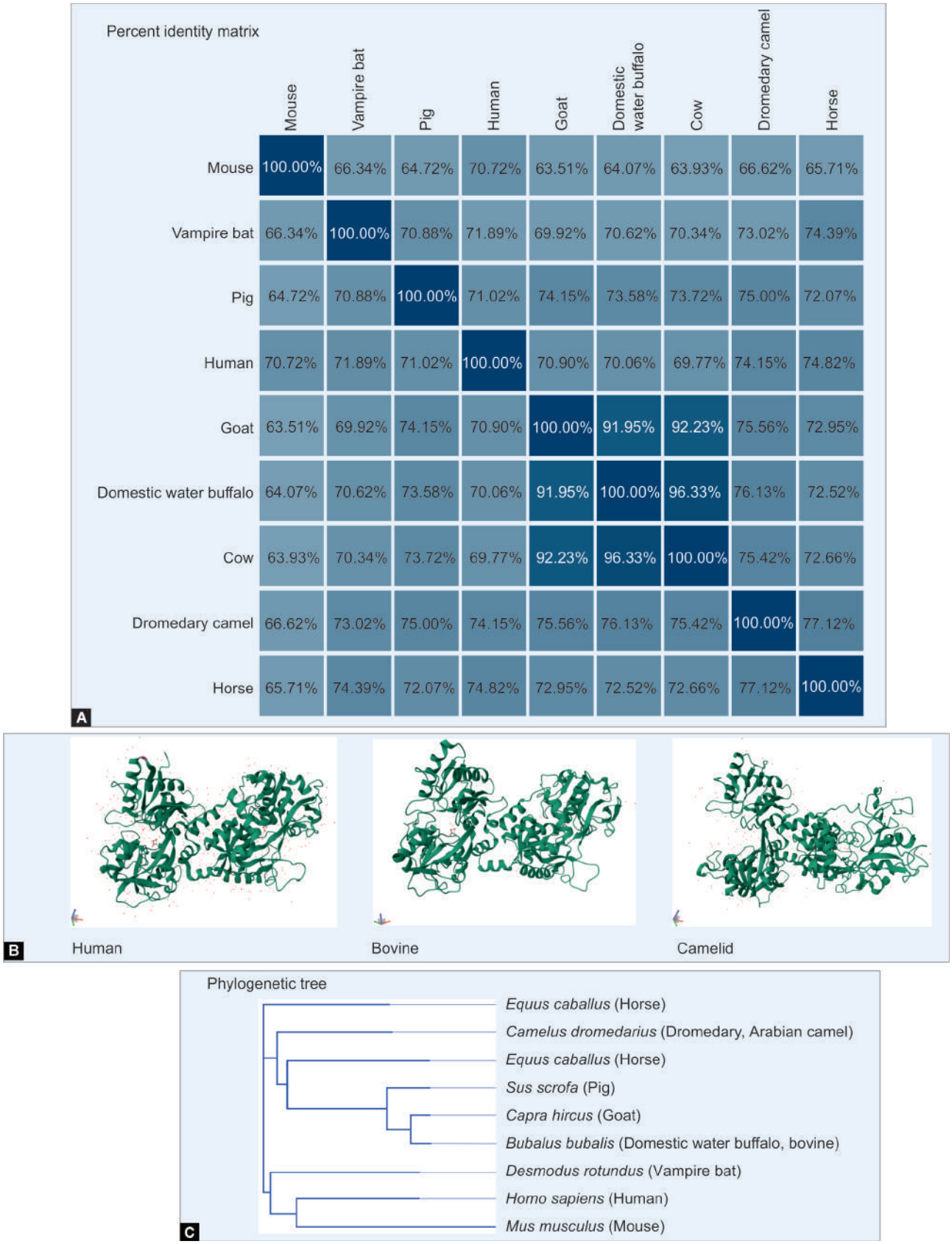
There is some species-related variability in the tertiary structure of iron-free apo-lactoferrin: (a) humans show an open *N*- but a closed *C*-lobe; (b) both lobes appear relatively closed in the equine apo-lactoferrin; and (c) both lobes remain open in the camelid protein as there are no interlobe interactions, likely due to a Pro418 substitution.[60,64,65] The *N*-lobe of camel apo-lactoferrin closely resembles that in humans.[64]

