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newborn

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Official Journal of the GNS Down Syndrome Foundation
Official Journal of the Autism Care Network Foundation
Official Journal of the Newborn Foundation of Azerbaijan
Official Journal of the GNS Bangladesh Newborn Foundation
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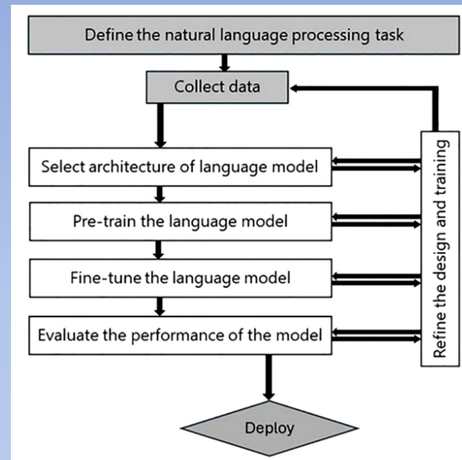
Official Journal of the Global Newborn Society Foundation of Italy
Official Journal of the Mongolian Association of Obstetrics Gynecology and Neonatology
Official Journal of the Foundation for Human Milk Feeding in the Islamic World
Official Journal of the Sociedade Brasileira de Atenção ao Recém-Nascido
Official Journal of the organization, Protecting Brains and Saving Futures, Brasil
Official Journal of the Association of Neonatologists in the United Kingdom
Official Journal of the Polish Nursing Association - Płock, Poland
Official Journal of the Panlibyan Neonatal Association
Official Journal of the Association for Indigenous Peoples in India
Official Journal of the Association for Newborn Care in Pakistan
Official Journal of the GNS Association for Perinatal Care
Official Journal of the Association for Infant Nutrition in the Middle East
Official Journal of the Uruguayan Neonatal Association
Official Journal of the Paraguayan Society of Pediatrics Committee for Neonatology
Official Journal of the Sociedad Latinoamericana de Residentes de Neonatologia (SOLAReNeo)
Official Journal of the Armenian Association of Neonatal Medicine
Official Journal of the Global Newborn Society Cardiology Association of Iraq
Official Journal of the Association of Pediatricians of Uzbekistan

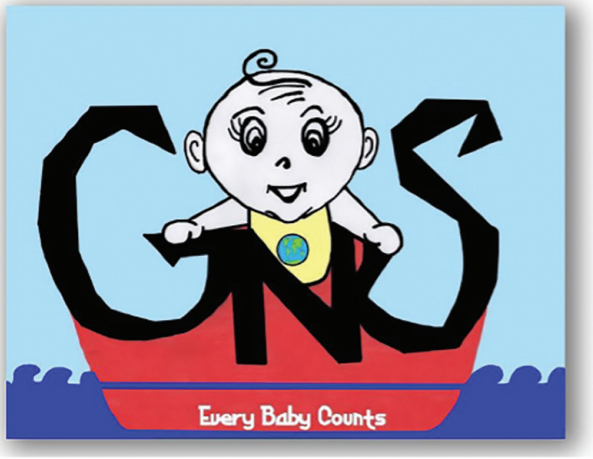
Highlighted articles:



Artificial Intelligence in Newborn Medicine
Down Syndrome: Let's Work Together to End the Stereotypes
Development of a Care-Bundle to Prevent Necrotizing Enterocolitis
Abnormalities of Corpus Callosum and other Inter-Hemispheric Commissures

Also available online at
https://www.globalnewbornsociety.org/our-scientific-journal-newborn

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.

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Contents

EDITORIAL

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We Need New Thinking to Save Babies

The neonatal period is the most vulnerable time for a child.[1] As all of us have discussed many a time—each time we lose an infant, we lose an entire life and all its potential. Babies do not talk,[2] or vote,[3] and so, need help.[4] Each year, we lose nearly 2.6 million 3rd trimester fetuses and 2.7 million neonates.[4] We need to clearly understand the needs—the schematic in **Fig. 1** shows the populations of ill newborns in the world in three subsets—total, accessible, and treatable. We have knowingly used ovals, not the rectangular depictions of the world;[5] the oval cartographic projections such as the Robinson[6]/Equal-Earth[7] are more appropriate for depicting global needs than the traditional Mercator views, which are skewed in favor of the North.[8] Further, the inside ovals are depicted in the lower part of the figure to emphasize that the Global South, with its higher fertility rates, has more babies than the North but there are limitations in access to healthcare facilities.[9-12] The green-shaded oval of treatable illnesses is similarly depicted in the lower part of the schematic as infectious diseases, which are often easier to prevent/treat than the non-infectious disorders, are more important as a cause of infant mortality in the South. These conditions can be cured with timely treatment but can be lethal if the chances are missed.[13] Some planning is needed, but therapeutic measures such as vaccination, antibiotics, and/or supportive measures can be provided.[14] In addition to the North and the South, we also need to recognize a liminal "Global East".[15] The fertility rates in Africa, the Middle East, South, and South-East Asia are higher, and consequently, the newborn populations are larger in these regions.[16] Hence, the ovals in this figure are displaced to the right (Eastward per the compass).[1] These issues need consideration when public funds are allocated.[17] Having said all this, the importance of non-infectious illnesses is not any lesser. We need to keep ourselves updated of new data that are always emerging about healthcare, outcomes, and changing economic status.[18] Conditions such as Down syndrome are seen all over the world and all of us need to join and work together.[19] The numbers can be estimated based on census data. For many such conditions, a fresh, thematic apperception[20] focusing on the total fertile-age population in specific regions can help.[21]

Our journal, the newborn, aims to cover fetal/neonatal problems that often begin during pregnancy, may be seen at the time of birth, or occur during the first 1000 days after birth. In this 2nd issue of the 3rd volume, we report several exciting new developments. First, six organizations, the Uruguayan Neonatal Association, the Paraguayan Society of Pediatrics Committee for Neonatology, the Sociedad Latinoamericana de Residentes de Neonatologia (SOLAReNeo), the Armenian Association of Neonatal Medicine, the Global Newborn Society Cardiology Association of Iraq, and the Association of Pediatricians of Uzbekistan have adopted the newborn as their official journal. We now have 23 partnering groups of care-providers that will use the *newborn* as their mouthpiece, the platform for all their official communications. The team is growing—we are now speaking together not only about overall care of newborns, but also specifically about issues such as Down syndrome, autism, infant nutrition, neonatal brain injury, and care of infants in hitherto understudied indigenous peoples. Just as in our previous issues, we present 8 important articles here (**Fig. 2**).

We bring to you a healthcare-focused article about Down Syndrome (DS); this was drafted jointly by GNS members from all the six majorly-populated continents in the world.[22] As we know, the General Assembly of our United Nations has marked 21 March of each year as the World Down Syndrome Day.[23] The goal is to raise public awareness of this condition so that we can all look for solutions together.[24] The incidence of DS is estimated to be about 1 in 1,100 live births worldwide, with some minor temporal, racial/ethnic, and geographical variability.[25,26] Most infants with DS have an extra copy of chromosome 21, although a small minority may have other chromosomal abnormalities such as Robertsonian translocations, the presence of an isochromosome, or a ring chromosome.[27] Interestingly, many of the frequently-seen phenotypic features may be rooted in sequential variability in a single band, the 21q22, and this gives hope that effective therapeutic strategies may be possible.[28] If we could understand the pathophysiology of DS just a little bit better, we could make a small change in this world.

We have an important article from the EpicLatino, a non-profit, public-service organization that includes 33 units in Colombia, Chile, Mexico, Ecuador, Peru, Argentina, Paraguay, Argentina, and Curacao.[29] They studied the use of antibiotics in their member units and have called for a cautious approach in the use of antibiotics. We are all aware of the difficulties in withholding antibiotics in critically-ill preterm infants. The possibility of infection is not always easy to exclude in these patients, and sepsis, if present, can progress rapidly and result in mortality. However, the concerns about secondary resistance to antibiotics are real.[30–32] This issue deserves further study, worldwide.[33]

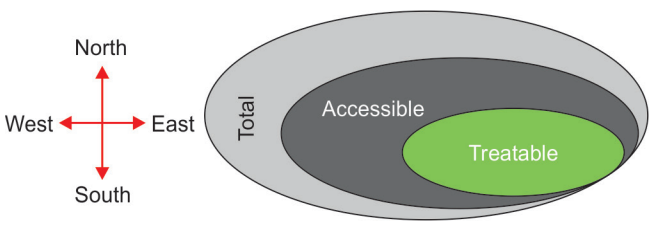

Fig. 1: Neonatal illnesses in the world can be viewed in three groups—total, accessible, and treatable. The fractions are skewed to the lower section of the oval to emphasize that the "Global South" has more babies who need more attention. Infectious diseases are seen more frequently in the South; these can be cured with timely treatment but could also be lethal if the chances are missed. We also need to recognize a "Global East" with high fertility rates and consequently, large newborn populations. These considerations are important when allocating public funds.

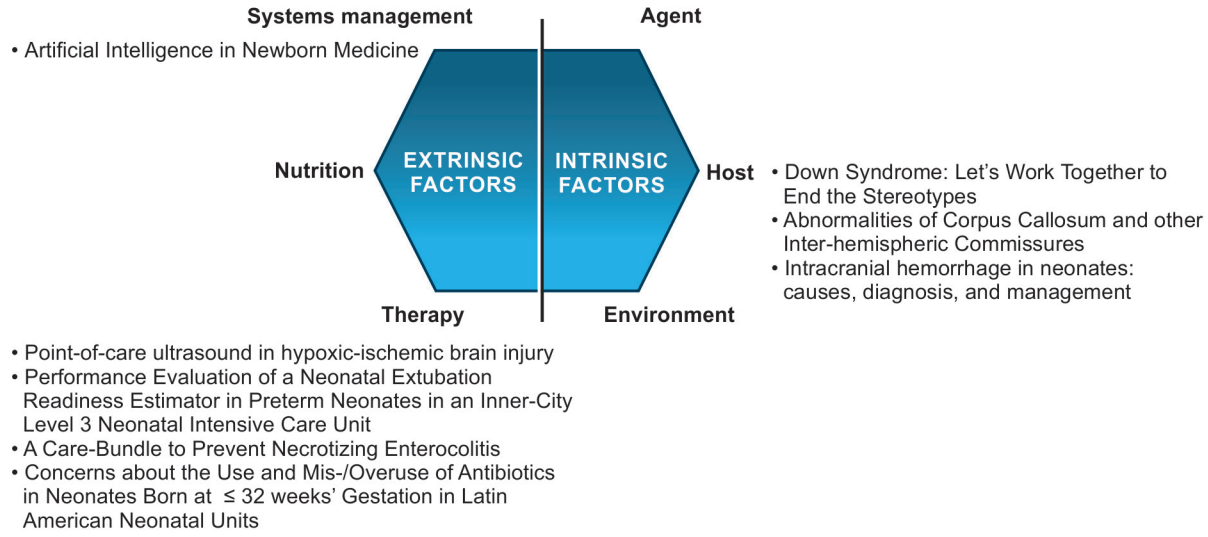

Fig. 2: Areas of focus in the *newborn*, Volume 3, Issue 2. We have expanded the traditional agent-host-environment trinodal disease model to a hexagonal system. The three additional foci represent extrinsic factors that can affect health—those originating in therapy, nutrition, and systems management are shown. This issue covers 3 nodes, namely host factors, treatment/monitoring systems, and systems management.

From this issue on, the *newborn* plans to feature healthcare "bundles", a concept of medical treatment first defined by the Institute of Health Care Improvement (IHI).[34-40] This prophylactic/therapeutic strategy involves simultaneous application of 3-5 evidence-based/traditionally-accepted interventions in all patients, unless contraindicated.[34,35,41,42] The concept of healthcare bundles is particularly attractive in premature/critically-ill infants as they typically show the highest severity of illness during the early postnatal period and/or at specific corrected gestational/post-conceptional ages.[43] Initial studies show low-strength but consistent, encouraging evidence to support this approach. In this issue, we present a care-bundle focused on prevention of necrotizing enterocolitis (NEC).[44] The authors have combined standardized feeding practices (human milk/feeding protocols), measures to prevent gut dysbiosis, avoidance of certain medications, management of severe anemia, and antenatal administration of corticosteroids.

Excitingly, this clinical care-bundles team is growingly rapidly and has planned a series of articles focused on various neonatal disorders for later issues of this journal; each will follow the same broad architecture as the NEC bundle. After much discussion, they have proposed a short acronym for their database: LAYA - ***L***ooking ***A***t ***Y***our practices in ***A***pplication. Interestingly, this word turned out to be meaningful in many languages, almost as if they had accidentally stepped on a lexical cognate. In Greek, the word *laya* is rooted in eulalia, meaning "fair speech". In Spanish and Portuguese, *laya* refers to "one single type/sort" in a classification. In Chinese, an analogous word, *lai*, means "dependable". In Russian, *laya* indicates "empathy". In Hindi/Sanskrit, *laya* means "rhythm'. In Urdu, the meaning is "fetched". In Persian (Farsi), it refers to "blessed/luck". The Arabic meaning is a "musical free spirit". In Filipino/Tagalog, the word indicates "free emancipated". And they could have found more.

There is increasing interest in the development of artificial intelligence (AI) algorithms for medical care, research, and even its documentation in manuscripts.[45] The reaction has evoked mixed-feelings, excitement but also concern about possible misuse.[46,47] These algorithms could turn out to be a transformational, continuous source of clinical and educational information.[48] Several AI algorithms with varying strengths and weaknesses are known, but the deep-learning pathways in Generative Pre-trained Transformers (GPT) seem to be particularly interesting for medical applications.[49,50] However, we need more validation.[47,51] If testing confirms the utility of these pathways, there is a possibility of a rapid advancement of tremendous value.[52] These tools can help examine large bodies of data that are available but are not being uniformly and comprehensively analyzed at all centers.[53,54]

Bhatia *et al*.[55] evaluated the accuracy of a neonatal extubation readiness estimator (ERE) algorithm in preterm neonates. Premature infants routinely require prolonged, invasive mechanical ventilation, which is associated with multiple secondary morbidities ranging from chronic lung disease, retinopathy of prematurity, to hearing disorders.[56] Infants on respiratory support often have higher medical care needs such as parenteral nutrition and have a high risk of secondary infections.[57,58] The need for respiratory support is a key determinant of the length of hospital stay;[58,59] if we could predict the timing of successfully extubation, we might be able to develop tailored treatment strategies, reduce morbidity, and shorten hospital stay.[60,61] Currently, our predictions of successful extubation are based primarily on clinical judgment, and as expected, the results have mixed accuracy. The availability of an accurate ERE algorithm would be helpful.[62] In this pilot study, the authors tested one such algorithm to assess ventilated VLBW infants; it was deemed safe but still had limited accuracy. Further studies are needed in larger cohorts to develop more refined scales.

There is a review of the corpus callosum (CC) and the anterior and the hippocampal commissures.[63] These white matter tracts connect the two neocortical cerebral hemispheres. About 7 persons per 1000 can have complete agenesis of the CC. The etiopathogenesis of these disorders is unclear. Many patients with agenesis of the CC manifest early with seizures, whereas others have a more subacute/chronic course with developmental delay and other neurological manifestations. Some are isolated abnormalities, whereas others might be a component of Aicardi syndrome, Andermann syndrome, Mowat-Wilson syndrome, or XLAG (X-linked lissencephaly with ambiguous genitalia).[47,64-66] CC can also undergo secondary destruction following infarction, hemorrhage, trauma, and in some metabolic

diseases.[67-70] Some patients with CC abnormalities show longitudinal white matter fascicles alongside the lateral ventricles; these are known as the Probst Bundles and can alter the clinical presentation and outcome of these patients.[71,72] As of now, there is no specific treatment for these commissural abnormalities.[65,73] Careful clinical and genetic evaluation is all we have for symptomatic management and for counseling the families.[74,75]

Kumar and colleagues[76] have reviewed the utility of point-of-care ultrasound in infants with hypoxic-ischemic encephalopathy (HIE).[77,78] They have described numerous changes seen in acute and sub-acute phases of HIE that can be used to monitor disease progression, provide prognostic information, and guide therapy.[79] Dynamic changes with hyperechogenicity of the thalamus, basal ganglia, and the altered appearance of posterior limb of the internal capsule are described.[80] They have also described the resistive index (RI), a pulsatility parameter that measures the resistance of a vascular wall using ultrasonography.[81] It is a hemodynamic index that can help assess vascular disease by measuring the resistance to blood flow.[82,83]

Finally, this issue brings an updated a review of intracranial hemorrhages (ICHs) in neonates.[84] As we are aware, ICH is a frequently-noted finding in neonates.[85] Severe hemorrhages can be seen in up to 1:2000 spontaneous births with devastating neurodevelopmental outcomes.[86,87] In term infants, ICHs are usually related to mechanical injury sustained during labor.[87] Preterm infants usually develop ICHs due to hemodynamic instability and fragility of the germinal matrix vasculature.[88] The neurodevelopmental outcomes vary according to the gestational maturity, etiology, and the severity of the hemorrhage.[89] Severe hemorrhages may be associated with developmental delay, seizures, cerebral palsy, and other neurological disorders.[90] In this article, the authors have reviewed the types, etiology, severity, and clinical outcomes of neonatal ICH.

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VIEWPOINT

Down Syndrome: Let's Work Together to End the Stereotypes

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Abstract

Each year, we observe the 21st day of March as our World Down Syndrome Day. The goal is to raise public awareness of Down syndrome (DS) and encourage all member states, relevant organizations of the UN system, all member states, other international organizations, non-governmental organizations, and the private sector to join this effort. The epidemiology of DS is complex. The incidence of DS is estimated to be somewhere between 1 in 1,000 and 1 in 1,200 live births worldwide, but there may well be some temporal, racial/ethnic, and geographical variability in the prevalence of DS. Most infants with DS have an extra copy of chromosome 21, which occurs due to the failure of chromosome 21 to separate during gametogenesis. However, a minority with the same phenotype may have a Robertsonian translocation, an isochromosome, or a ring chromosome. Increasing information suggests that many of the most frequently seen phenotypic features may be rooted in sequential variability in only one band, the 21q22. The characteristic facial appearance, cardiac anomalies such as the endocardial cushion defect, neurodevelopmental delay, and many dermatoglyphic changes could result from a small region including the genes for superoxide dismutase in the region 21q22.1, the amyloid precursor protein mapping in 21q11.2-21.05, and six probes for single-copy sequences: D21S46 in 21q11.2-21.05, D21S47 and SF57 in 21q22.1-22.3, and D21S39, D21S42, and D21S43 in 21q22.3. Speaking from this medical perspective, we need to understand the pathophysiology of DS to meet their healthcare needs. If we could do so, we could make a small change in this world.

Keywords: Age-standardized rate, Down syndrome international network, Infant, Isochromosome, Neonate, Newborn, Ring chromosome, Robertsonian translocation, Sociodemographic characteristics, United Nations General Assembly.

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Key Points

- Each year, we mark March 21st as the World Down Syndrome Day to raise public awareness of DS.
- The incidence of DS is estimated to be somewhere between 1 in 1,000 and 1 in 1,200 live births worldwide; it is seen in people of all races and economic levels.
- Down syndrome is a complex genetic disorder; most cases involve the failure of chromosome 21 to separate during gametogenesis. However, some cases may show a Robertsonian translocation, an isochromosome, or a ring chromosome.
- As we are beginning to understand the genetics of DS, most of the phenotypic features of this condition seem to arise in the chromosomal region 21q22.
- Each time we lose an infant, we lose, and entire life and its potential. The World Down Syndrome Day 2024 was yet another reminder. Let's work together, and we might be able to make a difference.

Introduction

In December 2011, the United Nations (UN) General Assembly decided that starting in 2012, 21st March would be our World Down Syndrome Day (A/RES/66/149).[1] The goal was to raise public awareness of Down syndrome (DS) and encourage all member states, relevant organizations of the UN system, other international organizations, non-governmental organizations, and the private sector to participate in this effort. The DS International Network hosted the 13th World Down Syndrome Day Conference at the UN headquarters on 21 and 22 March 2024 in New York.[2] In this article, authors from all the 6 majorly-populated continents joined together to share their understanding and viewpoints. DS affects all humanity, and we need to act together.

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The epidemiology of DS is complex.[3] The incidence of DS is estimated to be somewhere between 1 in 1,000 and 1 in 1,200 live births worldwide.[4] Each year, approximately 3,000–5,000 infants are born with this chromosome disorder.[1] The risk increases with maternal age (1 in 1,250 for a 25-year-old mother, 1 in 1,000 at age 31, 1 in 400 at age 35, and about 1 in 100 at age 40).[5,6] However, 75–80% of babies with DS are born to women under age 35 years.[7]

There may be some temporal, racial/ethnic, and geographical variability in the prevalence of DS.[3,8] In the past 30 years, the incidence/prevalence of DS, both overall and age-standardized, have shown both temporal and regional variance.[9] The prevalence has increased for both sexes in nearly all social-demographic index regions; the highest age-standardized incidence was noted in Brunei Darussalam, Ireland, and Haiti.[8,9] Georgia showed the highest increase in age-standardized rate, whereas Serbia has shown a decline in these numbers. The mortality has decreased gradually over the last two decades.[9]

In biological terms, nearly 96% of all persons with DS have an extra copy of chromosome 21 (Fig. 1), which occurs due to the failure of these chromosomes to separate during gametogenesis.[10] This results in an extra chromosome in all the cells of the body. Understanding the genetic pathogenesis of DS has been challenging because there are >200 protein-coding genes on chromosome 21, which can directly and indirectly affect homeostasis in cells, tissues, organs, and systems.[11] Furthermore, genetic alterations other than a canonical chromosomal 21 trisomy have also been identified in 3–4% of infants with DS. Many of these infants may have a Robertsonian translocation (Fig. 2), an isochromosome, or a ring chromosome.[12] The Robertsonian, or the translocation DS, is an unbalanced anomaly where the infant has three copies of the long arm of chromosome 21 instead of two.[13] As known, chromosome 21 is an acrocentric chromosome where the centromere is not central and is located near the end of the chromosome.[14] An isochromosome is a structural abnormality in a chromosome that causes the arms to mirror each other; a chromosome has two copies of either the long arm or the short arm.[15] The ring chromosome 21 is a rare abnormality in which the ends of chromosome 21 join and form a ring.[13] Finally, 1–2% of infants with DS are the so-called "mosaics", where some, not all, cells show a chromosome 21 trisomy.[16]

Overall, the phenotypic features cannot be used to predict the exact type of the above-mentioned genotypic abnormalities seen in DS. Still, infants with a ring chromosome 21 may have fewer distinctive features associated with DS. Some of these individuals develop normally and may be diagnosed only when tested due to infertility, multiple miscarriages, or when they have a child with DS phenotype.[17] However, others can have developmental delay and/or medical problems due to their having extra or missing genetic material on the ring.[18] This subset may present with short stature, microcephaly, seizures, neurodevelopmental delay, immunodeficiency, and other birth defects. Some males may have

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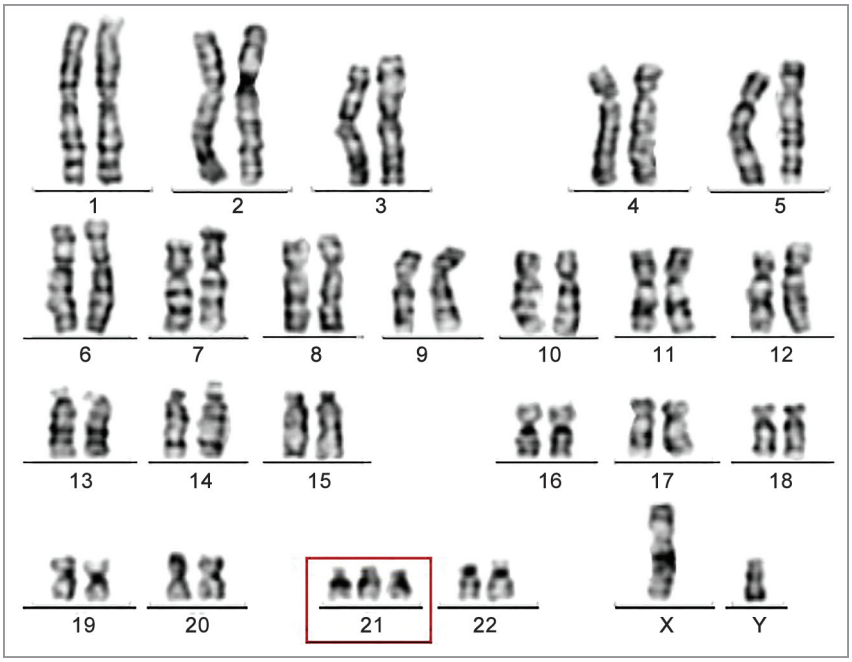
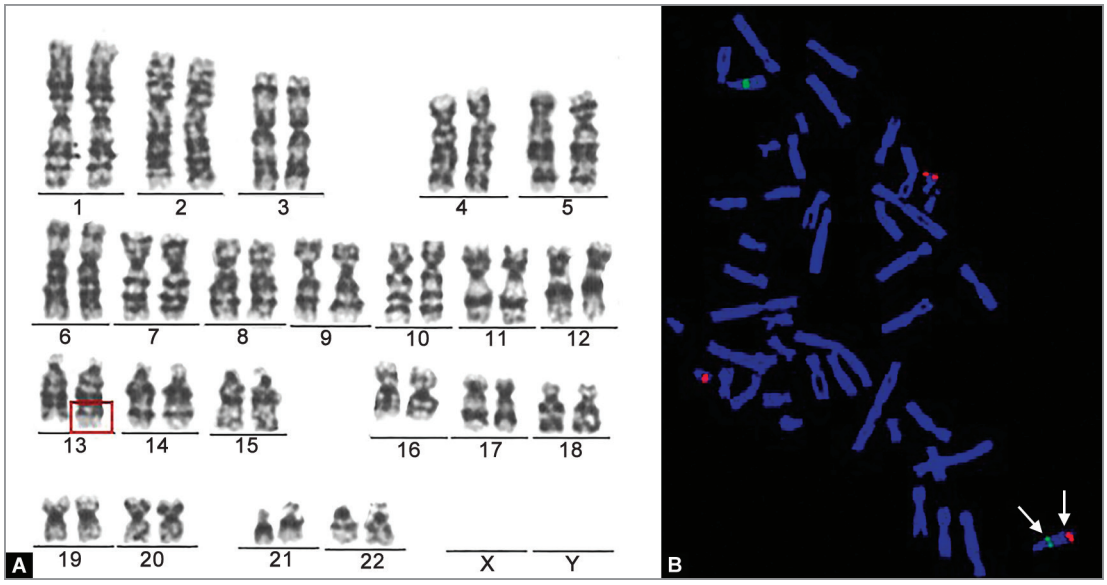


Fig. 1: Karyotyping on cells isolated from venous blood. GTG staining/banding; resolution 400×. The infant had trisomy 21 (as marked by the rectangle)



Figs 2A and B: (A) Karyotype: 46,_ _, add (13) (q133).ish der (13) [t(13;21) (q33;q21.3)] (D21S259+, D21S341+, D21S342+). There was a cryptic translocation between chromosomes 13 and 21, which was not easily detectable on cytogenetic analysis; (B) In the fluorescence *in situ* hybridization (FISH) image (right), the two chromosomes 13 showed a green-appearing signal for 13qter. Chromosomes 21 were identified by the orange-red signals. Interestingly, one of chromosome 13 (right lower corner) also showed a red-orange signal suggestive of a partial trisomy (translocation) of chromosome 21. These findings were identified in the karyotype (left; red rectangle). The other chromosome 13 did not show such a signal. This cryptic chromosome arrangement appears to be unbalanced with a partial trisomy 21 and partial monosomy 13. One of the parents was likely a carrier of this chromosome 13;21 translocation

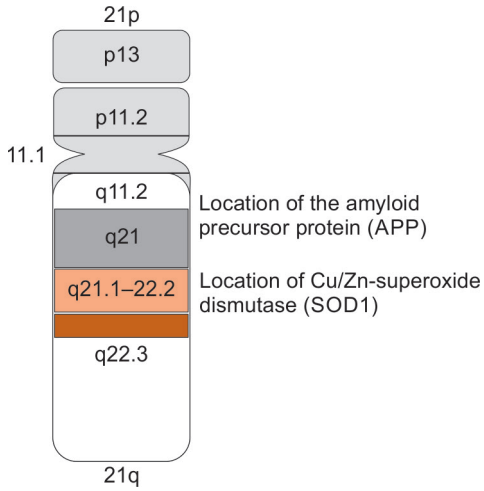


Fig. 3: Schematic diagram showing the major bands in chromosome 21

delayed puberty.[19,20] The ring chromosome 21 may be inherited from a parent, typically the mother, or it may occur sporadically.[19] Similarly, infants who are mosaics for DS may also have fewer clinical features that are typically seen in DS.[13]

The DS phenotype has been traditionally ascribed to the presence of an extra chromosome 21.[21] However, newer molecular and cytogenetic analyses suggest that many diagnostic features such as facial appearance, cardiac anomalies such as the endocardial cushion defect, neurodevelopmental delay, and dermatoglyphic changes could be rooted in a relatively small region of this chromosome. The gene for the Cu/Zn-superoxide dismutase (SOD1; Fig. 3) is located in 21q22.1, the amyloid precursor protein (APP) in 21q11.2-21.05, and six probes for single-copy sequences bind in a narrow, contiguous region: D21S46 in 21q11.2-21.05, D21S47 and SF57 in 21q22.1-22.3, and D21S39, D21S42, and D21S43 in 21q22.3.[22–25] All sequences located in 21q22.3 were present in three copies in the affected individuals, whereas those located proximal to this region were present in only two copies. Cytogenetic analysis with R and G banding of prometaphase preparations and *in situ* hybridization revealed a translocation of the region from very distal 21q22.1 to 21qter to chromosome 4q.[26] The deletion of chromosome band 4q35 is another important genotypic change. The variability in the DS phenotype may result from the variability of gene expression of transcription factors that are encoded both on chromosome 21 and also elsewhere in the genome, copy number polymorphisms, the function of conserved non-genic regions, microRNA activities, RNA editing, and perhaps DNA methylation.[27]

Healthcare providers need to understand the pathophysiology of DS in greater detail to meet the healthcare needs of these children.[28] If we can gain in our ability to understand, predict, detect, counsel, convince, track, mitigate, follow, and eventually ameliorate or correct even some of the DS-related morbidities, we could make a small change in this world.[29–31] For individuals with DS to achieve optimal quality of life, they definitely need parental and family care but can also use medical guidance and inclusive community-based support systems.[1,32] It's time we end the stereotypes–we all need to come together, bring information, and share our experiences.[31,33] Every baby counts-each time we lose an infant, we lose an entire life and its potential.[34] The World Down Syndrome Day 2024 was yet another reminder.[35] Let's work together.[36]

Here are some organizations that provide information and support for families with a child with DS:

- ACT Down Syndrome Association (Australia).
- Asociacion Guatemalteca para el Sindrome de Down (Guatemala).
- Asociacion Sindrome de Down de la Republica Argentina.
- Asociacion Sindrome de Down de Baleares (Spain).

- Association du Syndrome de Down de Down De L'estrie (Canada).
- Association Francaise pour la recherche sur la Trisomie 21 (France).
- Associazione Italiana Persone Down (Italy).
- Canadian Down Syndrome Society.
- Center for Disease Control and Prevention: Facts about Down Syndrome.
- Csupaszívek Társasága (Hungary).
- Down España (Spain).
- Downs forening en hovedstaden (Denmark).
- Down's Heart Group (UK).
- Down Syndrome Affiliates in Action.
- Down Syndrome Albania.
- Down Syndrome Australia.
- Down's Syndrome Association (Russia).
- Down Syndrome Association (Singapore).
- Down Syndrome Association of Minnesota.
- Down's Syndrome Association of Nepal.
- Down Syndrome Association of Nigeria.
- Down Syndrome Association of NT (Australia).
- Down Syndrome Association of Greece.
- Down Syndrome Association of Hamilton (Canada).
- Downs Syndrome Norge (Norway).
- Down Syndrome Association of Toronto (Canada).
- Down's Syndrome Association of Uganda.
- Down Syndrome Diagnosis Network.
- Down Syndrome Education International (UK).
- Down Syndrome International.
- Down Syndrome Foundation.
- Down Syndrome NSW (Australia).
- Down-Syndrome Netzwerk Deutschland e.V. (Germany).
- Down-Syndrome Österreich (Austria).
- Down Syndrome Resource Foundation.
- Down Syndrome Federation of India.
- Down Syndrome Ireland.
- Down Syndrome Queensland (Australia).
- Down Syndrome Research Foundation (Canada).
- Down Syndrome South Australia.
- Down Syndrome South Africa.
- Down Syndrome Tasmania (Australia).
- Downsyndroom Vlaanderen (Belgium).
- Down Syndrome Victoria (Australia).
- Down Syndrome WA (Australia).
- DSIJ (Japan).
- Edmonton Down Syndrome Society (Canada).
- Familias Extraordinarias (Mexico).
- FRUTOS (Ecuador).
- Fundação Síndrome de Down (Brazil).
- Fundacion Sindrome de Down del Caribe (Colombia).
- Fundacio Catalana Sindrome de Down (Spain).
- Fundación Iberoamericana Down 21 (Spain).
- Genetics Home Reference: Down Syndrome.
- Global Down Syndrome Foundation.
- German Down Syndrome InfoCenter (Germany).
- Gulf Kids (Saudia Arabia).
- Hong Kong Down Syndrome Association.
- Insieme 21 (Switzerland).
- International Down Syndrome Coalition.
- International Mosaic Down Syndrome Association.
- Jack's Basket.
- Japan Down Syndrome Society.
- Kids Health: Down Syndrome.
- La Asociacion Venezolana para el Sindrome de Down (Venezuela).
- Landsforeningen Downs Syndrome (Denmark).
- Laufclub Down-Syndrome Marathonstaffel e.V. (Germany).
- Libyan Down Syndrome Association.
- National Down Syndrome Congress.
- National Association for Down Syndrome.
- New Zealand Down Syndrome Association.
- Norsk Nettverk for Down Syndrome (Norway).
- National Down Syndrome Society.
- Sindrom Down Romania.
- Stowarzyszenie Rodzin i Opiekunów Osób (Poland).
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ORIGINAL RESEARCH

A Clinical Care Bundle to Prevent Necrotizing Enterocolitis

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

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Abstract

Necrotizing enterocolitis (NEC) is a leading cause of morbidity and mortality in very-low-birth-weight (VLBW) infants all over the world. Even thought the incidence of NEC has decreased over the past decade, it continues to affect 5–7% of premature infants born ≤ 32–33 weeks. The disconcerting part is that the incidence of NEC has not changed despite continuous efforts to understand its etiopathogenesis. Because of limited information about the cause of this disease, our group has increasingly focused on developing a clinical care bundle to treat these patients. As we know, a bundle is a structured attempt to improve the care of patients with a specific nosological entity, to improve outcomes. The team adopts a small number of, usually 3–5 evidence-based, proven practices which when performed reliably and consistently, have been shown to improve patient outcomes. In this article, we have focused on the use of human milk, including mother's own, that from donors, and of oral colostrum; standardized feeding practices; prevention of intestinal dysbiosis with antibiotic stewardship and use of probiotics; avoiding certain medications, such as histamine receptor blockers; adequate management of anemia; and antenatal use of corticosteroids. In these efforts, we have combined information from our own peer-reviewed clinical and preclinical studies with an extensive review of the literature from the databases PubMed, EMBASE, and Scopus.

Keywords: Care bundle, Human milk oligosaccharides, Intestinal injury, Intestinal failure, Institute of Health Care Improvement, Mother's own milk, NEC Newborn, Neonate, Preterm.

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Keypoints

1. Necrotizing enterocolitis (NEC) is a leading cause of morbidity and mortality in very-low-birth-weight (VLBW) infants all over the world.
2. Despite all efforts, the etiopathogenesis of NEC remains unclear. Hence, at our centers, we have focused on developing a clinical care bundle to address known risk factors.
3. Per accepted definitions of clinical bundles, this is a structured attempt to establish protocols to prevent/mitigate five major risk factors associated with NEC.
4. We have focused on efforts to promote human milk feedings, standardize feeding practices, prevent intestinal dysbiosis, manage anemia, and encourage prenatal use of corticosteroids.
5. This clinical care bundle is focused on risk factors seen in both temperate and the relatively disadvantaged peri-equatorial and tropical climate regions. There is a need for continued evaluation and refinement of the components of this bundle.