## Physicochemical and Biological Properties of Lactoferrin

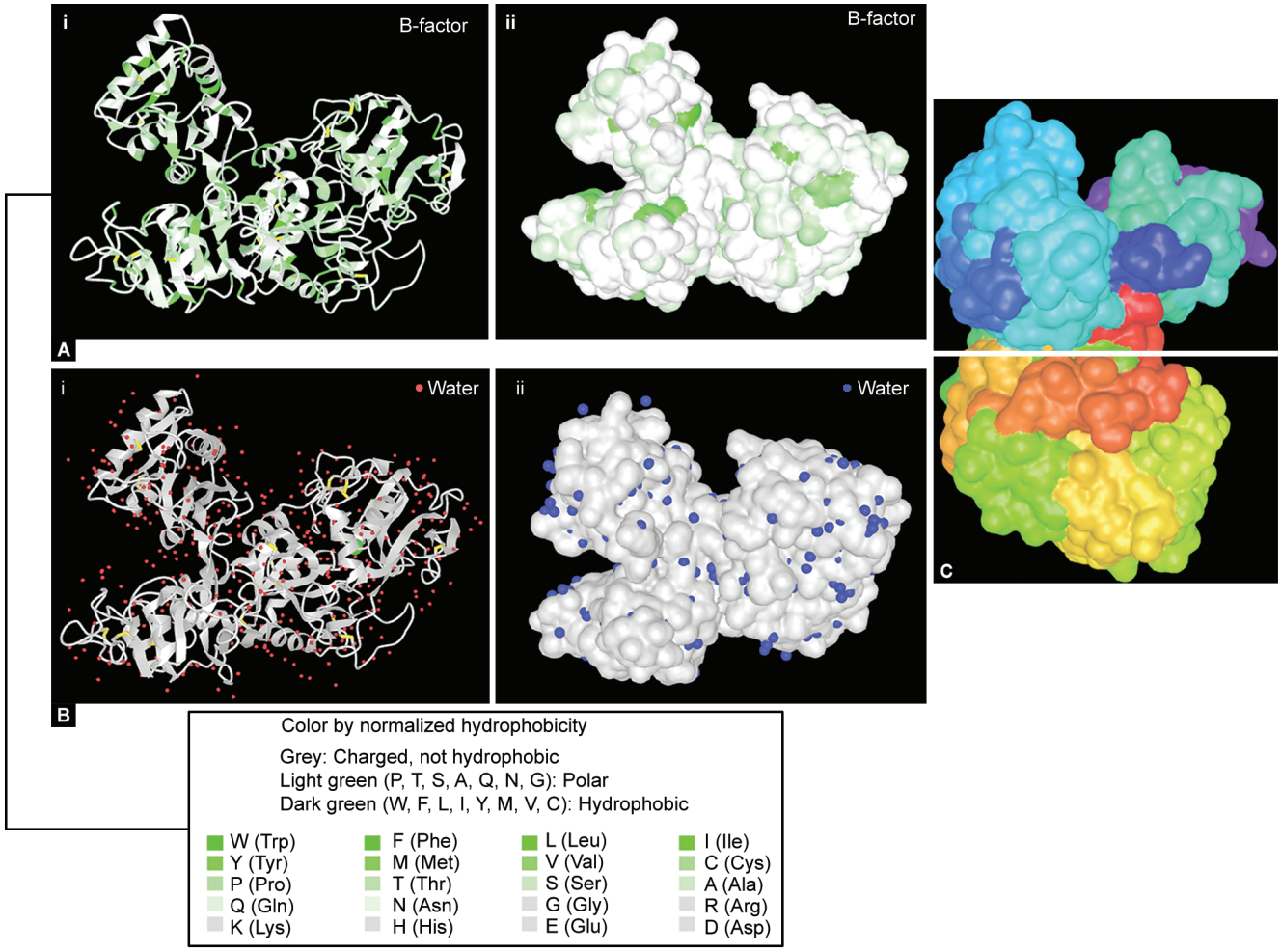
Lactoferrin is a hydrophilic protein.[66] In the primary ribbon structure, both hydrophilic and hydrophobic amino acid residues are evenly distributed.[9] However, in a space-filling model, it is apparent that the protein folding makes the surface more hydrophilic; the hydrophobic residues get buried away from the surface, inside toward the core of the protein (Fig. 6A).[67] The water solubility can been seen as evenly distributed in the folded protein and on the surface of the molecule (Fig. 6B).

The protein is seen in membrane-bound and free-floating forms. In the membrane-bound isoform, the exposed *N*-terminal domain is folded to be more water soluble than the intracellular portion.[68] The exposed portion also shows more antibacterial activity (Fig. 6C).[16]

As mentioned above, the lactoferrin protein carries a net positive charge, but surprisingly, it still carries ferrous and ferric cations (Fig. 4).[9] These ions are enclosed in negatively charged niches in the core of the two lobes. In terms of other physical proteins, lactoferrin is known to remain stable when heated to 65°C for 30 minutes, but there is some loss of activity at 75°C. Camelid and bovine milk lactoferrin show higher heat resistance.[69] This stability under heat and low pH makes lactoferrin a promising candidate for food preservation.[70]




**Figs 5A to C:** Lactoferrin protein has been conserved through evolution. (A) The percent identity matrix of the lactoferrin protein in some of the better-studied species; (B) Tertiary structures of human, bovine, and camelid show similarities; (C) Phylogenetic tree shows that the gene seems to have evolved from a common ancestor over time




**Figs 6A to C:** Lactoferrin a hydrophilic protein. (A) Predicted solvent-accessible surface area (SASA) is shown in a scale ranging from a deep green color at its low end to high white: (i) primary ribbon structure of the protein shows the green and white color residues as shown in the box below the figure as evenly distributed; (ii) solvent-accessible space-filling model predicts these surfaces as much whiter and hence, more hydrophilic, suggesting that many of the protein's hydrophobic green residues are buried away from the surface inside the core of the protein. (B) Schematic figures show the interaction of lactoferrin protein with water molecules: (i) large number of water molecules (small orange dots) seen near all parts of the protein underscores its water solubility; (ii) the interaction of the water molecules (large blue dots) on the protein surface. We have used the SASA method to produce this illustration. Relative solvent accessible area (RSA)/SASA are standard measures to describe the degree of residue exposure in the protein surface. There are many methods for estimation of RSA/SASA that focus on the Cα atom-distance matrix and use deep learning methods; some of the existing RSA estimators are based on coordination numbers, half-sphere exposure, and SphereCon, one of the recognized RSA-estimation algorithms; (C) Lactoferrin can be found in both free-floating and membrane-bound isoforms. The membrane-bound isoform is well-documented in human milk. In this isoform, the exposed *N*-terminus is more hydrophilic (shades of blue; membrane hypothetically depicted using the white outlined bar) shows antimicrobial activity as one, it binds and damages the bacterial cell membranes; and two, peptides derived from this *N*-terminus, known as lactoferricins, also exhibit antimicrobial properties. The base structure was adopted from the website https://www.ncbi.nlm.nih.gov/Structure/icn3d/full.html?showanno=1&mmdbid=56717. These illustrations were prepared using data/tools provided on the web portals of RCSB and NCBI PDBs, GenBank, RefSeq, TPA, UniProtKB/Swiss-Prot database, PIR, PRF, and Microsoft PowerPoint, Microsoft Illustrator, and/or Adobe Photoshop. Details of SphereCon can be seen at Bioinformatics 2020;36(11):3372–3378. DOI: 10.1093/bioinformatics/btaa159

Lactoferrin exhibits broad-spectrum antibacterial activity against bacteria, fungi, viruses, and parasites through three major mechanisms:[3,42]

- Bacteriostatic action: Chelates free iron; nutritional deprivation inhibits bacterial growth and proliferation.
- Membrane disruption: The cationic *N*-terminal increases membrane permeability via disruption of the cell membrane across the lipopolysaccharide layer.
- Antimicrobial peptides: Hydrolysis produces peptides with strong antimicrobial effects.