Introduction

Necrotizing enterocolitis (NEC) is one of the most dreaded illnesses of premature infants. Although the incidence has decreased over the past decade, it continues to affect 5–7% of premature infants born < 32–33 weeks. Even though we have had some success in reducing the incidence of NEC in the West, the absolute number of infants with NEC has increased globally with increasing survival of more premature infants all over the world.[1–3] NEC is not only associated with high morbidity and mortality, but it also lengthens the hospital stay, increases the cost of care, and affects the neurodevelopmental outcomes of premature infants.[4–6] Many studies have evaluated antenatal steroids, delayed cord clamping, exclusive use of mother's own milk (MOM)/human milk (HM), oral colostrum care, standardized feeding guidelines, antibiotic stewardship, reduced use of proton pump inhibitors (PPIs) and H2-blockers, administration of probiotics, and prevention of severe anemia as strategies to prevent NEC. These interventions have traditionally been assessed as singular measures[7–9] but now a combined, care bundle approach is emerging as an alternative, effective option.[10–12] In this article, we have described our efforts to identify, develop, evaluate, refine, and re-implement five chosen prongs of a care bundle to prevent NEC: antenatal practices, human milk feedings, enteral feeding practices, prevention of intestinal dysbiosis, and prevention of anemia.

Besides emphasizing specific practice measures, we also need a better understanding of implementation science to focus on compliance and continuing education.[13,14] The efforts to define/refine the care bundle have to be a continuous process.[15] If considered from a more global perspective, these efforts will have to be tailored for different parts of the world. For instance, maternal

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anemia might make delayed cord clamping particularly important in some regions.[16] The importance of probiotics might vary because the acquisition, spectrum, and expansion of gut microflora in the neonatal intestine might not be identical across the world.[17] The effects of these bacterial genera might change with the degree of prematurity.[18] Maybe even with climatic conditions.[19] Donated human milk might need to be stored differently.[20] There might be a genetic predisposition to many toxins and pathogens in different regions.[21] In short, we will continuously need more information.

Defining NEC

NEC is an inflammatory condition of the bowel. It has been defined/assessed for severity using Bell's criteria (1978)[22] and then with the modifications proposed in this staging (Walsh and Kliegman):[23]

i. Stage I (suspect): non-specific signs and symptoms, non-diagnostic radiographs;
ii. Stage II (definite): definite pneumatosis or hepatic portal venous gas on X-rays or intestinal ultrasound or surgical or autopsy diagnosis of NEC:
    IIa: mildly ill.
    IIb: moderately ill with systemic toxicity.
iii. Stage III (advanced): definite pneumatosis or hepatic portal venous gas on X-rays or intestinal ultrasound or surgical or autopsy diagnosis of NEC.
    IIIa: critically ill, Disseminated intravascular coagulation, shock, ascites, impending intestinal perforation.
    IIIb: critically ill, as in IIIa, with pneumoperitoneum.

Even though Bell's staging has been challenged and modified in the last decade with many state-of-the-art reviews,[24–26] defining it is beyond the scope of this article. Also, we must be cautious while defining NEC as there is a risk of misclassification with conditions that mimic NEC (NEC associated with congenital heart disease, cow's milk protein intolerance, transfusion-associated gut injury, and viral illness).[27,28] There is a controversy if spontaneous intestinal perforation (SIP) and NEC are the two spectrums of the same illness.[29,30] For all practical purposes, diagnosis of 'NEC-mimics' or radiographs showing pneumoperitoneum without pneumatosis or systemic signs are not considered NEC. It is always advisable to have the agreement of two neonatologists, with one involved in patient care or a neonatologist and a radiologist while confirming the diagnosis of NEC. NEC is a multifactorial pathogenesis that involves numerous pathways.[31] Intestinal immaturity, highly immunoreactive intestines, disturbed intestinal microbiota and colonization of the gut with bacteria are the most common etiopathogenesis of NEC.[32–34] Despite best understanding of the disease per se and many preventive interventions, NEC has got global burden of 20–30% mortality, with increased mortality in surgical cases with long-term complications being intestinal stricture, short bowel syndrome, and intestinal failure.[35–37]

Defining Care Bundle

Care bundles are a group of evidence-based interventions related to a disease or care process that when executed together, result in better outcomes than when these are implemented individually.[38] To improve medical care and adherence to evidence-based guidelines in ICUs, the concept of "care bundles" was strategized by the Institute of Health Care Improvement (IHI).[39,40] Care bundles were outlined to be a group of either evidence-based or nationally accepted guidelines consisting of 3–5 interventions to be applied to all patients unless contraindicated.[39–42] For NEC, a care bundle was first implemented in the East of England due to the high incidence of NEC in 17 local units. Aiming to decrease the incidence of NEC, 15 factors associated with NEC were evaluated and eventually, three – exclusive breast milk feeding, prevention of infection, and enteral feeding strategies were found evidence-based and easy to implement.[10] This care bundle became a routine practice in the region. Subsequently, many quality improvement initiatives were evaluated in the last decade for reinforcing the care bundle[10,12,43–45] but these were not found as effective. In one robust study, Belal et al.[11] from Canada studied the impact of bundled multidisciplinary guidelines over 10 years and noted a sustained reduction in the NEC in very preterm infants. This study showed that a multipronged approach can be important for preventing a disease with an uncertain, possibly multifactorial etiopathogenesis. Here, we have reviewed our NEC care bundle that is comprised of five prongs: exclusive HM feeds, enteral feeding practices, prevention of intestinal dysbiosis, prevention of severe anemia, and antenatal practices (Fig. 1).

NEC Care Bundle

1. Exclusive human milk (HM) feedings
    i) *Reinforcement of exclusive MOM*: HM, with its complex composition of nutrients bioactive factors, and immune components has been shown to play a crucial role in protecting the immature gut of neonates against NEC. Human milk oligosaccharides (HMOs), alongside antimicrobial factors such as lactoferrin and secretory IgA antibodies, inhibit harmful bacteria and promote gut health. Moreover, breast milk provides essential nutrients and growth factors, such as epidermal growth factor, vital for intestinal development and repair, reducing inflammation risks. Its diverse composition also fosters a healthy intestinal microbiota, aiding in long-term immune health. Overall, HM's multifunctionality makes it a vital defense against NEC. The correlation between the reduction of NEC and HM feeding has been extensively studied. Schanler et al., and later Sisk and colleagues and Meinzen Derr and co-workers confirmed that the effect of breast milk in reducing NEC is dose-dependent.[46–49] These studies showed that every 100 mL/kg increase in HM feeding during the first 2 weeks after birth reduced the subsequent risk of NEC or death (hazard ratio) by 0.87. Mavis et al.[45] reported focusing primarily on using exclusively HM, including HM-based fortifiers, and prioritizing MOM in infants born at less than 30 weeks' gestation reduced the incidence of NEC from 19.5 to 6%. In a systematic review, Anantham and her colleagues[50] showed that fortification with HM fortifier reduced the risk of NEC ≥ stage II and surgical NEC when compared with BM fortifier.
    ii) *Judicious use of donor HM*: There is enough literature to support the fact that donor HM remains the second-best choice when a MOM is not available. Quigley et al.[51,52] compared formula vs donor HM feedings in 1809 preterm and low-birthweight infants; the systemic review and meta-analysis showed that donor HM reduced the risk of NEC when compared with preterm formula. A meta-analysis of randomized controlled trials (RCTs) done by Altobelly et al.[53] showed a risk reduction of NEC vs HM to formula to 0.62 (0.42–0.93). The OptiMoM trial by O'Connor et al.[54] showed a statistically significant reduction in surgical NEC in the group receiving donor milk with HM-based fortifier group compared with those fed with formula. In another study, Lucas and Cole[55] showed that confirmed NEC was

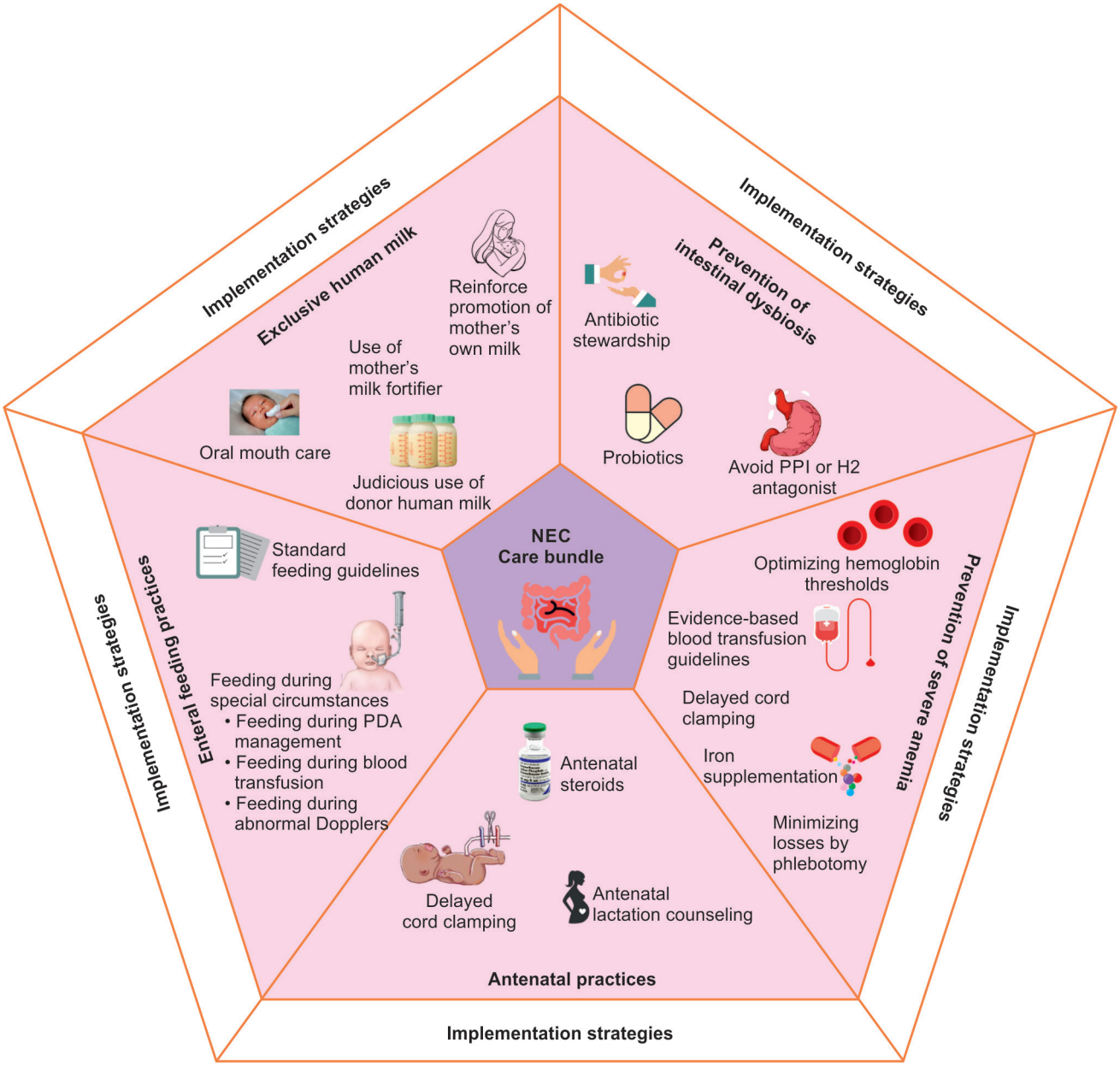

Fig. 1: NEC care bundle—an effort toward zero-NEC

6–10 times more frequent than that in exclusively formula-fed babies than in those fed HM alone and three times more common than in those who received formula plus HM. Cristofelo et al.[56] performed a RCT and showed that a higher risk of surgical NEC in extremely premature babies on formula feed vs HM feedings. Sullivan et al.[57] further found a 50% reduction in NEC and surgical NEC of nearly 90% in infants fed an exclusive HM diet compared with a diet containing BM-based products. In another study, Allana et al.[58] showed that donor HM in a community with restricted access to HM facilitated earlier commencement of enteral feeding with less NEC. However, some studies suggest that the benefits of HM still might be questionable, particularly for surgical NEC.[59]

iii) *Oral colostrum care*: HM colostrum is a rich source of proteins, immunoglobulins, minerals, and fat-soluble vitamins.[7] However, for various reasons, the availability of colostrum in adequate volumes for feeds is unavailable for extremely premature infants. Several studies support the use of colostrum for oral care as immunotherapy. A meta-analysis of RCTs showed the efficacy of this oral colostrum therapy (OCT) in the prevention of NEC.[60] A recent meta-analysis of eight RCTs showed that buccal application of colostrum increased IgA levels and reduced incidence of NEC.[61] However, there was no significant difference in the incidence of NEC in 4 RCTs with 148 subjects. There is a need for further study.

2. Enteral feeding practices

i) *Standardized enteral feeding protocol*

The standardization of feeding protocols (SFP) is an effective structured approach that requires physicians to follow

specified criteria to initiate, advance, fortify, or stop feeding. Standardization of feeding protocols is considered the most simple and effective method for improving nutritional care and reducing the risk of NEC in preterm neonates In 2015, a systematic review based on 15 observational studies[62] concluded that SFPs significantly decreased the incidence of NEC. The results remained statistically significant even after comparing studies in two meta-analyses (1978–2003 vs 2004–2016).[62] The authors also suggested that early introduction and advancement of enteral feeding do not increase the risk of NEC but helped prevent NEC. In 2017, Gephart et al.[9] reviewed studies and showed lower/unchanged rates of NEC when a SFP was used. A similar retrospective observational study[63] showed a decreased incidence of NEC stage II when unit-specific SFPs were used. All NICUs should adopt SFPs to ensure timely initiation and advancement of feedings even though these SFPs might vary widely; the following approaches have been used:[7,9] (a) preferred and onset of feeding substance; (b) advancement of feeding; (c) time and type of fortification; (d) conditions to hold and specified indications on when to resume feeding; (e) management of feeding intolerance; and (f) initiation and duration of trophic feedings.

ii) *Feeding during special circumstances*

- *Feeding guidelines in infants with abnormal Dopplers:* Umbilical Doppler flow abnormalities occur in 6% of high-risk pregnancies.[64,65] Antenatal Doppler disturbances are associated with fetal hypoxia, inducing brain-sparing vascular redistribution and compromising splanchnic circulation. This may reduce the thickness of the intestinal wall, villous length and weight, and crypt depth, which leads to dysregulation of motor, secretory, and mucosal functions predisposing to stasis and dysbiosis leading to feed intolerance and NEC. The persistence of circulatory changes in the superior mesenteric artery (SMA) and celiac axis even after birth, causes further concerns.[66] Neonates with AREDF (absent/reversal of end-diastolic flow) are twice at risk of NEC as infants with normal Dopplers.[66] Minimal enteral nutrition (MEN) should be started in all preterm infants with abnormal Dopplers. ADEPT (abnormal Doppler enteral prescription trial) randomized 404 infants to early feeding (24–48 hours) or late feeding (120–144 h) and found no difference in the incidence of NEC or sepsis.[67] Similarly, other studies suggest that delayed introduction of feeds in neonates with AREDF was associated with increased morbidities in neonates.[68] While advancing feeds, the ADEPT trial demonstrated continuing MEN for 2–3 days for <1000 gm, while >1000 gm received progressive feeds from postnatal day 2. A recent systemic review with 1499 preterm infants concluded that with early feeding initiation, there was a trend toward an increase in rates of feeding intolerance; however, the incidence of NEC did not increase.[69] The rate of advancement of feeds has wide variability. Evidence suggests that it is safe to increase feeds by 30–35 mL/kg/day in stable preterm neonates.[70] A randomized trial from India in infants weighing 1000–1499 gms has also shown that those in the rapid feeding advancement group (30 mL/kg/day) achieved full volume feedings significantly earlier than the slow advancement group (median 7 days vs 9 days) ($p < 0.001$), had fewer days of intravenous fluids (median 2 days vs 3.4 days) ($p < 0.001$), shorter length of stay in hospital (median 9.5 vs 11 days; $p = 0.003$), and regained birth weight sooner (median 16 vs 22 days) ($p < 0.001$). There was no difference in the number of infants with apnea and feeding intolerance intolerance.[71]
- *Feeding during management of patent ductus arteriosus (PDA):* The presence of hemodynamically-significant PDA (hs-PDA) poses a challenge in feeding premature infants due to the increased risk of gastrointestinal complications. In the presence of a ductal shunt, there might be a significant diminution of splanchnic perfusion and oxygenation depending on the magnitude of the left-to-right shunt volume through PDA. This "steal" phenomenon predisposes premature infants to feed intolerance and NEC. Furthermore, pharmacotherapy for the treatment of PDA with indomethacin, ibuprofen, and more recently, acetaminophen/paracetamol makes it more challenging as these pharmacological agents have been associated with gastrointestinal side effects like vasoconstriction of the SMA and consequent reduction in intestinal perfusion.[65,72] Although ibuprofen does not reduce gut perfusion, its high osmolality has caused concerns for gastrointestinal bleeding, NEC, and bowel perforation. Having said this, other studies have suggested that infants receiving trophic feeds during pharmacotherapy with indomethacin and ibuprofen required less time to reach full feeds and did not increase the incidence of NEC.[73,74] Again, the evidence to suggest that the hs-PDA and the benefits of continuing vs withholding feeding during pharmacological treatment of PDA are controversial. Due to a lack of sufficient data, it is difficult to standardize feeding guidelines during the pharmacological treatment of PDA in preterm infants and should be individualized as per the clinical and hemodynamic status of the infant.[75] In infants who undergo surgical closure of hs-PDA, the risk of composite adverse outcomes including mortality, intraventricular hemorrhage grade 3 or 4, periventricular leukomalacia, severe retinopathy of prematurity, bronchopulmonary dysplasia, or NEC stage II or III in preterm infants may be higher.[76] Studies have also highlighted that the timing of PDA ligation after 2–3 postnatal weeks may be associated with delayed in the achievement of full enteral feedings and higher incidence of NEC.[77,78] Similarly, there may be a higher incidence of post-ligation cardiac syndrome (PLCS), characterized by hypotension requiring cardiovascular support, oxygenation failure, and assisted ventilation.[78] However, the causal relation between PLCS and the risk of GI complications is not yet clearly defined.
- *Feeding during blood transfusions:* Apart from various known risk factors, NEC has increasingly been associated with packed red blood cell (RBC) transfusions. Transfusion-associated NEC (TANEC) is a clinical condition characterized by the development of NEC (Bell's stage II and above) within 48 hours of RBC transfusion.[79] Despite the plausibility of the association and strong preclinical evidence between

PRBC transfusion and NEC, the clinical evidence supporting a causal relationship remains uncertain.[80–82] The RCT, feeding during red cell transfusion (FEEDUR),[83] compared different regimens of feeding during transfusion and found no difference in the splanchnic oxygenation, when during transfusion, enteral feeds were either withheld, continued, or restricted. Another meta-analysis including RCT and quasi-randomized control trials was inconclusive in stopping feeds while blood transfusion in preterm infants to prevent TANEC.[84] Another multicenter RCT, WHEAT (withholding enteral feeds around packed cell transfusion) is underway to provide new insights and clarity.[85] Though retrospective studies have shown an association between transfusion of PRBC and NEC, RCT evidence is insufficient to recommend feeding guidelines during transfusion.[84] Continuing MEN during RBC transfusions is recommended and needs larger studies to devise feeding strategies during red cell transfusion.