Early studies connected the antibacterial properties of lactoferrin with the iron concentration.[16] Later, apo-lactoferrin binding to bacterial surfaces and consequent blockage of nutrient uptake was also considered important.[1] Lactoferrin also shows antiviral properties against human papillomavirus, herpes simplex virus 1 and 2, cytomegalovirus, human immunodeficiency virus,

hepatitis B and C viruses, respiratory syncytial virus, Hantan virus, rotavirus, poliovirus, adenovirus, and the SARS-CoV-2.[35,71] Some of the antiviral mechanisms include its binding to heparan sulfate proteoglycans on host cells, reducing viral attachment and entry.[35] Also, lactoferrin was shown as a direct inhibitor of viral adsorption to target cells, to bind viral proteins, and to disrupt intracellular viral transport and genome delivery.[42] The content of iron-saturated lactoferrins is important; apo-lactoferrin exhibits stronger antiviral potency than holo-lactoferrin.[35]

The antiviral and antibacterial activities of lactoferrins vary by their source of origin.[16] Camelid lactoferrin may inhibit hepatitis C virus more effectively than the human, bovine, and sheep isoforms.[72] Bovine lactoferrin may be more potent in inhibiting toll-like receptor 4-mediated activation of p38 mitogen-activated protein kinase.[73] Liposomal bovine lactoferrin can suppress tumor necrosis factor production. The apo- form may mitigate LPS-induced inflammatory bowel injury more strongly that the holo-lactoferrin.[74] One mechanism might be related to the function of the peroxisome proliferator-activated receptors-γ/6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3/nuclear factor-kappa B pathway.[74] Higher free iron and hyperferritinemia, as markers of iron dysregulation, could alter the free radical injury-mediated inflammatory response.[75] Bovine lactoferrin might be more potent in regulating these pathways.[76]

## Conclusion

Lactoferrin is a pleiotropic, highly-conserved protein that subserves important roles in innate immunity and nutrition. The greatest and the most cost-effective source of lactoferrin is milk from different species. Further research is required to understand the structural-functional relationship; there is potential for the protein or its parts to be used as nutraceutical.[77]

## Orcid

*Akhil Maheshwari* https://orcid.org/0000-0003-3613-4054

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CASE REPORT

# Cryptophthalmos

Girish Arora[1], Parishi Mehta[2], Kanav Gupta[3]

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## Abstract

Cryptophthalmos is a rare congenital disorder characterized by incomplete/total separation of eyelids and hence, a continuous layer of skin covering the globe. It can present as an isolated defect or as part of Fraser syndrome. Here, we describe a premature infant with bilateral cryptophthalmos. The lids were completely fused on the right; the left side showed partial fusion, but there were no responses to light. The infant was born in a nonconsanguineous marriage with no family history of the condition and no known exposure to drugs, radiation, and/or toxins. Sonographic examination showed an altered shape, aphakia, and cryptopthalmos in the right globe. The left side showed a microblepharon with an otherwise preserved anatomy. Echocardiography was suggestive of a mild peripheral pulmonary stenosis, and a cortical cyst was seen in both kidneys. Genetic studies showed known compound heterozygous variants with autosomal recessive inheritance, p.Arg2167Trp, in the gene *Fraser syndrome 1-related extracellular matrix protein 2* (*FREM2*). In this article, we have summarized the clinical presentation, diagnostic approach, and management strategies that are available for these infants.

**Keywords:** Abortive cryptophthalmos, Ambiguous genitalia, Aphakia, Case report, Conjunctival fornix, Fraser syndrome, *Fraser syndrome 1-related extracellular matrix protein 2*, Microblepharon, Microphthalmos, Rudimentary eyelids, Syndactyly.

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## Key Points

- Cryptophthalmos is a rare congenital disorder with anomalous eyelid development.
- The condition has been described in three subtypes: (a) complete, the most extreme presentation, with total occlusion of the eye sockets and fusion of the forehead and cheek skin with the cornea and conjunctival sac; (b) incomplete, with rudimentary eyelids and conjunctival sacs that may be smaller on the lateral ends; and (c) abortive cryptophthalmos, in which the upper lid may be absent and the forehead skin could cover most of the cornea.
- Cryptophthalmos can present as an isolated abnormality or as part of Fraser syndrome (FS), a multi-system condition inherited in an autosomal recessive pattern. Fraser syndrome may manifest with cryptopthalmos, syndactyly, genitourinary malformations, and other anomalies.
- Current management of cryptophthalmos largely remains supportive, with efforts to minimize pain. In patients with partial cryptophthalmos, efforts to prevent exposure keratopathy can help for cosmetic reasons. Surgical intervention(s) for eyelid reconstruction can be useful.

## Introduction

Cryptophthalmos is a rare congenital disorder with anomalous eyelid development.[1] The condition has been described in three subtypes with varying degrees of eyelid fusion: (a) complete, the most extreme presentation, with total occlusion of the eye sockets and fusion of the forehead and cheek skin with the cornea and conjunctival sac. There may be no eyebrows, lashes, or gland structures. Microphthalmos is frequent; (b) incomplete, with rudimentary eyelids and conjunctival sacs that may be smaller on the lateral ends. The under-developed eyelids may be fused to the abnormally developed small globe. The palpebral fissure may be only one-third of the normal length; and (c) abortive cryptophthalmos, in which the upper lid may be absent and the forehead skin could cover the upper 75% of the cornea.[2–4] The upper lid may not show a punctum or a conjunctival fornix. The covered cornea may be clear or opaque with keratinization. The globe could vary in size from small to near normal.[5]

The abnormality was first described by Zehender and Manz in 1872.[6] It occurs due to failure of eyelid development during embryogenesis. The complete form is more prevalent and associated with more severe anomalies of the globe.[7] In both complete and incomplete cryptophthalmos, an ocular cyst can be present. Cryptophthalmos can present as an isolated abnormality or as part of FS, a multi-system condition inherited in an autosomal recessive pattern. Fraser syndrome may manifest with cryptopthalmos, syndactyly in fingers and/or toes, ambiguous genitalia, kidney abnormalities, urinary tract malformations, narrowing of laryngeal and upper airways, vertebral defects or limb malformations, developmental delay, and other malformations of the ears, nose, and anal opening.[6,8] Fraser syndrome is generally an autosomal recessive disorder with mutations in the *Fraser Extracellular Matrix Complex Subunit 1 (FRAS1), Glutamate Receptor-interacting Protein 1 (GRIP1),* and/or the *FRAS1-related Extracellular Matrix 2 (FREM2)* genes.[9–11]