3. Prevention of intestinal dysbiosis
   i) *Antibiotic stewardship:* Premature infants and infants with co-morbidities are highly susceptible to infections; antibiotics are a cornerstone for neonatal care. However, non-specific presentation and lack of sensitivity and specificity value make unnecessary overuse of antibiotics, which is linked to adverse outcomes like NEC, sepsis, fungal infection, and mortality.[86,87] As prior bacterial infections are a known risk factor for NEC, there have been two schools of thought-prophylactic antibiotic usage for prevention of NEC and restrictive use of antibiotics to prevent intestinal dysbiosis and NEC.[88] A few RCTs such as the ones conducted by Tagare et al.,[89] Kenyon et al.,[90] and Owen et al.[91] concluded that there is no role of routine antibiotic use in the prevention of NEC. Moreover, a meta-analysis by Fan et al.[92] included 9 RCTs and retrospective cohort studies; they analyzed 5207 preterm infants but found no role of prophylactic antibiotics in the prevention of NEC in high-risk preterm infants. Other studies, actually show some evidence to suggest that prolonged use of empirical antibiotics might increase risk of NEC. Cotton et al.[93] showed that empirical use of antibiotics for more than 4 days in culture-negative sepsis increased the risk of NEC or death in extremely low birth weight infants. Implementing antimicrobial stewardship programs is a core element outlined by the Centers for Disease Control and Prevention (CDC) to promote thoughtful antibiotic use in NICUs. These programs advocate for targeted therapy with reduced duration and unnecessary consequences of antibiotic misuse. A multicenter study has demonstrated a 34% reduction in antibiotic use with implementation of antimicrobial stewardship guidelines.[94]
   ii) *Avoid using histamine-2 receptor antagonists (H2-receptor blockers) and PPIs:* Use of H2-receptor blockers and PPIs can alter the intestinal flora and consequently, increase the risk of NEC.[95–99] H2-blockers and PPIs make the gastric pH alkaline, increase the risk of gastrointestinal infections, especially with Gram-negative bacteria,[100] and also increase intestinal motility and contractility, which could all increase the risk of NEC.[101] Guillet et al. concluded in their case-control study that there is an increased risk of NEC (>Bell's stage II) with the use of H2 blockers.[95] In a multicenter trial, Terrin et al.[102] showed a 6.6-fold increase in the risk of NEC with the use of H2-blockers. A systematic review and meta-analysis of three observational studies further supported this association.[103]
   iii) *Probiotics*: These are live microorganisms that can confer health benefits to the host when administered in adequate amounts.[104] Probiotic bacteria prevent gut dysbiosis, an imbalance between pathogenic and commensal microbes, which is a predisposing factor for both NEC and late-onset sepsis (LOS) in VLBW infants.[105–108] Dysbiosis can predispose the premature gut to a pro-inflammatory state, with increased cytokine production and altered immunomodulation.[109] The administration of probiotics has been evaluated with >50 RCTs and >10,000 participants.[110] In a systematic review and meta-analysis of preclinical studies, Athalye-Jape et al.[111] included a total of 29 RCTs (Rats: 16, Mice: 7, Piglets: 3, Quail: 2, Rabbit: 1; N~2,310), and concluded that probiotics significantly reduced NEC via beneficial effects on immunity, inflammation, tissue injury, gut barrier, and intestinal dysbiosis. The 2023 Cochrane review by Sharif et al. included 60 randomized control trials with 11,156 preterm infants. They showed that probiotics may reduce the risk of NEC in preterm VLBW infants (RR: 0.54, 95% CI: 0.46 – 0.65; I^2 = 17%; 57 trials, 10,918 infants; Certainty of evidence/CoE: low). The number needed to treat for an additional beneficial outcome (NNTB) was 33 (95% CI: 25–50). In the ELBW population, limited data show that probiotics may have little or no effect on NEC (RR; 0.92, 95% CI: 0.69–1.22, I^2 = 0%; 10 trials, 1836 infants; CoE: low). Given the low to moderate CoE for probiotic supplementation effects on the risk of NEC and associated morbidity and mortality, the authors recommended further large, high-quality trials to provide evidence of sufficient validity and applicability to inform policy and practice.[112] Deshmukh et al.[113] included 30 good-quality non-RCTs (n = 77,018) from 18 countries. The meta-analysis showed that routine probiotic supplementation was associated with reduced NEC ≥ Stage II. Subgroup analysis showed decreased NEC ≥ Stage II (4.5% compared with 7.9%) in ELBW infants supplemented with probiotics. Multi-strain probiotics (MSP) were more effective than single strains.[113]

   Wang et al.[114] assessed the comparative effectiveness of alternative prophylactic strategies (including probiotics) for preventing mortality and morbidity in preterm infants through an NMA (network meta-analysis) of RCTs. A total of 106 trials involving 25,840 preterm infants were included. Only MSP were associated with reduced all-cause mortality compared with placebo or in combination with oligosaccharides; these were effective interventions to reduce severe NEC (NEC ≥ stage II). Combination products, including single- and MSP combined with prebiotics or lactoferrin, were associated with reduced morbidity and mortality.[114]

   Morgan et al.[115] performed another NMA and noted that the combination of one or more *Lactobacillus* spp. and *Bifidobacterium* spp. was associated with decreased all-cause mortality. In another such study, Beghetti

et al.[116] examined 51 RCTs (10,664 infants, 29 probiotic interventions). Thirty-one studies (19 different probiotic regimens) were suitable for subgroup analysis according to type of feeding. In the overall analysis, *L. acidophilus LB* was the most promising strain for reducing NEC risk. Subgroup analysis showed that *B. lactis Bb-12/B94* reduced the risk of NEC stage ≥ 2 in both feeding type populations, with a discrepancy in the relative effect size in favor of exclusively HM-fed infants.

Thomas et al.[117] identified probiotic strains with maximum benefit in preventing neonatal mortality, sepsis, and NEC using Bayesian NMA. Twenty-nine RCTs enrolling 4,906 neonates and evaluating 24 probiotics were included. All studies compared probiotics with a placebo; none had a head-to-head comparison of different probiotic species. Compared with placebo, the combination of *B. longum, B. bifidum, B. infantis*, and *L. acidophilus* may reduce the risk of NEC (RR: 0.31; 95% CI: 0.10–0.78; CoE: uncertain). A single probiotic species, *B lactis*, may reduce the risk of mortality (RR 0.21; 0.05–0.66) and NEC (RR 0.09; 0.01–0.32; CoE: low). However, given the low to very low certainty of evidence, no firm conclusions were made on the most optimal probiotics for use in preterm neonates in low- and middle-income countries.[117]

In the most recent systematic review in the Cochrane library, Sharif and co-workers[112] presented current evidence on the protective effects of probiotics against NEC in very preterm (born at ≤32 weeks' gestation) and very low-birthweight infants. They found 60 trials with 11,156 infants; most of these studies were small (median sample size 145 infants) with some design flaws that might have biased their findings. The most common preparations contained *Bifidobacterium* spp., *Lactobacillus* spp., *Saccharomyces* spp., *and Streptococcus* spp., alone or in combination. Probiotics were generally seen as safe. However, the authors were very cautious in drawing inferences about benefit. Probiotics may reduce the risk of NEC (RR 0.54, 95% CI: 0.46–0.65; I^2 = 17%; 57 trials, 10,918 infants; low certainty). The number needed to treat for an additional beneficial outcome (NNTB) was 33 (95% CI: 25–50). Probiotics probably reduce mortality slightly (RR 0.77, 95% CI: 0.66–0.90; I^2 = 0%; 54 trials, 10,484 infants; moderate certainty); the NNTB was 50 (95% CI: 50–100). Probiotics probably have little or no effect on the risk of late-onset sepsis (RR 0.89, 95% CI: 0.82–0.97; I^2 = 22%; 49 trials, 9876 infants; moderate certainty). Probiotics may have little or no effect on neurodevelopmental impairment (RR 1.03, 95% CI: 0.84–1.26; I^2 = 0%; 5 trials, 1518 infants; low certainty).

The data from extremely preterm or ELBW infants were limited. In this population, probiotics may have little or no effect on NEC (RR 0.92, 95% CI: 0.69–1.22, I^2 = 0%; 10 trials, 1836 infants; low certainty), all-cause mortality (RR 0.92, 95% CI: 0.72–1.18; I^2 = 0%; 7 trials, 1723 infants; low certainty), or late-onset invasive infection (RR 0.93, 95% CI: 0.78–1.09; I^2 = 0%; 7 trials, 1533 infants; low certainty). No trials provided data for measures of neurodevelopmental impairment in extremely preterm or ELBW infants.

The authors opined that the methods used in the included trials may have exaggerated the benefits of giving probiotics to very preterm and VLBW infants. The effects could have been biased by a small number of subjects in these trials and unreliable methods. They suggested a need for caution; further evidence is needed before drawing firm conclusions about the benefits of altering the natural temporal changes in gut microbial flora.

Instead of extrapolating information from the West, we might need specific evaluation of probiotics in tropical/peri-equatorial climates. Increasing information suggests that the bacterial strains causing neonatal sepsis/inflammatory illnesses in these warmer regions might differ from those in the temperate zones.[118] In tropical regions, Gram-negative bacteria seem to be a notable component of the vaginal flora and the patterns of bacterial colonization in the neonatal intestine might differ from those in the West. Padhi et al.[119] evaluated 15 studies in a random-effects meta-analysis; Gram-negative bacteria constituted 23.2% (95% CI: 11.77–37.08, I^2 = 99.79%) of the flora in the birth canal. In a systematic review, Zelellw et al.[120] have shown that in the warmer regions, early-onset neonatal sepsis is often caused by Gram-negative pathogens such as *E. coli* and *Klebsiella*, whereas late-onset neonatal sepsis is frequently caused by Gram-positive organisms like *Staphylococcus* spp. and *S. pneumoniae*. We hence, we need to be cautious when drawing inferences about the impact of probiotics across different climatic regions.

Position Statements of Committees

In 2023, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Special Interest Group on Gut Microbiota and Modifications provided updated recommendations for the use of probiotics for the management of NEC. Clinicians may recommend *L. rhamnosus* alone at a dose of $1–6 \times 10^9$ colony-forming units (CFU) or a combination of *B. infantis, B. lactis*, and *S. thermophilus* (dose: $3–3.5 \times 10^8$ CFU of each strain) while citing the importance of product quality control for safety (CoE: low).[121]

In 2020, the American Gastroenterological Association recommended a combination of *Lactobacillus* spp. and *Bifidobacterium* spp. for NEC prevention in preterm infants. They compared this regimen with another with no or other probiotics in preterm infants (CoE: moderate).[122] In 2012, the American Pediatric Surgical Association Committee review recommended probiotics to decrease the incidence of NEC in preterm LBW infants.[123]

4. Adequate management of anemia

Anemia is the most common hematopathological condition seen in preterm infants. It is observed that almost 100% of extremely preterm and 94.6% of very preterm infants developed anemia.[124] Neonatal anemia relates to intestinal injury in preterm infants.[125] In a murine model, RBC transfusions caused NEC-like intestinal damage in severely-anemic, but not in non-anemic controls; the severity of bowel injury was proportional to the degree and duration of anemia.[126] Many human studies have shown a similar association between the severity of anemia and the risk of NEC following transfusions.[127,128] Even though the activation of inflammatory macrophages by free circulating hemoglobin is the best-supported mechanism, many other possibilities have been considered: (i) activated T-crypt antigen, which results in the use of washed blood components;[129] (ii) hypoperfusion-reperfusion

injury and chronic anemia; (iii) enteral nutrition resulting in splanchnic ischemia during RBC transfusions; and (iv) extended RBC storage that may enhance RBC adhesion and reduce nitric oxide in these cells.[79]

RBC transfusions are very frequently administered in severely anemic infants; around 40% of VLBW infants and 80% of extremely low-birthweight infants require at least one blood transfusion before discharge.[79] Despite these transfusions being a life-saving intervention, it was found to be associated with a higher incidence of complications such as NEC. Transfusion-associated NEC (TANEC) is a clinical condition characterized by the development of NEC (Bell's stage II and above) within 48 hours of RBC transfusion.[130] Around 20–35% of all NEC cases are associated with transfusions.[126] TANEC typically occurred at a later age when compared with NEC which is unrelated to blood transfusions.[81] Transfusion-related immune triggers, impaired intestinal blood flow from severe anemia, and ischemia-reperfusion injury are some factors that might increase the risk of TANEC.

(i) Prevention and management strategies for anemia
- *Optimizing hemoglobin thresholds for transfusions*: Studies are needed to determine the optimal hemoglobin thresholds for transfusion in preterm infants to balance the benefits of correcting anemia with the risks of transfusion-related complications, including NEC;[131]
- *Delayed cord clamping*: Delayed cord clamping (DCC), a practice that allows placenta-to-neonate transfusion at birth, allows the passive transfer of blood from the placenta to the newborn infant. DCC can help prevent severity of anemia during the neonatal period and the need for RBC transfusions.[132] Such interventions might be particularly important in regions with higher frequency of nutritional anemia, such as due to iron deficiency, in pregnant mothers.[133]
- *Minimizing losses from phlebotomy*: Blood loss due to repeated phlebotomy is considered one of the major causes of anemia in preterm infants. In critically ill neonates, the blood volumes removed during the 1st few weeks of life may be as much as 58% of the total blood volume.[134] In one study, the blood draws for laboratory testing in the NICU were 19% higher than what the hospital laboratory had requested; the authors suggested that using tubes with explicit markings could help prevent these over-draws.[135] In ELBW infants, point-of-care analyzers can reduce the mean volume of RBC transfusions by 43%.[136]

(ii) Characteristics of blood products
To minimize the transmission of the cytomegalovirus and to prevent transfusion-associated graft vs host disease in infants weighing less than 1200 gms, RBC transfusions for premature infants should be leukocyte-depleted and irradiated, respectively.[137]

(iii) Iron supplementation
Enteral iron supplementation is recommended once infants are on full enteral feedings to prevent iron deficiency anemia and reduce the need for blood transfusions. Preterm newborns should begin receiving 2–3 mg/kg of elemental iron per day starting at the age of 2 weeks, and newborns receiving exogenous erythropoietin should receive up to 6 mg/kg of iron according to ESPHGAN guidelines on enteral nutrition in preterm neonates 2022.[138]

5. Antenatal practices
   (i) Antenatal Steroid–Antenatal corticosteroids (ACS): These are an effective intervention for improving outcomes for preterm neonates. Steroids confer benefits by crossing the placenta and accelerating the structural maturation of many vital organs.[139] The administration of ACS to a woman at risk of imminent preterm birth is strongly associated with decreased neonatal morbidity and mortality. A recent Cochrane review showed that ACS can significantly lower the incidence of respiratory distress syndrome (relative risk [RR], 0.85; 95% confidence interval [CI], 0.77–0.93), intracranial hemorrhage (RR, 0.58; 95% CI, 0.45–0.75), neonatal death (RR, 0.78; 95% CI, 0.70–0.87), and NEC (RR, 0.50; 95% CI, 0.32–0.78) in the newborn infant.[140] In NEC, ACS can reduce both the incidence and morbidity; the mechanisms are unclear. One possibility is accelerated maturation of the intestinal mucosa;[141,142] Israel et al.[143] have shown in an animal model that ACS accelerated the maturation of the git mucosal barrier with lower intestinal permeability, reduced uptake of macromolecules, and consequently, decreased bacteria translocation.
   (ii) Delayed cord clamping (DCC): Delayed cord clamping is defined as umbilical cord clamping delayed for at least 30–60 seconds after birth.[144] It allows the placental transfusion of oxygenated blood into newborns. In preterm infants, DCC can reduce the need for blood transfusion, the severity of respiratory distress syndrome, NEC, and intraventricular hemorrhage.[145] During the early postpartum period, DCC can prevent transitional phase hypovolemia and fluctuations in cardiac output and promote hemodynamic stability.[146,147] DCC may reduce the risk of NEC by preventing severe anemia and the need for transfusions.[127] These effects were also seen in a systematic review (RR 0.59, 95% CI: 0.37), although the findings might be less important as the age of onset of NEC becomes progressively more delayed in premature infants.[148] There is a need for large high-quality trials, with sufficient power to reliably assess the role of DCC in the prevention of NEC. As mentioned above, DCC might be very important in the less-advantaged parts of the world.[133]

Implementation Science

To improve the clinical outcomes in ICUs, the bundle approach can be an effective strategy.[149–151] However, a high level of compliance with the care bundles is essential. We still do not know the most optimum timing and sequence in which these bundles can be implemented in NICUs. Implementation science focuses on various strategies that might be recommended to improve standardization of care bundles across multiple ICUs, with an eventual goal of consistent application of best practices and reduction in variation. A number of ways have been described in the literature to improve the compliance of care bundles.[152,153] Both single and multifaceted strategies have been used.[150,154] One of the most important interventions to improve the implementation of care bundles was an improvement of the organizational culture,[150] including senior leaders, team leaders, and frontline staff. This model facilitated change in the management to execute the planned intervention.