[1–3]Department of Pediatrics, Rainbow Hospital, Panipat, Haryana, India

**Corresponding Author:** Girish Arora, Department of Pediatrics, Rainbow Hospital, Panipat, Haryana, India, Phone: +91 996203823, e-mail: drgirisharora@gmail.com

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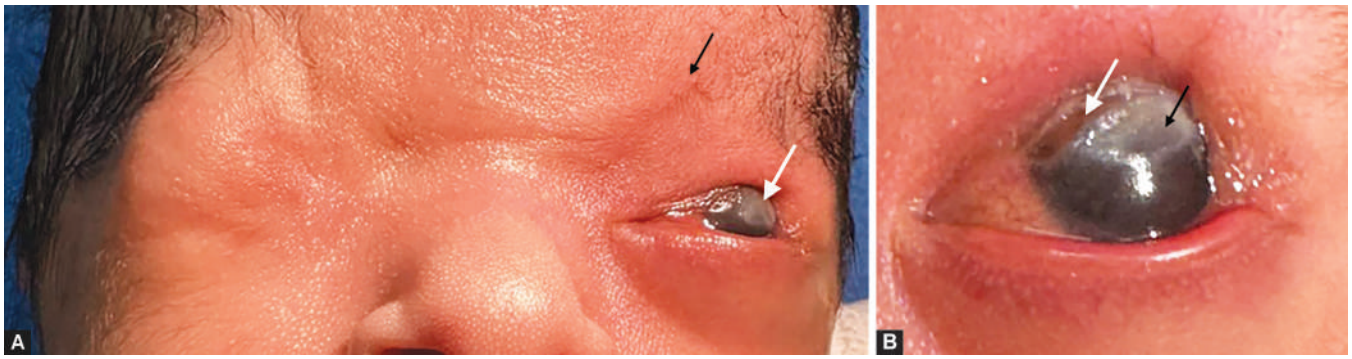


**Figs 1A and B:** Frontal view of a neonate showed (A) a complete cryptopthalmos on the right orbit. A skin envelope completely covered this region without an eyebrow, palpebral aperture, eyelids, or eyelashes. On the left side, there was a partial cryptophthalmos with a better-preserved globe anatomy. The upper eyelid was still less developed and seemed fused to the globe. There were a few strands of hair that could have represented a rudimentary eyebrow (black arrow). The palpebral fissure looked smaller in length than normal. There was a large corneal opacity (white arrow) and the eye tested as completely unresponsive to light; (B) A closer view of the left eye showed an area of exposure keratopathy (white arrow) near the corneal opacity (black arrow). The partial fusion of the eyelids on the outer side was also more evident

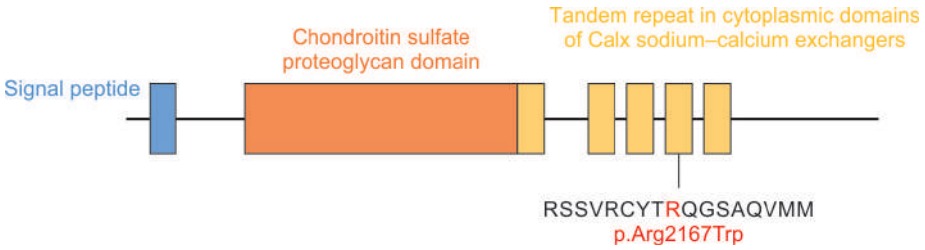


**Fig. 2:** Homozygous mutation p.Arg2167Trp in the *FREM2* gene was identified in our patient. This mutation has been identified with cryptophthalmos. Chondroitin sulfate proteoglycan domains are glycosaminoglycan chains that decorate protein cores. These domains play crucial roles in cell adhesion, growth, receptor binding, and cell migration
Calx is a sodium–calcium exchanger membrane protein that uses the energy of sodium gradients to transport calcium ions across the cell membrane.
R = Arginine; S = Serine; V = Valine; C = Cysteine; Y = Tyrosine; Q = Glutamine; G = Glycine; M = Methionine

This report describes a case of congenital cryptophthalmos, highlighting the clinical presentation, diagnostic approach, and possible management strategies available at the time.

## Case Description

A 4-hour-old premature infant assessed to be of 34 weeks' gestation was admitted to our neonatal intensive care unit. There was a complete cryptopthalmos on the right and a partial cryptopthalmos in the left eye (Fig. 1). As mentioned, the right eye was completely covered by a skin envelope with no eyebrow or any signs of a palpebral aperture, eyelids, or eyelashes. The left eyelids were fused incompletely, but the eye was completely unresponsive to light.

The infant was born to a 24-year-old gravida 4 para 3 mother from a non-consanguineous marriage. There was no significant family history of comparable inherited conditions, infections, or exposure to radiation or toxins. There were no other defects seen in FS.