Table 1: Strategies to improve standardization of an NEC care bundle

1. Exclusive human milk feeds	• Antenatal and postnatal lactation counseling • Breastfeeding education, training, handouts, video-based learning • Maintaining daily records and frequent reminders of milk expression • Encouraging expression of MOM during nights as these milk samples contain more fats and hence, caloric content • Early and frequent pumping, educating about hands-on pumping, manual and electrical pumps • Mother and nurse champions supporting MOM • Colostrum collection kits in the labor room for OCT
2. Standard enteral feeding practices	• Formatting an evidence-based standardized enteral feeding guidelines of the unit • Adherence to the feeding protocol in general and specific circumstances like PDA, blood transfusion, and Doppler abnormalities • Standardized protocols for holding feedings in infants with feeding intolerance
3. Prevention of intestinal dysbiosis	• Antibiotic Stewardship – Prevention of prolonged use of empiric antibiotics, limiting empirical use of antibiotics only to infants with risk factors for sepsis, treatment guided by antibiotic susceptibility in culture reports • Avoid using proton pump inhibitors and H2 blockers • Judicious use of probiotics • Involving a nurse and a pharmacist in maintaining daily logs and feedback loops
4. Adequate management of anemia	• Optimizing hemoglobin thresholds for transfusion • Delayed cord clamping • Minimizing phlebotomies in NICU • Preference for leukodepleted and irradiated blood products • Enteral iron supplementation • Observation for transfusion-associated organ injury
5. Antenatal practices	• Antenatal steroids • Delayed cord clamping

Table 2: Grade description for quality of evidence

Grade	*Description for evidence*	*Certainty of evidence**
A	Strong – Consists of studies from strong research	High
B	Moderate – Consists of studies of strong research design but there are inconsistencies in results, generalizability, and/or risk/bias	Moderate
C	Weak – Studies show inconsistent results and there are serious concerns with conclusions, generalizability, and/or risk/bias	Low
D	A conclusion is either not possible or limited: evidence is unavailable and/or is of poor quality and/or is contradictory	Very low

*Quality of evidence classified as:

– I: Systematic review with meta-analysis of homogeneous randomized controlled trials (RCTs)

– II: Well-designed RCTs meta-analysis of non-homogeneous RCTs

– III: Cohort or quasi-experimental trials

– IV: Descriptive

– V: Expert opinion or consensus

Additional lower-case letters are used as follows: a, good quality and b, lesser quality.

Following this, a systematic review including 47 studies was done by Borgert et al.[155] and concluded that education, reminders, audits, and feedback are important strategies to implement successful care bundles. Further work is needed to develop protocols and optimize the implementation.

Conclusion

The care of premature and critically ill infants requires the implementation of multiple interventions in a timely fashion. As has been seen in multiple RCTs, many interventions have statistically significant benefits, but the effect size is often small. There is a risk that the benefits accrued from a few appropriately-applied interventions could be nullified if some others are not. Hence, the strategy of developing care bundles might be useful. In the following Tables 1 to 3, we have summarized the information provided to standardize the five interventions to reduce the incidence and severity of NEC.

Summary of Recommendations with Evidence

The Neonatal Gut Health group utilized the grading of recommendations, assessment, development and evaluation

Table 3: Summary of recommendation

Recommendation	*Description*	*Grade*	*Quality of evidence*
Exclusive mother's own milk (MOM)	Providing exclusive MOM as first choice of milk for all the preterm infants	A	Ia
Donor human milk	To be used as second-best source of milk for preterm infants if MOM is unavailable	A	Ia
Antenatal corticosteroids	Administration of antenatal corticosteroids to all the mothers expectant of delivery ≤$34^{+6/7}$ weeks of gestation	A	Ia
Oral colostrum care	Use of colostrum for oral care as immunotherapy	B	IIb
Probiotics	*Lactobacillus – Bifidobacterium* combination	B	Ib
Standardized feeding guidelines	Implementation of evidence-based guidelines in the neonatal unit	B	IIIa
Prevention of severe anemia	Using antenatal and postnatal precautions and standardized blood transfusion protocols to prevent anemia	C	IIIa
Avoid H2 blockers and proton pump inhibitors	Histamine blockers and proton pump inhibitors increase the risk of NEC	C	IIIb
Antibiotic stewardship	Avoid prolonged use of empirical antibiotics (>36 hours in full-term and >48 hours in preterm infants)	C	IIIa
Avoid use of cow's milk protein fortifiers	Use of human milk fortifier is preferred over cow's milk fortifier	C	IIb
Holding feeds during blood transfusion	Holding plain and/or hyperosmolar (fortified) feedings during/around the time of transfusions	D	IIIb
Delayed cord clamping	Prevention of anemia and the need for transfusions	D	IIIb

(GRADE) system[156] to explain the level of evidence of various risk factors of NEC.[157]

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ORIGINAL RESEARCH

Concerns about Mis-/Overuse of Antibiotics in Neonates Born at ≤32 Weeks Gestational Age in Latin American Neonatal Units: Eight Years of Experience in the EpicLatino Database

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Abstract

There is considerable variability in the duration of antibiotic in neonatal intensive care units (NICUs) all over the world and is highly dependent on gestational ages (GA). It is difficult to withhold antibiotics in critically ill preterm infants because the possibility of infection is difficult to exclude in these patients and the acuity of illness can progress rapidly with potentially disastrous consequences. Available data encouragingly suggest that the incidence of early onset sepsis (EOS) might be lower in EpicLatino units in Latin America compared with Canadian research network (CNN) in 2022 in <30 weeks, but late onset sepsis (LOS) is more frequent at different GA. However, there is an overall scarcity of detailed information from many countries. The annual reports from EpicLatino database do show a high degree of variability in outcomes and a need for cautious interpretation of these figures. However, we still need to establish clear standards for antibiotic use in premature infants; these drugs are essential for combating infections and saving lives but mis-/overuse can exacerbate the risk of late-onset infections, necrotizing enterocolitis (NEC), bacterial resistance, and increase the cost of care. In this study, we aimed to find information on the patterns of antibiotic use in infants born at ≤32 weeks' gestation in the EpicLatino units during the period 2015–2022. A specifically designed questionnaire was sent to unit medical directors to determine whether the total antibiotic use per unit per 1,000 patient-days correlated with the incidence-rate ratios. This is a data-collecting/descriptive study that it will help us in designing further efforts and choosing the sites for intervention.

Keywords: Antibiotics per 1,000 patient-days, Antibiotic use practices, Baby, EpicLatino database, Infant, Latin America and the Caribbean, Mortality, Neonatal intensive care units, Neonatal outcomes, Neonates, Newborn, Premature neonates.

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Key Points

- The utilization of antibiotics in neonatal intensive care units (NICUs) in patients ≤32 weeks gestational age (GA) at birth worldwide shows considerable variability across countries and its study is constrained by ethical and practical limitations that impede comprehensive investigation.
- Antibiotics might be essential for treatment of premature and critically ill infected infants, but over-/misuse of these drugs can exacerbate the risk of late-onset infections, necrotizing enterocolitis, infections with resistant bacterial strains, and increase the cost of care.
- We need to establish clear parameters to guide antibiotic use in patients ≤32 weeks GA at birth, based on severity-of-illness and positive blood or cerebrospinal fluid cultures.
- In this study, we examined the data in the EpicLatino database to compare antibiotic use in patients ≤32 weeks GA at birth at different NICUs. This database helped obtain a statistically relevant sample, more than the numbers we could find in individual units.
- We aggregated antibiotic days per 1,000 patient-days for each unit in patients ≤32 weeks GA at birth over an extended period of 8 years. A logistic regression analysis was performed to identify the most critical factors. Data from the unit with the best results were used as the baseline.

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Introduction

Antimicrobial agents are one of the most frequently prescribed class of medications in NICUs.[1] A point prevalence study across 29 NICUs, Clark et al. revealed that 47% of infants were receiving at least one antibiotic at the time of data extraction.[2] In 2021, a global assessment of antimicrobial agents prescribed to NICU infants found that 26% of infants across 84 NICUs from 29 countries received at least one antimicrobial agent. The most common reasons for antibiotic use were "rule-out" sepsis (32%) and "culture-negative" sepsis (16%). Antibiotic use remained frequent and prolonged regardless of culture results, with units employing step/down programs showing reduced antibiotic usage.[3] Critically ill preterm infants pose a challenge for withholding antibiotics due to the difficulty in excluding infection, potentially leading to rapid progression of illness if untreated.[4]

In high-income countries, blood cultures confirmed early/late-onset infection (early were defined as early those seen within the first 72 hours after birth and late thereafter), in 0.4–0.8/1000 term infants.[5–8] While antibiotics may be life-saving for infants with culture-negative sepsis, culture-negative presumed sepsis significantly contributes to high antibiotic consumption in NICUs.[8,9] Antibiotics may be life-saving for a few infants who actually have culture-negative sepsis.[10] Nevertheless, the statistics in culture/negative sepsis is problematic since there is no way to confirm that those patients did have bacterial sepsis, and most units will complete full curse assuming it was a bacterial sepsis. There are concerns that overuse of broad-spectrum antibiotics can promote colonization with antibiotic-resistant bacteria.[11,12]

The management of neonates born at >36 weeks' gestation with suspected or proven early onset bacterial sepsis has changed dramatically in the last decades.[13] New tools like the Kaiser Permanente neonatal early onset sepsis (EOS) risk calculator and NICE guideline for full term based on incidence in each unit, has been useful to decrease the antibiotic use identifying asymptomatic cases.[14,15] However, the diagnosis of EOS in babies <36 weeks are more challenging, and delivery characteristics of extremely preterm infants present an opportunity to identify those with a lower risk of EOS and may inform decisions to initiate or extend antibiotic therapies.[16]

The EpicLatino database originates data from Latin American units from middle-income countries with culture laboratory facilities. The conventional categorization of medical literature into high-income (HIC) and low-to-middle income (L/MIC) is inconvenient for middle-income countries due to statistical disparities.[17] The EpicLatino database comprises units sharing common Spanish ancestry, language, Catholic religion, history, customs, and values, making it an ideal source for statisticalanalysis.

Although EpicLatino shows lower relatively lower rates of EOS than in other peri-equatorial/tropical regions in the world, caution is warranted due to limited site representation and the need for careful interpretation.[18,19] The belief that blood cultures may confirm infections in only half or less of all infants with suspected sepsis, creates important ethical and practical constraints in withholding antibiotics.[20,21] However, confirming infection solely through positive cultures remains the gold standard, since many culture-negative infections may not be caused by bacteria. It is for this reason that many studies require infections demonstrated by cultures. For example, the data of the Canadian neonatal network (CNN) from which EpicLatino was born, only count bacterial sepsis as those with a positive blood or CSF culture.[22]

We looked for information in the records in the EpicLatino database. A high degree of variability in clinical practice is readily noticeable with a need for clear standards for antibiotic use. There was a high degree of variability and a clear need for standards for antibiotic use.[23] These are essential for combating infections and saving lives, but the mis-/overuse of these drugs can also exacerbate the risk of late onset sepsis (LOS), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia, prevalence of multi-drug resistant bacterial strains, and higher costs-of-care.[24]

In the clinical setting, we often initiate antibiotics due to multiple reasons; one important factor that alters the risk-to-benefit ratio is inadequate maternal/fetal clinical information such as a suspicion of chorioamnionitis. We need consensus-based guidelines that might include acute phase reactants, positive blood or cerebrospinal fluid cultures, and others to guide the choice and duration of specific treatment. Over time, as the group gains confidence, it might be possible to tighten these protocols. A better understanding of various predisposing factors will facilitate clear and timely decisions.

Objective

In this study, we recorded the duration of antibiotic therapy and standardized these data using statistical methods. We also sought to identify the determinants of the duration of antibiotic therapy. This is an exploratory study, but these figures are extremely important for us in designing further studies/choosing sites for intervention.

Materials and Methods

We examined the EpicLatino database, which includes data from 32 units in Latin America and the Caribbean, from the period 2015–2022 (Table 1) for infants born with a GA ≤32 weeks.[25] We designed a questionnaire (Table 2) and sent it to directors of EpicLatino units to find whether the total antibiotic use per unit per 1,000 patient-days correlated with incidence rate ratios (IRRs). We included all patients in the database to avoid bias related to the severity of illness.

We used negative binomial regression with standard errors and confidence intervals (CIs) computed for IRRs to analyze comparative statistics on antibiotic days per 1,000 patient-days between units using the unit with the best results as a baseline.[26–28] Stata 18 software was used for statistical analysis. The variables used to adjust the regression analysis were NEC, GA at birth, infected patients (positive blood or cerebrospinal fluid cultures), length of stay, time-period (before/after 2020), and mortality. We reviewed other variables such as inborn/outborn, suspected chorioamnionitis, SNAPEII score, but as we found no significant difference with the use of antibiotics, we did not include them in the logistic regression so as not to lose power.

Results

Figure 1 illustrates the antibiotic usage in units compared with Unit 2, which we used as our baseline as it had the lowest number of antibiotic days per 1,000 patient-days, and sufficient case numbers. The light blue color on the graph represents the number of cases in

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Table 1: Units belonging to the EpicLatino network

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

each unit. The two numbers next to each dot represent the number of antibiotic days per 1,000 patient-days alongside the adjusted IRR and its 95% CI adjusted for the mentioned variables.

Table 3 shows the criteria used by Unit 2 to reduce antibiotic use. All units that responded to the questionnaire (representing 99.5% of records) exhibited 1–6 differences compared with the baseline unit. There was no apparent correlation between responses and IRRs for each unit. Notably, among units that perceived themselves as using few antibiotics (as indicated in the final question), the average IRR for these units was 2.4, and three of them had an IRR above 3.

Discussion

In this study, we found that there is a fair degree of variability in antibiotic administration practices in the EpicLatino units even after adjusting with a regression analysis for GA, NEC, infections (positive blood or cerebrospinal fluid cultures), length of stay, time-period (before/after 2020), and mortality. These findings suggest a potential for improvement in our clinical practice with continuing education and development of clinical care protocols to reduce regional variability. As in most retrospective studies, the gaps in data points, are an important limitation. Extending the study in a retrospective-prospective format or a completely new study might have benefits. Many new variables may need to be included such as an index for severity-of-infection. Some of the maternal factors may have to be included in more detail; we only had chorioamnionitis as a single variable in this analysis. Presumed or histopathologically proven chorioamnionitis could be differentiated even if antibiotic use in the newborn may not change the results.[29,30] Measurement of acute phase reactants in cord blood or early neonatal period could be considered.

In this study, we utilized GA rather than birth weight because this parameter is more accurately recorded in EpicLatino database. In most existing studies, gestational age at birth has been viewed as a more precise indicator of fetal maturation than birth weight.[31] In this context, newer machine learning methods could offer low-cost alternatives.[32] IUGR is a frequently seen variable and could be an independent negative confounder in many neonatal outcomes.[30,33]

To understand the practices leading to this marked disparity in the duration of antibiotic administration, our questionnaire on antibiotic use practices has identified the knowledge, attitudes, and practices as important determinants of success of such an approach in different regions.[34] We did not find a clear association with IRRs and this needs further study.[35] Units that believed they used few antibiotics may not be fully aware of their higher antibiotic usage.[36,37] On the other hand, even though antibiotic overuse and resistance are being identified ever more frequently but under-recognition of sepsis remains an issue resulting in campaigns from the World Health Organization (WHO).[38]

The phenomenon of variation in clinical practices needs study. In many cases, the variation in the utilization of health services cannot be explained by variation in patient illness.[34] Such variations can be substantial, persistent, and might be even difficult to understand in some locations. There could well be hitherto unknown, associated cultural and/or professional factors. The variations in clinical practice have been described by many investigators across many healthcare settings and these are not always easy to explain.[34,39–43] On possible reason could be the "professional uncertainty" perceived by the medical care-providers in certain situations.[40,41] These choices might get influenced by environmental circumstances and local standards.[44] Hence, application and acceptance of protocols in a consortium as large as the EpicLatino will take persistence and time.[45]

One model of medical care views three major domains to explain residual unwarranted variation: capacity (allocative decisions, organizational design, and lack of acumen), evidence (lack of adherence to guidelines, unjustified deviation of evidence base) and agency (providers' needs and preferences, lack of engagement).[48] Overall, some variation is a norm and we need to monitor its impact on outcomes. It is noteworthy that a significant number of units claim to adhere to internationally recognized concepts of good antibiotic usage practices.[49] However, some units may report their desired practices rather than actual practices.[37,50] It might be beneficial for each EpicLatino unit to explore possibilities for reducing antibiotic usage as a quality plan.[51]

Table 2: Questionnaire sent to the EpicLatino units, to correlate practice with outcomes

1. Do you initiate antibiotics in premature infants ≤32 weeks gestation as follows:
   A) Initiate antibiotics in all or almost all premature infants ≤32 weeks GA after birth due to the risk of infection?[46]
   B) Select premature infants ≤32 weeks gestation for antibiotic administration based on risk factors or laboratory tests.
2. If premature infants ≤32 weeks gestation are born outside your institution, do you manage them the same way as those born in your institution?[47]
   A) Yes
   B) No
3. If the mother has received prenatal antibiotics, do you use the same criteria to initiate antibiotics in premature infants ≤32 weeks gestation?
   A) Yes
   B) No
4. Do you take blood cultures, if possible, for all premature infants who are going to receive antibiotics?
   A) Yes
   B) No
5. If you select the premature infants to whom antibiotics will be administered at birth (skip this question if you administer them to almost all infants):
   A) Select premature infants based on risk factors
   B) Select premature infants based on laboratory results obtained within the first 24 hours
   C) Do not perform tests and rely on clinical follow-up
   D) Both A and B
6. For premature infants who undergo blood cultures:
   A) If the premature infant is stable and the blood cultures are negative, antibiotics are discontinued within 24–72 hours
   B) Despite negative results, antibiotics are often continued for 5–10 days due to a lack of confidence in the results
7. In addition to blood cultures, what laboratory tests do you use to decide whether to initiate/continue antibiotics?
   A) Complete blood count
   B) C-reactive protein
   C) Procalcitonin
   D) No tests are used to make this decision
   E) Other tests not listed
   F) A and B, or A and D

Antibiotics initiated after the second day of life:

8. If a premature infant deteriorates (increased apnea, dusky color, lethargy, persistent vomiting, abdominal distension, among others):
   A) Blood cultures are taken, and antibiotics are initiated regardless of the results of other tests, if performed.
   B) Blood cultures and other tests are taken, and antibiotics are initiated based on the results of the other tests.
   C) Antibiotics are initiated before taking blood cultures or other tests, if performed.
9. For premature infants who received antibiotics:[8]
   A) If the premature infant is stable, there have been no changes in the laboratory findings, and blood cultures are negative, antibiotics are discontinued within 24–72 hours.
   B) Despite negative blood cultures, antibiotics are often continued for more than 72 hours due to a lack of confidence in the results.
10. Duration of antibiotic treatment in premature infants ≤32 weeks gestation with positive blood cultures:[15]
    A) Antibiotics are discontinued when symptoms resolve or 2–3 days later, regardless of the treatment duration.
    B) Antibiotics are only discontinued if a new blood culture is negative and/or the previously positive laboratory tests completely normalize, regardless of symptoms.
    C) The duration depends on the type of organism.
    D) The established treatment duration in the unit is always completed (7, 10, 14, 21 days).
    E) Options C and D include our management in the unit.
11. Use of antibiotics in premature infants ≤32 weeks gestation with negative blood cultures:[15]
    A) It is common to complete the antibiotic course, even if blood cultures are negative due to a lack of confidence in them.
    B) It is uncommon to continue antibiotics with negative blood cultures, only in highly symptomatic patients or in conditions such as enterocolitis.
    C) All premature infants at a predetermined GA (<30, <28, or <26 weeks gestation) receive antibiotic regimens of 7, 10, 14, or 21 days regardless of symptoms or laboratory tests.