An ultrasound of the orbits showed the right globe as abnormally shaped with aphakia and cryptopthalmos. The left side showed a normal globe anatomy, but the lids were short with a mild microblepharon. A two-dimensional echocardiography showed a mild peripheral pulmonary stenosis, a known association with FS.[12] Sonographic examination of the abdomen showed small renal cortical cysts on both sides, which have also been previously noted in FS.[13]

Genetic studies showed an autosomal recessive inherited compound mutation p.Arg2167Trp in both *FREM2* genes, which has been previously associated with this condition (Fig. 2).[14]

## Discussion

Cryptophthalmos represents a failure of embryologic eyelid separation during the weeks 7–10 of gestation.[15] It is often associated with FS with associated syndactyly, genitourinary malformations, and craniofacial anomalies.[16] Surgical intervention can be challenging, and visual prognosis depends on the presence of a functional globe and optic nerve development. Early diagnosis is crucial for planning appropriate reconstructive procedures and ensuring the most optimal functional/cosmetic outcomes.[17]

Nearly 77% cases of cryptophthalmos have been seen with manifestations of FS, and hence, the *FRAS1*, *FREM2*, and *GRIP 1* genes should be sequenced.[18] In the *FREM2* gene, compound heterozygous variants such as the c.4537G>A (p.D1513N) and c.7292C>T (p.T2431M) have been defined.[19] These proteins are known to play a critical role in epithelial-mesenchymal interaction, important for eye development during the embryonic period.[20] Other metabolic situations may be seen; in mice with *FREM2* mutations, many genes involved in amino acid metabolism and energy metabolism can be differentially expressed. In one murine study, transcriptomic analysis showed that 821 (39.89%) up-regulated and 320 (32.99%) down-regulated genes were seen.[21] A total of 92 significantly

different metabolites were identified, including creatine, guanosine 5′-monophosphate, cytosine, cytidine 5′-monophosphate, adenine, and L-serine. Interestingly, major shifts related to ATP-binding cassette transporters (ABC transporters) and the biosynthesis of amino acids in the composition of the embryonic metabolome were observed.[22–24]

Cryptophthalmos can also be associated with other conditions such as the Manitoba-oculo-tricho-anal (MOTA) syndrome, the ablepharon-macrostomia syndrome, and genetic variants in the *CELSR2* gene.[18,25–27] Environmental factors such as maternal infections, vitamin A deficiency, and exposure to toxins may contribute in the pathogenesis of FS.[28]

Our management largely remains supportive with efforts to minimize pain. In patients with partial cryptophthalmos, efforts to prevent exposure keratopathy can help for cosmetic reasons.[29] Surgical intervention(s) for eyelid reconstruction can be useful.[30] The families need support with a multidisciplinary approach with experts from ophthalmology, genetics, plastic surgery, and neonatology.[5] Follow-up clinics may need to focus on airway, renal, and/or limb defects.[30]

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CASE REPORT

# Non-surgical Expectant Management led to a Complete, Timely Recovery from Traumatic Subdural Hemorrhage and Related Status Epilepticus in a Neonate: A Case Report

Sruthi Nair[1], Prashanth R Raghavendra[2], Medha Goyal[3], Anitha Haribalakrishna[4]

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## Abstract

We report our recent experience with a 10-day-old neonate who was admitted with continuous seizures following an accidental fall from a hammock. Computerized tomography of the head revealed an extradural hemorrhage (EDH) along the left parietal region with a mass effect causing a midline shift of 3 mm. Considering the high severity of illness, we counseled the family very cautiously and managed the neonate conservatively in the intensive care unit without surgical intervention. Interestingly, the infant recovered from the status epilepticus as the hemorrhages resolved over the next 48–72 hours. The infant was discharged home in a fully functional status with normal feeding and no detectable abnormalities in sensorium or neuromotor status. This case suggests that all subdural hematomas, even if associated with midline shift, might not need surgical intervention. We may need to re-evaluate our currently accepted indications for surgery in these patients.

**Keywords:** Baby, Brain injury, Case report, Infant, Neonate, Newborn, Status epilepticus, Subdural hemorrhage, Traumatic brain injury.

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## Case Description

A 10-day-old male term infant was recently admitted to our neonatal intensive care unit (NICU) for management of status epilepticus.[1] The seizures began after an accidental fall from a two-feet high hammock at home (Supplementary Video 1). Physical examination revealed a tender 8 × 12 cm soft and fluctuant swelling over the left parieto-occipital region. The anterior fontanelle was bulging, and the sutures were widely separated. The left ear was swollen, anteriorly displaced, and bruised, although the tympanic membrane was intact. There were some minor ecchymoses over the left eyelid, and both pupils were equally reactive to light. However, the posterior pole of the left retina showed changes of Berlin's edema that have been associated with blunt trauma (*commotio retinae*).[2,3] Neurological assessment showed generalized hypotonia, but there was spontaneous eye opening, intact limb movements, and a consolable cry; the Pediatric Glasgow Coma Scale (PGCS) measured at 14.[4]

Computed tomography (CT) scan of the head showed a fracture of the left parietal bone with a subjacent extradural hemorrhage (EDH).[5] This side also showed coronal sutural diastasis, effacement of adjacent sulci, and a hemorrhage in the underlying parietal lobe and thalamus with intraventricular extension (Fig. 1).[6] The EDH was estimated to measure approximately 10–15 cm and cause a midline shift of 3 mm. These data were derived using DICOM (an acronym for "Digital Imaging and Communications in Medicine," a system used for handling information in medical imaging) viewer. Hemorrhage volumes were estimated using the ABC/2 index, which is computed as one-half of the product of the diameters of hemorrhage in the longest dimension (A) with the one perpendicular to it (B) and the number of CT slices with hemorrhage multiplied by the slice thickness (C).[7] A subgaleal hematoma was seen along the left pre-septal and right parietal occipital region. No fractures were seen elsewhere in the body.

We consulted neurosurgical services. Evaluation of the clinical condition of the patient showed a high severity of cranial injury but relatively preserved PGCS scores. Hence, the potential benefits of intervention had to be evaluated along with the risk of iatrogenic complications. We counseled the family very cautiously and decided in favor of conservative management without surgical intervention. We had planned to administer anti-epileptic medications but eventually withheld these drugs in view of the observed gradual improvement, at least no worsening, in the electroencephalograms.[8] A repeat CT scan in 24 hours showed some resolution of the EDH over the left parietal convexity and in its intraventricular extension from subacute to chronic stage. The seizures became less frequent and then resolved during this period with improvement in muscle tone. The neonate began to feed in 48–72 hours and was discharged at the age of 3 weeks after birth with a normal neurological assessment.