Use of antibiotics in your unit:

12. In your unit, do you think that:
    A) Antibiotics are used excessively.
    B) Antibiotics are used sparingly.

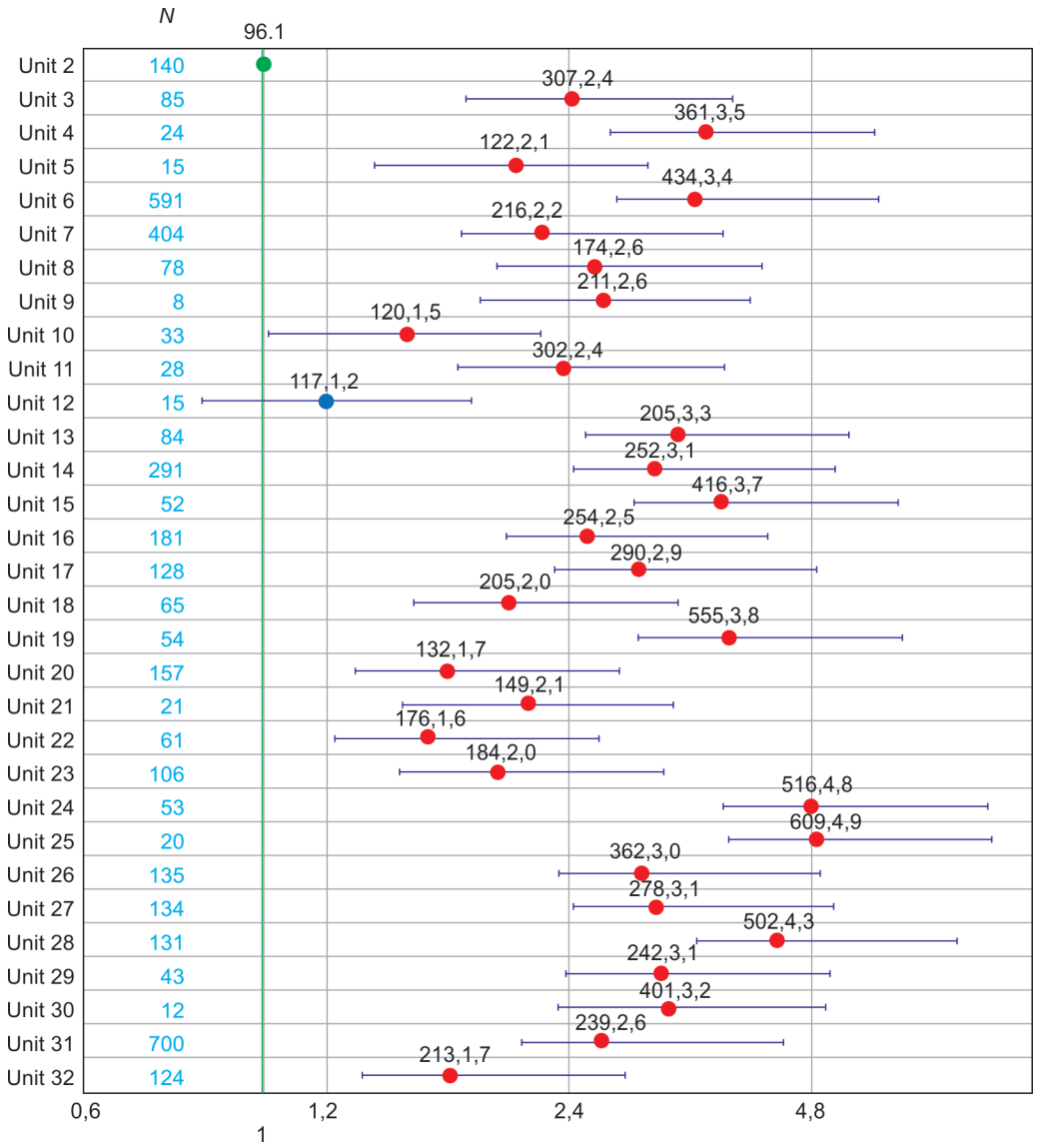

Fig. 1: EpicLatino Database 2015–2022. Premature infants ≤32 weeks GA, actual value [days of antibiotics per 1,000 patient-days (DA/P)] and adjusted incidence rate ratio (IRR) (95% CI) on logarithmic scale adjusted for GA, positive blood/CSF cultures, length of stay, NEC, time period and death

Table 3: The base unit (Unit 2 for statistical calculation) uses the following criteria to minimize antibiotic use, which served as the basis for the comparison

1.	Premature infants ≤32 weeks gestation who will receive antibiotics are selected based on risk factors and/or laboratory tests.
2.	Antibiotics are not used solely based on being born outside the institution or maternal antibiotic use.
3.	Antibiotics are only administered if clinical symptoms are present and confirmed by laboratory data (complete blood count and C-reactive protein).
4.	If the premature infant is stable and blood cultures are negative, antibiotics are discontinued within 24–72 hours, provided that the clinical picture and laboratory results allow it.
5.	If the premature infant deteriorates during their stay, tests are conducted, and a collective decision is made whether to initiate antibiotics or not.
6.	Antibiotics are discontinued when symptoms disappear or 2–3 days later, regardless of the treatment duration. Continuation of antibiotics with negative cultures is very rare.
7.	In reality, this unit genuinely uses a minimal amount of antibiotics.

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ORIGINAL RESEARCH

Predictive Validity of a Neonatal Extubation Readiness Estimator in Preterm Neonates: A Retrospective, Pilot Analysis in an Inner-city Level-3 Neonatal Intensive Care Unit

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Abstract

Background: Successful extubation of very-low-birth-weight (VLBW) infants supported with assisted ventilation is associated with lower rates of morbidity and a shorter hospital stay. In this article, we assessed the performance of an extubation readiness estimator (ERE) in VLBW infants.

Methods: We conducted a retrospective chart review including 64 intubated infants who were born at a gestational age of ≤30 weeks with a birth weight of ≤1500 gm. Our primary outcome assessed the performance of the ERE for the prediction of successful extubation using the area under the receiveroperating curve (AUROC).

Results: Fifty-three neonates were extubated successfully. Eleven of these infants had to be intubated again within 5 days of the first attempt. Forty infants had ERE scores <80%; 6 needed reintubation. Among 24 infants with ERE scores ≥80%, 5 required reintubation. The performance of the ERE tool in our population was poor (AUROC = 0.49; sensitivity 36%, and specificity 54%).

Conclusion: In our pilot study, an ERE-based approach to extubation of ventilated VLBW infants was deemed safe but could not accurately predict the transition to noninvasive ventilation. We are continuing to use clinical judgment-based extubation for now. Further studies are needed with more refined scales in larger cohorts.

Keywords: Extubation, Extubation readiness estimator, Fraction of inspired oxygen, Mean airway pressure, Neonate, Pilot study, Respiratory severity score, Spontaneous breathing test trials, Ventilation, Very-low birth weight.

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Highlights

- Very-low birth weight (VLBW; birth weight ≤1500 gm) infants contribute disproportionately to the burden of neonatal morbidity, mortality, and the cost of intensive care.
- The timing of neonatal extubation is widely based on clinical judgment. There is a need for optimized weaning protocols, methods to determine the best timing of extubation, and clear definition/criteria of extubation failure.
- In this study, we have reviewed a predictive model based on an extubation readiness estimator (ERE) scale to determine extubation readiness in extremely preterm infants.
- A total of 105 VLBW infants born at a gestational age of below <30 weeks, who were intubated and received assisted ventilation were studied. In this cohort, the ERE score using a cut-off of 80% did not accurately predict extubation success.
- We are aware that the study is not adequately powered and so it should be viewed only as a pilot report. However, the comparisons did not harm and have justified a larger, hypothesis-based study.

Introduction

Very-low birth weight (VLBW, birth weight ≤1500 gm) infants constitute a small proportion of births globally but contribute disproportionately to the burden of neonatal morbidity, mortality, and the cost of intensive care.[1–3] These infants routinely require prolonged, invasive mechanical ventilation, which is associated with multiple comorbidities ranging from bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), hearing disorders, and

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require a prolonged need for parenteral nutrition, and hospital stay.[4,5] Hence, successful early extubation is a crucial determinant in decreasing overall morbidity and mortality in VLBW neonates.

The timing of neonatal extubation is widely based on clinical judgment, which may involve consideration of various clinical parameters such as ventilator settings, blood gas analysis, physical examination, weight at birth and at the time of evaluation, and the overall clinical stability of the patient.[6] There is a wide variation in protocols between various neonatal intensive care units (NICUs) for neonatal extubation throughout the world; some use unit-based guidelines, whereas others rely on spontaneous breathing test trials.[7,8] As our ability to salvage ever-smaller infants improves, the need for optimized weaning protocols, methods to determine the best timing of extubation, and clear definition/criteria of extubation failure remains. In this context, we reviewed the predictive model developed by Gupta et al.[9] to determine extubation readiness in extremely preterm infants. They have developed an ERE scale for easy guidance.

In this pilot study, we tested this aforementioned ERE scale for safety and reliability to assess extubation readiness of VLBW infants who were being treated with assisted ventilation. Our thinking was that it showed promise, we will test it in larger studies and aim to eventually develop protocols to replace our current practice of extubation based on subjective, clinical assessment of their readiness. We also explored the significance of additional parameters associated with successful extubation, morbidities associated with failed extubation, and the correlation between the mode of respiratory support after extubation and failure or success.

Methods

We conducted a retrospective chart review including all intubated infants gestational age <30 weeks with a birth weight ≤1500 gm, who were admitted to our level-3 inner-city NICU during the period between January 2016 and December 2020 and extubated within the first 60 days. The parameters of the original Gupta ERE were recorded.[9] To minimize confounding factors, infants with major congenital malformations and those intubated for elective surgical procedures were excluded. The local institutional ethics board approved this retrospective analysis and exempted the need for informed consent.

We recorded demographic variables including maternal and neonatal characteristics. Maternal data included prolonged premature rupture of membranes, gestational diabetes mellitus, gestational hypertension, preeclampsia, histopathologically confirmed chorioamnionitis, and administration of antenatal steroids. Neonatal variables included birth weight, gestational age, age at extubation, ventilator settings, preextubation blood gas results, respiratory severity score (RSS) at 6 hours after birth [mean airway pressure (MAP) × fraction of inspired oxygen (FiO_2)], surfactant administration, caffeine use, and weight at extubation. Other morbidities such as spontaneous intestinal perforation (SIP), necrotizing enterocolitis (NEC), late-onset sepsis, ROP ≥stage 2, and chronic lung disease/bronchopulmonary dysplasia (CLD/BPD) [National Institute of Child Health and Human Development (NICHD) classification] were compared in two groups formed based on different ERE scores. Similar to the original ERE study, an extubation attempt was recommended for a score with ≥80% probability of success whereas extubation was not recommended for a score <80% (Table 1).[9]

Our unit currently does not have set criteria for extubation; most neonates are extubated based on subjective clinical assessment, oxygen requirements, and ventilatory settings. Assessment for extubation readiness varies among neonatology care providers. After extubation, most infants receive noninvasive respiratory support with nasal continuous positive airway pressure (nCPAP), noninvasive mechanical ventilation (NIMV), or noninvasive neural-adjusted ventilatory assist (NAVA). For study purposes, extubation failure was defined as neonates requiring reintubation within 5 days postextubation for respiratory support.

Statistical Package for the Social Sciences (SPSS), version 28.0 (IBM, USA) software was used to compare maternal and neonatal characteristics in both groups. Parameters such as caffeine use, steroid use, and RSS at 6 hours of life were compared using univariate and multivariate analyses. The association between risk factors and extubation failure was reported as odds ratio (OR)

Table 1: Comparison of maternal risk factors, neonatal variables, and outcomes in reintubation vs successful extubation groups

	Neonatal extubation estimator probability score (<80%)			*Neonatal extubation estimator probability score (>80%)*		
Variable	*Reintubation N = 6 (%)*	*Successful extubation N = 34 (%)*	*p-value*	*Reintubation N = 5 (%)*	*Successful extubation N = 19 (%)*	*p-value*
Caffeine use	6 (100%)	34 (100%)	NA	5 (100%)	19 (100%)	NA
Prenatal steroids	5 (83%)	30 (88%)	0.738	5 (100%)	17 (89%)	0.449
Surfactant use	6 (100%)	32 (94%)	0.542	5 (100%)	19 (100%)	NA
NEC/SBP	2 (33%)	8 (23%)	0.054	0	2 (11%)	0.449
Late-onset sepsis	2 (33%)	5 (15%)	0.268	1 (20%)	3 (16%)	0.822
ROP stage 2 or greater	1 (17%)	11 (32%)	0.440	4 (80%)	4 (21%)	0.013
Chronic lung disease	6 (100%)	28 (82%)	0.264	5 (100%)	8 (42%)	0.021
Maternal PPROM	1 (17%)	11 (32%)	0.440	2 (40%)	2 (11%)	0.116
Gestational DM	0	0	NA	0	1 (5%)	0.600
Preeclampsia	1 (17%)	4 (12%)	0.738	1 (20%)	4 (21%)	0.959
Intra-amniotic infection	0	1 (2%)	0.671	1 (20%)	2 (11%)	0.569

DM, diabetes mellitus; NA, not applicable; NEC/SBP, necrotizing enterocolitis/spontaneous bowel perforation; PPROM, premature prolonged rupture of membranes

Table 2: Neonatal variables in reintubation vs successful extubation groups

Neonatal extubation estimator probability score	*Neonatal variables*	*Reintubation N (mean ± SD) Total N = 11*	*Successful extubation N (mean ± SD) Total N: 53*	*p-value*
Less than 80%	Gestational age (weeks)	6 (24 ± 1)	34 (25 ± 1)	0.481
	Birth weight (gm)	6 (698 ± 154)	34 (738 ± 114)	0.459
More than 80%	Gestational age (weeks)	5 (24 ± 3)	19 (28 ± 3)	0.012
	Birth weight (gm)	5 (752 ± 291)	19 (1012 ± 251)	0.058

SD, standard deviation

Table 3: Analysis of risk factors associated with reintubation

	Univariate analysis		*Multivariate analysis*	
Variable	*ORs (95% CI)*	*p-value*	*Adjusted ORs (95% CI)*	*p-value*
Gestational age	0.66 (0.44–0.99)	0.049	0.78 (0.28–2.19)	0.648
Birth weight <1250 gm	0.997 (0.99–1.00)	0.129	0.99 (0.98–1.00)	0.384
Antenatal steroids	1.277 (0.13–11.8)	0.830	2.168 (0.07–65.66)	0.657
Maternal diabetes mellitus	–	–	–	–
Preeclampsia	1.25 (0.23–6.88)	0.798	1.413 (0.041–48.7)	0.848
Intra-amniotic infection (confirmed placental pathology)	1.67(0.16–17.7)	0.672	1.2 (0.019–74.8)	0.931
Maternal PPROM	1.15 (0.23–05.00)	0.848	0.529 (0.043–6.51)	0.619
Surfactant use	–	0.99	–	0.99
Weight at extubation	1.001 (0.99–1.003)	0.570	1.002 (0.998–1.006)	0.391
RSS (first 6 hours)	1.67 (1.15–2.62)	0.004	3.19 (1.26–8.34)	0.018
NEC/SBP	–	–	–	–
Late-onset sepsis (culture positive)	2.1 (0.46–9.6)	0.34	0.31 (0.016–5.80)	0.430
ROP stage ≥2	2.1 (0.56–7.97)	0.27	0.58 (0.05–6.54)	0.660
Chronic lung disease	–	0.998	–	0.997

and 95% confidence intervals (CIs) using the Chi-square test. Risk factors with a $p < 0.1$ were included and adjusted for in the multiple logistic regression model; $p \leq 0.05$ was considered statistically significant. We produced receiver-operating characteristic curves and calculated the area under the receiver-operating characteristic curve (AUROC) as a measure of predictive probability for reintubation.

Results

We studied a total of 105 infants with gestational age below 30 weeks and weight ≤1500 gm, who were intubated and received assisted ventilation during the study period. Forty-one intubated infants were excluded from the study because of death prior to extubation or the nonavailability of complete data. The remaining 64 neonates were assessed for the probability of successful extubation. Fifty-three neonates were extubated successfully, while 11 required reintubation within 5 days of the first attempt. Forty infants had an ERE score below 80% and 6 of them required reintubation. Twenty-four had an ERE score ≥80% and 5 required reintubation.

In those with an ERE score of below 80%, there was no significant difference in major morbidities among infants who were reintubated (Table 1). Gestational age was significantly lower among infants with an ERE score ≥80% who failed extubation, but the birth weight did not differ significantly. The incidence of CLD and ROP ≥ stage 2 was significantly higher among those reintubated who had the ERE score ≥80% (Table 2). Lower gestational age and RSS at 6 hours after birth were significant risk factors for reintubation (Table 3). The ERE model was not accurate in our sample (AUROC = 0.49; Fig. 1) and logistic regression indicated no significant utility in predicting reintubation. In our study, sensitivity and specificity at probability scores of ≥80% were 36 and 54%, respectively.

Of 34 neonates who were extubated successfully and had an ERE score below 80%, 8 were extubated to CPAP, 23 to NIMV, and 3 to NAVA. Out of six neonates who failed extubation in this group, two received support with bubble CPAP and four were placed on NIMV. In those with ERE ≥80%, 19 were successfully extubated; 9 received nCPAP and 10 were treated with NIMV. Among the five infants who failed extubation in this group, four were placed on NIMV and 1 on NAVA (Table 4).