[1,2,4]Department of Neonatology, Seth G.S. Medical College and King Edward Memorial Hospital, Mumbai, Maharashtra, India

[3]Department of Neonatology, Seth G.S. Medical College and King Edward Memorial Hospital, Mumbai, Maharashtra, India; Division of Neonatology, McMaster Children's Hospital, Hamilton, Ontario, Canada

**Corresponding Author:** Prashanth R Raghavendra, Department of Neonatology, Seth G.S. Medical College and King Edward Memorial Hospital, Mumbai, Maharashtra, India, Phone: +91 9846940526, e-mail: prash2635@gmail.com

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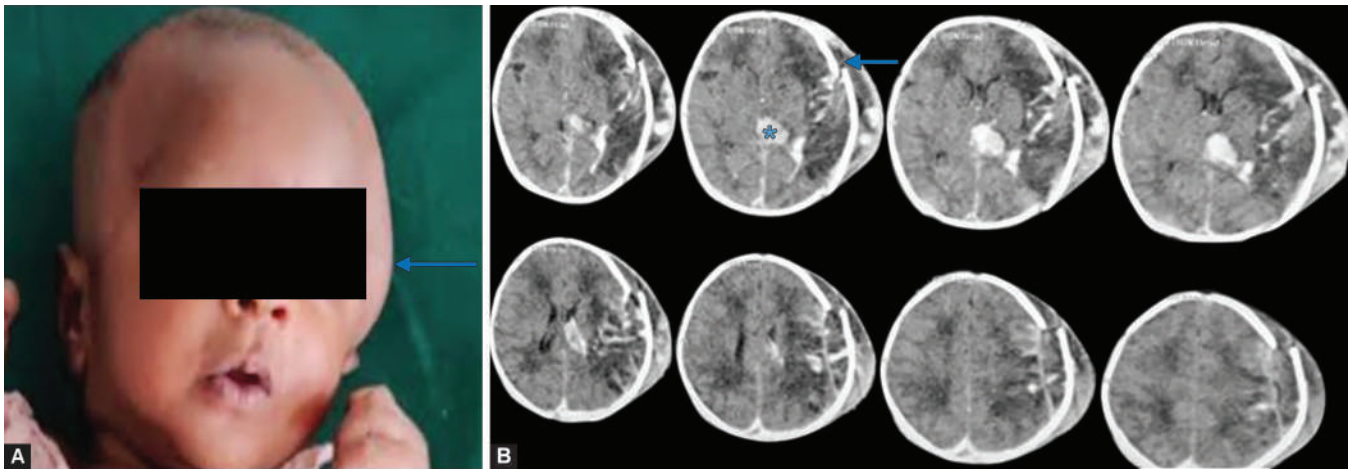
**Patient consent statement:** The author(s) have obtained written informed consent from the patient's parents/legal guardians for publication of the case report details and related images.



**Figs 1A and B:** (A) Infant with a swelling over the left parieto-occipital region due to an acute epidural hemorrhage on the left parietal region (arrow) with left coronal suture diastasis; (B) A thalamic hemorrhage is also seen (star, *)

## Discussion

Traumatic acute EDH constitutes 2–3% of all pediatric head injuries, although it might be seen less frequently in infants below 1 year of age.[9] A pliable, soft skull with open sutures and fontanelle may protect the neonatal brain with its unique mechanical properties, such as better absorption of mechanical forces.[10] However, procedures such as craniotomy may be indicated when signs of impending herniation are seen, such as hypertension with bradycardia or tachycardia, anisocoria, abnormal breathing pattern, hemiplegia, decerebrate/decorticate posturing, or PGCS < 8.[11,12]

In adults, in addition to the clinical condition, decisions for surgical evacuation are often based on the presence of a hematoma volume >30 mL with a thickness of >15 mm (as in our case) and a midline shift of >5 mm.[13] In neonates, due to their smaller cranial size, smaller hematomas that measure 5–10 mL in volume and 10 mm in thickness may be considered significant.[13–16] Abnormal pupillary responses at admission, detection of hypothermia, and the mechanism of injury, such as a fall from a height, have been associated with poor survival and outcomes.[13] More information is needed to refine the indications for conservative management vs surgical interventions in infants such as our index case.

## Supplementary Material

Supplementary video is available online on the website of www.jnb.org

## Orcid

*Prashanth R Raghavendra* https://orcid.org/0000-0002-1263-8197

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CASE REPORT

# Some Neonates with Congenital Adrenal Hyperplasia may Need Disproportionately High Doses of Mineralocorticoids

Tatsiana Sergeevna Pratasevich[1], Valentina Alexandrovna Zhemoytiak[1], Natalya Ivanovna Denisik[2], Hashini Promodhya Thenabadu[3], Ayesh Riqaq Mohamed Hajzab[3], Ranasingha Arachchige Shanika Lakmini[3], Muthuthanthrige Supuni Sanjana Perera[3], Iryna Nikolaevna Matsiuk[4], Santhiyapu Hewa Chamodya Hemali Thathsarani[3]

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## Abstract

**Introduction:** Infants with congenital adrenal hyperplasia need hormone replacement beginning in early infancy to avoid abnormal metabolic effects and progression of masculinization. In this article, we describe a patient who showed a need for rapid escalation in the doses of mineralocorticoids in the first 3 postnatal weeks. These patients need to be closely observed in the neonatal period to avoid the risks of adrenal insufficiency.

**Methods:** Serum electrolytes and 17-hydroxyprogesterone levels were measured, and sonographic evaluation of adrenal and pelvic structures was done. Molecular genetic diagnostics and karyotype were tested. Serum electrolyte levels have been closely monitored for titration of hormone replacement therapy.

**Results:** Venous blood showed low sodium and higher potassium levels from postnatal day 7. The diagnosis was established in the early neonatal period, and hormone replacement (gluco- and mineralocorticoid) was started to prevent life-threatening complications. The infant showed increasing needs for fludrocortisone, from an initial 50 µg/day to 300 µg/day during the neonatal period.

**Conclusions:** Congenital adrenal hyperplasia, particularly the salt-wasting form, often require disproportionately higher doses of mineralocorticoids than would be needed in adults who have lost adrenal function. The underlying reasons remain unclear and likely reflect multiple mechanisms. There is a need to closely monitor these patients during the early weeks to avoid inadequate treatment and potentially life-threatening adrenal crises during this period.