Discussion

To our knowledge, this is the first study that evaluated the performance of a neonatal ERE in VLBW babies. This scale is based on demographic and clinical parameters are available to the authors; the analysis was adjusted following the first elective attempt, and included higher gestational age, chronologic age at extubation, higher blood gas pH before extubation, and lower preextubation FiO_2, along with lower values for highest RSS in the first 6 hours after birth (as per the timing of RSS used in the

original calculator).[9] In our study, the ERE score using a cut-off of 80% did not accurately predict extubation success. It is possible that applying the ERE in clinical practice may have resulted in prolonged intubation and invasive mechanical ventilation in our population. These data differ from those of a different, previously reported cohort.[10] There is a need for further studies in larger cohorts.

In our study, we have been able to successfully extubate neonates at a lower percentage score. The sensitivity and specificity based on the ERE were lower in our population. Our data showed that sensitivity and specificity at an ERE cut-off of ≥80% were 36 and 54%, respectively. These thresholds were significantly lower (54 and 81%) than the original study that was used to formulate the estimator.[9,11] Finally, the AUROC in our population was 0.49, and logistic regression showed no significant utility of the ERE in predicting reintubation or successful extubation.

In many institutions, a trial of spontaneous breathing with endotracheal CPAP is used to evaluate the readiness for extubation. In the meta-analysis of Teixeira et al.,[12] 6 studies evaluated intubated infants with spontaneous breathing trials (SBTs) using endotracheal CPAP for 3–5 minutes. Failure was defined as significant desaturations and bradycardia. Although SBTs showed high pooled sensitivity (0.97, 95% CI) to correctly identify neonates as "ready" for successful extubation, pooled specificity was still low at 0.40 at 95% CI. Hence, although SBT in premature infants can accurately predict extubation success, there is still a lack of evidence to support its use as an independent predictor for extubation failure in preterm neonates.[12]

The RSS is computed as a product of MAP and the FiO_2. Oxygen supplementation and mechanical ventilation are essential for the survival of premature infants at the expense of long-term morbidities such as CLD and the need for frequent hospitalizations, especially during the first few years of life.[13] RSS has been used to make a decision for extubation in preterm infants. We found lower RSS at 6 hours after birth to predict successful extubation in both univariate and multivariate analysis. Surfactant use, antenatal steroids, and caffeine use did not differ between groups, but these need further evaluation in larger cohorts.

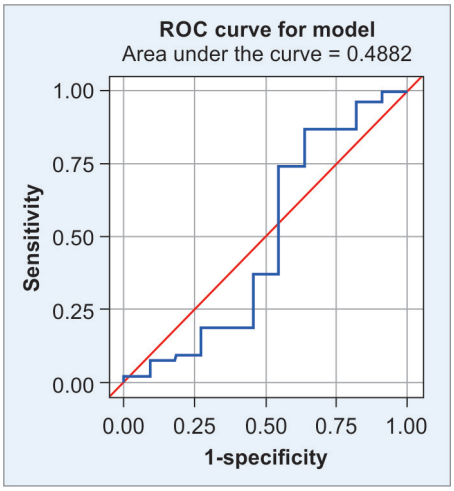

Fig. 1: Receiveroperating characteristic curve shows sensitivity and 1-specificity for the probability of reintubation

Prolonged mechanical ventilation is associated with severe morbidities in premature infants, and hence, it is essential to limit the duration of invasive mechanical ventilation. Strategies to preserve spontaneous respiration, such as patient-triggered ventilation may reduce the incidence of these complications. The use of respiratory stimulants such as caffeine and weaning modes of respiratory support may help in early extubation. A study by Shi et al. showed that extubating preterm neonates to NIMV from higher ventilator settings may be helpful.[14,15] Although not statistically significant, our data suggested that compared to nCPAP, more babies were extubated to NIMV support of ventilation in the low-probability group and remained successfully extubated.

Antenatal steroids decrease the length of stay by enhancing lung maturity and reducing oxygen demand and ventilator dependence. The antenatal administration of steroids may be important as a variable for developing an objective probability estimator. In a systematic review conducted by McGoldrick et al.,[16] which included 27 studies from 20 countries (with 11,272 randomized women and 11,925 neonates), continued use of a single course of antenatal corticosteroids reduced the risk of perinatal death, neonatal death, respiratory distress syndrome (RDS), and intraventricular hemorrhage (IVH) by enhancing the lung maturity regardless of the resource setting.[16] Our sample size was small to explore this correlation or determine the effect of the timing of steroid administration on the success of extubation. Similarly, surfactant use may also be an important variable in predicting the success or failure of extubation in newborns.[17] Most infants in our study had received surfactant, and it remains unclear whether this could be deemed a significant factor for successful extubation. Gestational age and weight at extubation may be two important confounding variables that might alter the effect of surfactant use.

The incidence and severity of ROP are inversely related to gestational age and birth weight, and the risk increases with hyperoxia and prolonged ventilation.[18–20] In our study, the incidence of ROP ≥stage 2 was significantly higher in the reintubation group with a probability score ≥80% category. Similarly, CLD is one of the common sequelae of preterm birth. The incidence of CLD increases with lower gestational age and birth weight. Additional important risk factors include intrauterine growth restriction, sepsis, and prolonged exposure to mechanical ventilation and supplemental oxygen.[21] Sucasas Alonso et al.[22] studied 202 newborns (mean gestational age 29.5 ± 2.1 weeks); CLD was independently associated with gestational age ($p < 0.001$; OR = 0.44 with 95% CI = 0.30–0.65) and the need for mechanical ventilation on the first

Table 4: Weaning mode after extubation

	Neonatal extubation estimator probability score (<80%)		*Neonatal extubation estimator probability score (>80%)*	
Mode of respiratory support	*Reintubation N = 6*	*Successful extubation N = 34*	*Reintubation N = 5*	*Successful extubation N = 19*
Nasal CPAP	2	8	0	9
NIMV	4	23	4	10
NAVA	0	3	1	0

day after birth ($p = 0.001$; OR = 8.13 with 95% CI = 2.41–27.42).[22] Our study showed a similarly increased risk of CLD in neonates with prolonged intubation in the setting of extubation failure and being dependent on mechanical ventilation.

Prolonged mechanical ventilation may increase the length of stay and increase hospital costs associated with it. Russell et al.[23] reported that the mean hospital costs for preterm infants with common morbidities of prematurity were 4–7 times higher than their gestational age-equivalent healthy controls. With prolonged intubation, the risk of comorbidities increases exponentially which are potentially associated with increased hospital costs in managing low birth weight babies. In a review study conducted in 2007 prolonged intubation-associated comorbidities were associated with an increase in direct hospital costs by $13,500 with the presence of brain injury, $17,000 with NEC, $31,500 with CLD, and $11,000 with late-onset sepsis.[23,24]

Gestational age and birth weight are the most important factors for successful extubation. The lower the gestation, the higher the risk of extubation failure. Brix et al.[25] showed that a 2-week lower gestational age increased the odds of failure of the INtubation-SURfactant-Extubation (INSURE) procedure by a factor of 1.8. Predictors for INSURE failure were low gestational age and hemoglobin <8.5 mmoL/L. Predictors for mechanical ventilation for >24 hours were as follows: Gestational age, Apgar at 5 minutes <7; oxygen need >50%, CO_2 pressure >7 kPa (~53 mm Hg), pH <7.3, lactate >2.5 mmoL/L, need for inotropes, and surfactant administration shortly after birth.[25] In our study, lower birth weight and gestational age were important variables to be considered while deciding on extubation. Finally, the AUROC in our population was 0.49, and logistic regression showed no significant utility of the ERE in predicting reintubation or successful extubation.

Available data do not provide clear-cut tools to help clinicians decide to successfully extubate a preterm infant. Limitations of our study were a retrospective design, a relatively small sample size, and being a single-center study. We are aware that the study is not adequately powered and so this should be viewed only as a pilot report. Considering that the total number of cases with successful extubation was 53 while 11 required reintubation, the AUROC of the neonatal ERE score in predicting successful extubation was 0.452. We used the R-Studio package pROC for these estimations.[26] The code used in these estimations was the power.roc.test (number of cases in the two groups as 53 and 11, the area under the curve = 0.452, and significance level = 0.05. Using these calculations, the power of the study was only 7.34%. The 2-sided α-error was consistent with these calculations. Having said this, the study showed that the comparisons did no harm, and justified a larger, hypothesis-testing study. All clinicians who provide care to extremely premature infants have battled with difficulties in determining the optimum timing for extubation.

Conclusion

We believe that our pilot study served its purpose. The primary purpose of these studies is to understand (A) the clinical relevance of fundamental questions; (B) feasibility; and (C) the need for specific modifications while designing larger, ensuing hypothesis-testing studies. If the objectives are clearly understood, this exercise can be beneficial.

In our study, extubation based on the ERE tool was safe but not predictive of successful extubation. If we had used clinical judgment for extubation as earlier, most of these infants would have received a trial of extubation in our NICU at probability scores ≤60%. The ERE in our population showed a lower predictive sensitivity and specificity than the cohort in the original study that was used to formulate the estimator. A large multicenter prospective study is needed to develop a more robust and accurate calculator to predict successful extubation in extremely preterm infants.

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Authors' Contributions

KB: Conceptualization, methodology, data collection, data analysis, wrote the manuscript.
BT: Data collection, data analysis, and writing of the manuscript.
FS: Conceptualization, data analysis, and writing of the manuscript.
RT: Data collection and writing of the manuscript.
MMG: Data Analysis, review, and revision of the manuscript.
CT: Data analysis, review, and revision of the manuscript.
SR: Conceptualization, data analysis, review, and revision of the manuscript.

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REVIEW ARTICLE

Artificial Intelligence in Newborn Medicine

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Abstract

The development of artificial intelligence (AI) algorithms has evoked a mixed-feeling reaction, a combination of excitement but also some trepidation, with reminders of caution coming up each time a novel AI-related academic/medical software program is proposed. There is awareness, with some hesitancy, that these algorithms could turn out to be a continuous, transformational source of clinical and educational information. Several AI algorithms with varying strengths and weaknesses are known, but the deep-learning pathways known as the Generative Pre-trained Transformers (GPT) have evoked the most interest as clinical decision-support systems. Again, these tools still need validation and all steps should undergo multiple checks and cross-checks prior to any implementation in human medicine. If, however, testing eventually confirms the utility of these pathways, there is a possibility of a non-incremental advancement of immense value. Artificial intelligence can be helpful by facilitating appropriate analysis of the large bodies of data that are available but are not being uniformly and comprehensively analyzed at all centers. It could promote appropriate, timely diagnoses, testing for efficacy with less bias, fewer diagnostic and medication errors, and good follow-up. Predictive modeling can help in appropriate allocation of resources by identifying at-risk newborns right at the outset. Artificial intelligence can also help develop information packets to engage and educate families. In academics, it can help in an unbiased, all-inclusive analysis of medical literature on a continuous basis for education and research. We know that there will be challenges in protection of privacy in handling data, bias in algorithms, and in regulatory compliance. Continued efforts will be needed to understand and streamline AI. However, if the medical community hesitates today in overseeing this juggernaut, the inclusion (or not) of AI in medicine might not stop—it might just gradually get extrapolated into patient care from other organizations/industry for cost reasons, not justification based on actual clinical data. If we do not get involved in this process to oversee the development/incorporation of AI in newborn medicine, the questions in making decisions will just change from who, to which, when, and how. Maybe this will not be the most appropriate scenario. To conclude, AI has definite benefits; we should embrace AI developments as valuable tools that can assist physicians in analyzing large and complex datasets, which will facilitate the identification of key facts/findings that might be missed if studied by humans. On the other hand, a well-designed and critical expert review board is mandatory to prevent AI-generated systematic errors.

Keywords: Critical, Generative pre-trained transformers, Neonate, Patient triage, Predictive modeling techniques, Premature, Resource allocation, Telemedicine consultations, Timely detection.

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Key Points

- The development of artificial intelligence (AI) algorithms is evoking a mixed-feeling reaction, some excitement and some trepidation, as new medical possibilities emerge every day.
- AI could strengthen clinical support systems to assist healthcare providers in timely detection of neonatal diseases, in making evidence-based decisions, reducing diagnostic errors, and in improving patient outcomes.
- Predictive modeling techniques can enable the identification of at-risk newborns and the early intervention of complications, such as sepsis and neurological disorders.
- In newborn health care, AI could help optimize resource allocation, patient triage, and telemedicine consultations, thereby enhancing access to medical expertise, particularly in underserved regions.
- To reiterate, there is a need for extreme caution in evaluation of these programs. This could be a paradigm shift, and like those in the past, we need cautious multi/inter-disciplinary collaboration to test and if viable, develop it, not outrightly reject it.

Introduction

Artificial intelligence (AI) encompasses various techniques and approaches that can be applied to medicine to improve healthcare delivery, precision diagnosis, treatment, and patient outcomes.[1] These tools show immense promise in transforming various aspects of newborn medicine, ranging from early detection and diagnosis of neonatal conditions to personalized precision

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treatment and long-term care.[2] This article explores the potential uses of AI in newborn medicine, highlighting its value in the timely detection of neonatal diseases and developmental abnormalities, analysis of vital signs, medical images, and genetic information.[3,4] It can also process information, ranging from medical literature pertaining to research articles, clinical trials, and/or case studies.[5] However, despite all strengths and the significant potential of AI in newborn medicine, challenges such as data privacy, algorithm bias, and regulatory compliance need to be addressed to ensure the responsible and ethical deployment of AI technologies.[6] By leveraging the capabilities of AI, newborn medicine stands to benefit from improved diagnostic accuracy, personalized treatment strategies, and enhanced healthcare delivery, ultimately leading to better health outcomes for neonates.[7]

One particular set of algorithms, the Generative Pre-trained Transformers (GPTs), has emerged as an important tool in natural language processing (NLP).[8,9] These can be developed with relatively limited training data, analyze large volumes of neonatal data, streamline clinical documentation, and provide clinical decision support systems.[4] By automating these tasks, GPT can reduce administrative burden, improve accuracy of documentation, and enhance the efficiency of clinical workflows while enhancing the physicians wellness and limiting the risk of physician burnout.[10,11] Indirectly, this can promote evidence-based decisions, reduce diagnostic errors, and improve patient outcomes.[12] GPT-powered chatbots and virtual assistants can also engage families and provide personalized medical information, answer medical queries, and facilitate remote consultations.[13] These virtual assistants can enhance patient satisfaction and empower families to make informed decisions.[14] GPT can also help generate patient-friendly educational materials, such as articles and videos, promoting health literacy and adherence to treatment regimens.[15] Predictive modeling techniques can enable the identification of at-risk infants and promote early intervention in conditions related to the severity-of-illness such as sepsis.[16] This information can help optimize healthcare delivery with resource allocation, patient triage, and telemedicine consultations.[17] This can enhance access to newborn care services, particularly in underserved regions.[18]

Please note GPT models can promote continuing medical education of care-providers.[19] The algorithms can help identify questions relevant for clinical/translational research, identify important studies conducted in the past, and summarize complex findings for education.[20] It could identify the most important clinical needs where new drugs are needed, predict drug interactions, and optimize drug design.[21] To summarize, GPTs have emerged as valuable tools in medicine, in healthcare delivery, medical research, and patient engagement. By leveraging the power of NLP, GPT enhances clinical documentation, facilitates medical literature analysis, improves patient communication, and accelerates drug discovery efforts.

In this article, we have focused on the strengths and weaknesses of GPT, particularly its version 3.5. It can help determine infrastructure needs for processing and information systems, costs, biases, and the evaluation metrics.[5] For application in clinical medicine, there is a need to ensure compliance with the Health Insurance Portability and Accountability Act, collaborate with healthcare providers, and ensure access and technical understanding of these software tools.[22] These software models are being continuously updated to improve the human-like logical and intellectual responses to prompts.[23] However, there is a need for caution as questions remain about safety and accuracy before its full-scale operationalization and its use in clinical practice and research. Here, we introduce AI and GPT for its capabilities, considerations for its implementation and operationalization in clinical practice, and the need for caution and well-designed control mechanisms.

History of Development of AI

These developments have involved a series of events in scientific research, technological advancements, and interdisciplinary collaboration over several decades:

Early Foundations

- In the 1950s, the field of AI emerged with the seminal work of researchers such as Alan Turing, John McCarthy, Marvin Minsky, Allen Newel, and Herbert Simon.[24]
- Alan M Turing, an English mathematician, computer scientist, cryptanalyst, philosopher, and theoretical biologist is considered the father of theoretical computer science and artificial intelligence.[25,26] During the Second World War, he was involved with the British code-breaking center that produced ultra-intelligence. His work assisted breaking the German naval ciphers, most importantly the enigma machine.
- John McCarthy coined the term "Artificial Intelligence" as early as 1955.[25] He organized an 8 week summer research conference in Dartmouth, New Hampshire in 1956 where 11 mathematicians and scientists laid the foundation for AI as a new scientific field. The topics of the meeting focused on computers, NLP, neural networks, theory of computation, abstraction, and creativity. The expertise of the participants was very diverse, including economists, political scientists, cognitive psychologists, computer scientists, and electrical engineers to mention a few.
- Early AI research focused on symbolic AI, which used symbolic representations and logic-based reasoning to simulate human intelligence.[27]
- Key developments during this period included the development of expert systems, logical reasoning systems, and early forms of machine learning (ML) algorithms.[28]

Period of Low Progress

- During the 1970s–1980s, AI research faced significant challenges and setbacks, leading to a period known as the "AI winter."[29]
- Financial support for AI research declined, and there was skepticism about the feasibility of achieving human-level intelligence with existing approaches.
- Despite these challenges, research continued in areas such as expert systems, NLP, and robotics.[24]

Rise of Machine Learning (ML)

- In the 1980s and 1990s, ML emerged as a dominant paradigm in AI research.[30]
- Researchers explored various ML techniques, including neural networks, genetic algorithms, and statistical methods, to develop AI systems that could learn from data.[31]
- Key developments during this period included the back propagation algorithm for training neural networks, the development of support vector machines (SVMs), and the rise of Bayesian methods in ML.[32]

Computational Advances

- The 2000s witnessed significant advances in computational power, data availability, and algorithmic innovation, fueling rapid progress in AI research.[33]

- Deep learning (DL), a subfield of ML, focused on training deep neural networks, gained prominence due to its ability to learn hierarchical representations from data.[34]
- Breakthroughs in DL, such as the development of convolutional neural networks (CNNs) for image recognition and recurrent neural networks (RNNs) for sequence modeling, revolutionized AI applications in computer vision, NLP, and robotics.[35]
- The IBM Watson Health was launched in 2017 after IBM-Watson defeated two human "Jeopardy" champions in 2011. The initial experience showed that AI, DL, and ML require a careful review of the quality and size of the input data, the applied algorithm, and the validity of the output results before it can be rolled out in clinical healthcare.