**Keywords:** 11-deoxycortisol, 17-hydroxyprogesterone, Adrenal crisis, Case report, Clitoral hypertrophy, Congenital adrenal hyperplasia, *CYP21A2*, Ehlers-Danlos Syndromes, Fludrocortisone, *GDF3*, *GDF6*, *Growth Differentiation Factor-6*, Heterozygous mutations, Klippel-Feil syndrome, Masculinization, *MEOX1*, *Mesenchyme Homeobox 1*, Mineralocorticoids, *Myosin-XVIIIb*, *MYO18B*, Newborn, *RIPPLY2*, *Ripply transcriptional represso 2*, Scrotal labia majora, *Tenascin XB*, Urogenital sinus, Virilization.

*Newborn* (2025): 10.5005/jp-journals-11002-0128

## Key Points

- Infants with congenital adrenal hyperplasia (CAH) need hormone replacement to avoid abnormal metabolic effects and progression of masculinization.
- Congenital adrenal hyperplasia has been linked with 21-hydroxylase deficiency, due to homozygous or compound heterozygous mutations in the *cytochrome P-450 C21* gene.
- Congenital adrenal hyperplasia infants often require proportionately higher doses of mineralocorticoids than would be needed in adults with lost adrenal function. These manifestations likely involve multiple molecular mechanisms.
- Neonates with CAH should be monitored closely for serum electrolytes and 17-hydroxyprogesterone levels. Some patients may need rapid escalation in the doses of adrenal hormones during periods of physiological crises.

## Background

Congenital adrenal hyperplasia (CAH) is an autosomal recessive genetic disorder that affects the adrenal glands.[1,2] It affects specific enzymes required in the production of cortisol, aldosterone, and androgen.[3] The disorder has been broadly viewed in classic and

[1]2nd Department of Pediatrics, Grodno State Medical University, Hrodna, Grodnenskaya, Belarus

[2]2nd Neonatal Department, Grodno Regional Children's Hospital, Hrodna, Grodnenskaya, Belarus

[3]Faculty of Foreign Students, Grodno State Medical University, Hrodna, Grodnenskaya, Belarus

[4]Department of Genetics, Grodno Regional Clinical Perinatal Center, Hrodna, Grodnenskaya, Belarus

**Corresponding Author:** Tatsiana Sergeevna Pratasevich, Division of Neonatology, 2nd Department of Pediatrics, Grodno State Medical University, Hrodna, Grodnenskaya, Belarus, Phone: +80295684359, e-mail: tprotas16@gmail.com

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nonclassic (mildest) forms.[2] The nonclassic form is seen more frequently than the classic form.[4]

The classic form of CAH can be categorized into a severe salt-wasting and a relatively moderate simple-virilizing form.[1,5,6] In the salt-wasting form, the adrenal glands produce low levels of cortisol and aldosterone but higher levels of androgen.[7] Due to insufficient amount of aldosterone, sodium (Na) and chloride (Cl) are lost in urine; this leads to dysregulation of serum Na and potassium (K). Blood level of Na are low and K are high. The serum electrolyte levels of all infants with 21-hydroxylase deficiency should be monitored because the extent of virilization is not a reliable indicator of the degree of adrenal insufficiency.[8] In the simple virilizing form, the salt loss is mild and adrenal insufficiency is not readily evident, except in stressful circumstances.[2]

Congenital adrenal hyperplasia is caused by mutations in the different genes encoding steroidogenic enzymes involved in cortisol biosynthesis.[9–13] More than 90% of these patients show homozygous or compound heterozygous mutations in the *cytochrome P-450 C21 (CYP21A2)* gene causing 21-hydroxylase deficiency.[14] In its severe form, excess adrenal androgen production starting in the first trimester of fetal development causes virilization of the female fetus and life-threatening hypovolemic hyponatremic shock (adrenal crisis) in the newborn. The 21-hydroxylase deficiency impairs conversion of 17-OHP to 11-deoxycortisol.[15] Therefore, 17-OHP is markedly elevated, serving as the clinical marker for diagnosis.

In this report, we present the clinical course of an infant with salt-wasting CAH who required proportionately higher doses of mineralocorticoids than would be needed in adults with lost adrenal function. The underlying reasons remain unclear and likely reflect multiple mechanisms. There is a need to closely monitor these patients during the early weeks to avoid inadequate treatment and potentially life-threatening adrenal crises during this period.

## Case Description

We present an infant with CAH, salt-wasting form. He was born to a gravida 2 mother after 40 weeks of gestation after an unremarkable pregnancy. The vaginal delivery was normal; Apgar scores were 8 and 8 at 1 and 5 minutes, respectively. The birth weight was 3.5 kg, the head circumference was 35 cm, and the body length was 53 cm.

The systemic examination showed some dysmorphic features, including ocular hypertelorism, wide nasal bridge, low-lying auricles, and a short neck. There was generalized hypotonia. Spontaneous motor activity was moderate, but newborn reflexes were symmetrical. The external genitalia were not differentiated; there were signs of virilization with a urogenital sinus, clitoral hypertrophy, and scrotal labia majora. The pigmentation of the genitalia was detected.

The 17-hydroxyprogesterone (17-OHP) levels measured at 241.14 nmol/L (normal value: 0.4–8.3 nmol/L). The initial diagnosis was CAH with salt-wasting along the course. On postnatal day 7, 17-OHP levels were again measured high at >60 nmol/L. The Na levels began to drop and were measured as 128 mmol/L; K levels rose to 5.8 mmol/L. The adrenocorticotropic hormone levels were high at 1598 pg/mL (normal range in our laboratory: 104–136 pg/mL. Cortisol level was 90 ng/mL (normal range: 6–25 µg/mL); testosterone level was 10.4 ng/mL (normal range: 7.5–40 ng/mL). Ultrasonography showed enlarged adrenal glands; the right measured at 38 × 25 mm, and the left 25 × 11 mm. The shape of the glands, and the overall structure and differentiation of the layers were preserved (Fig. 1).

The karyotype was normal female, 46-XX. The DNA analysis showed the proband as a compound heterozygote with deletions of exons 1–7 of the *CYP21A2 (cytochrome P450 family 21 subfamily A member 2)* gene and exon 35 of the *tenascin XB (TNXB)* gene and deletions of exons 6–7 of the *CYP21A2* gene. The proband's mother was found to be a heterozygous carrier of the deletion of exons 6–7 of the *CYP21A2* gene. The proband's father was found to be a heterozygous carrier of a region deletion: Exons 1–7 of the *CYP21A2* gene and exon 35 of the *TNXB* gene.

Ultrasonography of the pelvic organs was unremarkable; the uterus showed normal placement, shape, size, contour, endometrial characteristics, and dimensions of the uterine cavity. The ovaries appeared largely normal but could not be studied in detail because of covering intestinal loops. Transfontanelle sonograms of the brain were normal. Echocardiography and sonograms of abdominal organs were also unremarkable. Electrocardiogram did not show any abnormalities.

We are currently treating the infant with hydrocortisone (30 mg/m$^2$/day) and fludrocortisone (300 µg/day) and have titrated the doses based on electrolyte and 17-OHP levels. Fludrocortisone therapy was started at 50 µg orally once a day, but we had to increase the doses gradually to 300 µg/day within the first 3 weeks based on the serum electrolyte levels. This increasing need for mineralocorticoids cannot be explained on the basis of increased body weight or resistance in postreceptor signaling.[16] There could be hitherto unexplained mechanisms involving the

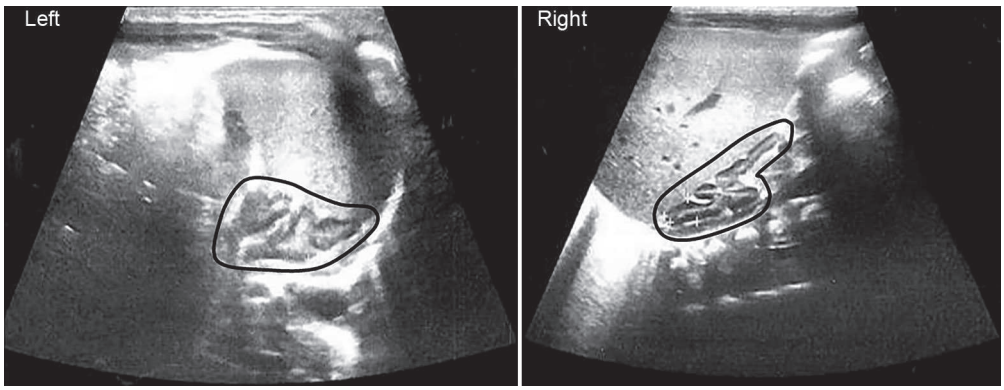


**Fig. 1:** Ultrasonographic images of adrenal glands. The adrenal glands were enlarged per local standards; the right measured at 38 × 25 mm, and the left 25 × 11 mm. The shape of the glands, and the overall structure and differentiation of the layers were preserved

number or distribution of receptors, or limitations in conversion of cortisol into cortisone. We are closely following her growth and neurodevelopmental status; so far, the tone has gradually improved, and she is acquiring major milestones on time. The family has contacted and received support from social and religious organizations.

## Discussion

With two elevated serum 17-OHP levels, altered serum electrolytes, sonographic findings, and genotypic findings, we are following this infant as having CAH, salt-wasting type. Considering her facial dysmorphological findings and CAH, we did consider the possibility of Klippel–Feil syndrome (KFS).[10,17,18] Many of the findings we saw in our infant, including hypotonia, ocular hypertelorism, wide nasal bridge, low-lying auricles, and a short neck, have been noted in KFS. However, existing information has associated KFS with only a few genes: *Growth differentiation factor-6 (GDF6)*, *GDF3*, and *mesenchyme homeobox 1 (MEOX1)*, *myosin-XVIIIb (MYO18B)*, and *ripply transcriptional repressor 2 (RIPPLY2)*; *CYP21A2* or *TNXB* was not identified in our patient.[19–23]

The *TNXB* gene mutations have been associated with Ehlers–Danlos syndrome, which is identified with large fontanelle with delayed closure, down-slanted and short palpebral fissures, hypertelorism, blue sclera, a short nose with a hypoplastic columella, low-set, posteriorly rotated ears, a long philtrum, a thin vermilion of the upper lip, a small mouth, a high palate, and micro- or retrognathia.[24,25] Our infant matched here only in having hypertelorism. The *CYP21A2* mutations have not been associated with major dysmorphological features.[26]

We have been cautiously following the doses of glucocorticoid therapy in our patient to ensure adequate treatment.[27] When therapy is initiated in early infancy, abnormal metabolic effects and progression of masculinization can be avoided.[28] Glucocorticoid therapy should be initiated as soon as possible; initial doses of hydrocortisone usually range from 10 to 20 mg/m$^2$/day given orally in three divided doses and are then adjusted for growth and during periods of stress.[29] Serum 17-OHP levels are also measured to ensure the adequacy of treatment.[30] Maintenance replacement therapy can then be continued with oral cortisol, and is needed lifelong.[31]

This increasing need for mineralocorticoids in patients with CAH likely involves multiple molecular mechanisms. Increasing needs for sodium for growth and development, immature renal function, and resistance in postreceptor signaling have been noted.[16,32] There could also be hitherto unexplained mechanisms involving the number or distribution of receptors, or limitations in conversion of cortisol into cortisone.[33]

## Conclusion

Newborn infants with CAH can show increasing needs for mineralocorticoid doses for replacement in the first few weeks after birth. Fludrocortisone acetate is typically started at a dose of 50–100 µg, orally, per day. However, in our infant, the dose may have to be increased to 300 µg per day. Factors such as weight gain may have to be considered. Although mineralocorticoids are not "stored" in a readilyreleasable reservoir, these are synthesized and released as needed in response to physiological stimuli such as blood pressure changes. We discharged our infant after stabilization of body weight and laboratory parameters at the postnatal age of 3 weeks. The family continued with breastfeeding ad lib and hormone replacement therapy with weekly monitoring of serum electrolytes and 17-OHP levels. The hydrocortisone doses will be increased in stressful situations such as with infections.

## Orcid

*Tatsiana Sergeevna Pratasevich* https://orcid.org/0000-0002-7810-3611

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