Interdisciplinary Collaboration and Applications (Present)

- AI research today involves interdisciplinary collaboration between computer scientists, mathematicians, engineers, neuroscientists, and domain experts from various fields.[36]
- These technologies have been applied to a wide range of domains, including healthcare, finance, transportation, agriculture, and entertainment, and has transformed industry.[37]
- Ongoing research in AI focuses on addressing challenges such as data privacy and governance, fairness, interpretability, and ethical considerations, as well as advancing the capabilities of AI systems to achieve or surpass human-level intelligence in complex tasks.[38]

Overall, the development of AI has been a gradual process, driven by scientific curiosity, technological innovation, and real-world applications. It has involved contributions from researchers and practitioners across multiple disciplines. In addition, the development of AI algorithms also has significant economic implications and potential. Many for profit organizations are progressively offering commercial AI solutions.

Potential Importance of AI in Healthcare

AI has been viewed as a promising advancement in medicine. Specific medical tasks, available data, computational resources, and regulatory considerations seem to be important determinants.[7,39–42] Here are some types of AI commonly used in the broader picture of healthcare and medicine:

Machine Learning (ML)

ML is focused on the development and study of statistical algorithms that can learn from data, generalize the paradigms to unseen data, and then perform tasks without explicit instructions.[43] ML models can be trained on large datasets of medical images, including objective imaging-based scalars such as apparent diffusion coefficients or concentration of metabolic markers; patient records; genomic data; and other healthcare data to assist in diagnosis, treatment planning, and personalized medicine.[44–50] These techniques seem to be particularly effective for tasks such as medical image analysis, disease classification, predictive modeling, and clinical decision support.[51] There are three broad patterns:

- *Supervised learning:* These algorithms are trained on labeled datasets, where input–output pairs are used to learn the mapping between input features and target labels. Supervised learning techniques are used in medical image analysis, disease classification, and predictive modeling.[52]
- *Unsupervised learning:* These involve training algorithms on unlabeled data to discover hidden patterns or structures within the data. Unsupervised learning techniques are used in clustering, anomaly detection, and dimensionality reduction tasks in medicine.[53]
- *Semi-supervised learning:* These combine elements of supervised and unsupervised learning by leveraging a small amount of labeled data and a larger amount of unlabeled data to improve model performance. Semi-supervised learning techniques are used when labeled data are scarce or expensive to obtain in medical applications.[54]

Deep Learning (DL)

DL is a subfield of ML. It has shown remarkable success in various medical imaging tasks, including radiology, pathology, and dermatology. DL models, such as CNNs and RNNs can learn hierarchical representations from raw data, enabling automatic identification of patterns from medical images and signals.[55,56] DL techniques are also used in medical NLP tasks, such as clinical documentation, medical transcription, and patient data extraction from electronic health records (EHRs). There are three broad patterns:

- *Convolutional neural networks (CNNs)*: These networks are DL models designed to process structured grid-like data, such as images. CNNs are widely used in medical imaging tasks, including image classification, segmentation, object detection, and pattern recognition.[57]
- *Recurrent neural networks (RNNs):* These are DL models with recurrent connections that enable them to capture sequential dependencies in data. RNNs are used in tasks involving sequential data, such as time-series analysis, NLP, and EHR analysis.[58]
- *Transformer models:* These include GPT (Bidirectional Encoder Representations from Transformers) and Bidirectional Encoder Representations from Transformers (BERT), which are DL architectures designed to process data with self-attention mechanisms.[59] Transformer models are used in medical NLP tasks, including language translation, text summarization, and clinical documentation. Later in this review, we have focused on GPT and its importance in medicine and its branches such as neonatology.[60]

Expert Systems

These are AI systems designed to mimic the decision-making processes of human experts in specific domains. Expert systems use rules-based approaches and knowledge representation techniques to reason and make decisions. Expert systems are used in medical diagnosis, treatment planning, and clinical decision support systems.[61] These systems are particularly useful in domains where expert knowledge is well-defined and can be codified into rules or algorithms, such as pathology, radiology, and dermatology.

Natural Language Processing (NLP)

NLP involves techniques for processing and understanding human language. These algorithms can help in:

- *Processing unstructured text data* in medicine, including in clinical notes, research articles, and communication between healthcare providers and patients.[62]

- *Retrieval of information* from medical texts. Natural language processing can then help with sentiment analysis and to summarize documents- and answer-related questions.[63]
- *Medical literature mining* to develop clinical decision support systems and patient communication platforms.[64]

Computer Vision

These involve techniques for analyzing and interpreting visual data, such as medical images and videos. Computer vision techniques are used in medical imaging modalities, including radiology, pathology, and dermatology, to assist in diagnosis, image interpretation, and treatment planning.[65] Pattern recognition of imaging findings has been useful in neonatal and pediatric neuroradiology.[66,67] In these programs, feeding new magnetic resonance imaging data evokes an output with a list of differential diagnoses, with probabilities and 95% confidence intervals for each entity; specific data on the MRI findings of few cases could be added to the database to improve the experience and accuracy of the program.

Reinforcement Learning (RL)

These modules involve training agents to interact with an environment and learn optimal actions through a trial-and-error process. Reinforcement learning techniques are used to plan optimized, personalized treatments adaptive therapies and medical robotics.[68,69]

These are just a few examples of the types of AI that can be used in medicine. The choice of AI techniques depends on the specific task or application, as well as factors such as available data, computational resources, and regulatory considerations. Reinforcement learning techniques are still relatively new in medicine but hold promise for addressing complex and dynamic healthcare challenges. Integrating multiple AI techniques and approaches can lead to more robust and effective solutions.

Generative Pre-trained Transformers (GPTs), An ML Algorithm Used in Medicine

GPT is one of many AI models that have been used in medicine. The preference for GPT over other AI algorithms depends on the specific tasks or applications in the medical domain.[70]

Possible Advantages of Using GPT and Similar Language Models in Medical Tasks

- *Natural language understanding (NLU):* GPT excels in understanding and generating human-like text, making it valuable for tasks such as medical documentation, literature analysis, and patient communication. Its ability to process and generate text in natural language allows it to assist healthcare professionals in writing clinical notes, summarizing medical literature, and engaging with patients effectively.[71] This may also positively impact the health and resilience of healthcare professionals by reducing administrative tasks. The GPT has also been found to be effective with minor differences in syntax and accents.
- *Flexible and versatile:* GPT is a highly flexible and versatile model that can be fine-tuned for a wide range of medical tasks and applications. It can be adapted to different medical specialties, languages, and healthcare settings by training it on domain-specific data and fine-tuning its parameters for specific tasks, such as medical question answering, clinical decision support, and medical image analysis.[28]
- *Large-scale pre-training:* GPT is typically pre-trained on large amounts of text data from diverse sources, enabling it to learn rich representations of language and knowledge from a broad range of domains. This large-scale pre-training helps GPT capture complex linguistic patterns, domain-specific terminology, and contextual information relevant to medical tasks, making it effective in understanding and generating medical text.[12]
- *Contextual understanding:* GPT models, particularly those with large numbers of parameters like GPT-3, excel in capturing contextual information and understanding the nuances of language. This contextual understanding allows GPT to generate coherent and contextually relevant responses to queries, making it useful for tasks such as medical question answering, clinical documentation, and patient education.[72]
- *Continuous learning:* GPT can be continuously updated and improved over time by fine-tuning it on new data and tasks. It can adapt to evolving medical knowledge, guidelines, and practices, ensuring that it remains up-to-date and relevant for medical applications.[73]

GPT offers several advantages for certain medical tasks, but it is important to recognize that no single AI model is universally "better" than others in all contexts. Different AI models, including neural networks, ML algorithms, and statistical models, have their own strengths and limitations, and the choice of model depends on factors such as the task requirements, available data, computational resources, and ethical considerations.

Types of GPT Codes Used in Medicine

In medical AI research and applications, many versions of GPT have been tested. Three versions of GPT are best-known:

- *GPT-1* was the first version of GPT released by OpenAI. It had 117 million parameters and was trained on a diverse range of internet text. GPT-1 demonstrated strong performance on various NLP tasks but was later surpassed by more sophisticated models integrating larger data sets and parameter.
- *GPT-2* was a significant advancement over GPT-1, featuring 1.5 billion parameters. It was trained on a massive dataset scraped from the internet, allowing it to generate highly coherent and contextually relevant text. GPT-2 attracted attention due to concerns about its potential misuse for generating fake news or deceptive content, leading OpenAI to initially release it in a controlled manner. However, the full version was later made publicly available.
- *GPT-3* is a powerful version of the model, boasting a staggering 175 billion parameters. It is the largest publicly known language model to date. GPT-3 demonstrated remarkable capabilities in generating human-like text, understanding context, and performing a wide range of NLP tasks, including translation, question answering, text completion, and more. GPT-3 has been widely used and studied by researchers and developers across various domains.[74]
- *GPT-4* is a multimodal large language model that was released in early 2023. It is a transformer-based model where pre-training uses both public data and "data licensed from third-party providers." The model has been fine-tuned with reinforcement learning feedback from humans and AI for human alignment and policy compliance.

Each version of GPT has built upon the advancements of its predecessor, with improvements in model architecture, training data, and scale. The increasing size and complexity of these

models have contributed to significant advancements in natural language understanding and generation, enabling a wide range of applications across industries.[75] Below is a simplified flow diagram outlining the general process of developing a GPT model for a specific application, such as medicine:

```
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Start
|
|– Define Task and Objectives
|
|– Collect Data
| |– Gather Raw Text Data
| |– Pre-process Data (Tokenization, Cleaning, etc.)
| |– Create Training, Validation, and Test Sets
|
|– Pre-train GPT Model
|  |– Initialize Model Architecture
|  |– Train on Large Text Corpus (Unsupervised Learning)
|  |– Fine-tune Hyperparameters
|  |– Monitor Training Progress
|
|– Fine-tune GPT Model
|  |– Initialize Pre-trained Model
|  |– Fine-tune on Domain-specific Data (Supervised Learning)
|  |– Fine-tune Task-specific Head (if applicable)
|  |– Validate and Tune Hyperparameters
|  |– Evaluate Performance on Validation Set
|
|– Evaluate and Test
|  |– Evaluate Model Performance on Test Set
|  |– Assess Metrics (Accuracy, Precision, Recall, etc.)
|  |– Iterate and Refine Model (if necessary)
|
|– Deployment
|  |– Integrate Model into Application or Workflow
|  |– Monitor Model Performance in Real-world Settings
|  |– Provide Updates and Maintenance as Needed
|
End
```

This flow diagram outlines the main steps involved in developing and deploying a GPT model for a specific task, such as medical text generation or medical question answering. Each step involves a series of subtasks, such as data collection, pre-processing, model training, fine-tuning, evaluation, and deployment. Additionally, there may be iterative loops where the model is refined based on performance feedback or changes in requirements.

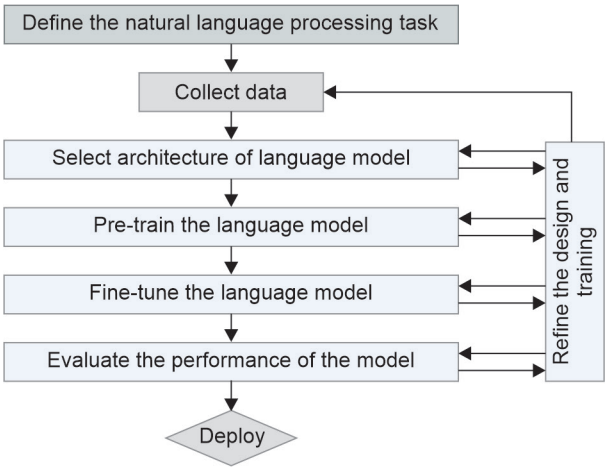


Fig. 1: An algorithm to develop a problem-solving model based on machine learning/natural language processing

Customized Versions of GPT

Customized versions of GPT can be developed for specific needs with appropriate expertise in ML and NLP.[76,77] Here are some general steps (Fig. 1):

- A clearly defined specific NLP task, such as text generation, text classification, sentiment analysis, language translation, or summarization.
- Collection of data: A large dataset of good quality and diversity is desirable.
- Selection of the architecture of the NLP model: A transformer-based architecture resembling GPT or other models can be used per requirements/constraints of the project.
- Pre-training of the NLP model on the dataset using self-supervised/supervised learning; this involves training the model to predict the next word(s) in a sentence given the context.
- Fine-tuning of the pre-trained model on specific examples or relevant tasks. These polishing steps improve its performance on the target task.
- Evaluation of the performance of the model on a separate validation or test dataset to assess its effectiveness and identify areas for improvement.
- Iterative refinement of the design, training, and evaluation process to improve the model. This may need change in hyperparameters or architectures, or testing with additional data.
- Once the customized language model looks satisfactory, the model can be deployed in the application or integrated into the workflow to start making predictions or generating text.

This flow diagram provides a high-level overview, and the specific details and implementation may vary depending on the task, dataset, model architecture, and research goals. Additionally, newer developments and research in the field may introduce variations or improvements to the overall process. Customized versions of GPT or a similar language model can be developed for specific needs, although it might require significant expertise in ML and NLP. Here are some general steps to consider:

Designing and training a customized language model can be a complex and resource-intensive process, requiring expertise in ML, NLP, and data engineering. Additionally, there might be a need for powerful computing resources, such as graphics processing units or Tensor Processing Units to train large-scale models effectively.

Parameters Used in the Development of GPT for Medicine

This is an evolving process.[78] Here are some general information about the parameters typically included in training GPT models for medical applications:

- *Model architecture:* The GPT models are based on a transformer architecture, which consists of multiple layers of self-attention mechanisms and feedforward neural networks.[79] The number of layers, hidden units, attention heads, and other architectural parameters can vary depending on the size and complexity of the model.
- *Pre-training data:* Models pre-trained on large amounts of text data to learn language representations can be useful.[78,80] The pre-training data may include various sources of biomedical literature, clinical notes, EHRs, drug labels, and other healthcare-related text. These datasets can range from millions to billions of tokens.
- *Fine-tuning data:* After pre-training, GPT models are fine-tuned on domain-specific data to adapt them to specific tasks or applications.[81,82] This fine-tuning may focus on clinical notes, medical questions/answers, EHR, and other healthcare-related documents. The size of the fine-tuning dataset can vary depending on the specific task.
- *Training hyperparameters:* Various hyperparameters involved in training GPT models, such as learning rate, batch size, optimization algorithm, and dropout probability are typically tuned empirically to optimize model performance on the target task or dataset.[83,84]
- *Task-specific head:* In some implementations, GPT models may include a task-specific head or output layer tailored to the specific medical task at hand.[85] For example, in medical question answering, the output layer may consist of a softmax classifier trained to predict the most likely answer to a given medical question.[86]
- *Evaluation metrics:* During training and evaluation, many metrics may help evaluate GPT models on medical tasks.[87] Evaluation metrics include accuracy, precision, recall, F1 score, and perplexity, depending on the specific task and evaluation criteria.

Notably, the exact parameters used in GPT development for medicine may vary with specific implementation, datasets, task requirements, and research goals. Newer developments and research in the field may introduce variations or improvements to the training and fine-tuning processes.

GPT Models Used in Medicine

GPT models have been utilized for various applications in medicine.[88,89] Although we still do not have specific GPT models for these tasks, the GPT architecture, particularly in GPT-3, has been adapted for medical use. Here are some examples:

- *BioGPT:* A version fine-tuned specifically for biomedical applications.[90] It has been trained on biomedical literature and clinical text to understand medical terminology, concepts, and contexts. BioGPT has been used for tasks such as medical text generation, clinical documentation, and medical question answering.
- *Clinical GPT:* Clinical GPT is another variant fine-tuned on EHRs, medical literature, and healthcare-related text to assist healthcare providers in clinical documentation, patient management, and decision support.[91] It aims to improve clinical workflows while ensuring compliance with healthcare regulations and standards.
- *GPT-M:* A modified version of GPT-3 optimized for medical text generation and understanding. It has been trained on a curated dataset of medical documents, including clinical notes, research articles, and drug labels. The GPT-M can generate medical reports, summarize patient information, and answer queries accurately.
- *MedGPT:* A variant designed specifically for answering medical questions and knowledge retrieval.[92] It aims to assist healthcare professionals in accessing medical knowledge efficiently to support clinical decision-making.

To summarize, GPT models have been adapted and customized for medical applications on domain-specific data and tasks. By leveraging the power of NLP, these specialized GPT models contribute to improving healthcare delivery, clinical decision support, and medical research. Many GPT and other large language models have several applications in the field of medicine, including:[93]

- *Clinical documentation and note generation:* GPT can be used to assist healthcare professionals in generating clinical notes, summaries, and reports.[94] By providing relevant patient information as input, the model can generate structured, accurate documentation to improve the efficiency of medical record-keeping.
- *Medical literature summarization:* GPT can help summarize large volumes of medical literature, including research articles, clinical trials, and case studies.[95] This can assist healthcare professionals in staying up-to-date with the latest advancements in their field and making informed decisions about patient care.
- *Medical chatbots and virtual assistants:* These can provide patients with personalized medical information, answer their questions about symptoms, treatments, medications, and even schedule appointments.[96] These virtual assistants can improve patient engagement, provide continuous support all over the day, and alleviate the burden on healthcare providers.
- *Clinical decision-support systems:* GPT can be integrated into clinical decision support systems to assist healthcare providers in making diagnostic and treatment decisions.[97] By analyzing patient data, medical history, and symptoms, GPT can provide recommendations for appropriate diagnostic tests, treatment options, and medication dosages.
- *NLP for electronic health records (EHR)*: GPT can help extract information from unstructured EHR. This includes identifying key medical concepts, relevant information for research or analysis, and improving the accuracy of coding and billing.[98]
- *Patient education and health communication:* GPT can generate patient-friendly educational materials, such as articles, pamphlets, and videos, to help patients better understand their medical conditions, treatment options, and preventive care measures.[99] This can improve health literacy, patient engagement, and adherence to treatment plans.
- *Drug discovery and development:* GPT can help analyze biomedical literature, clinical trial data, and molecular structures to accelerate drug discovery and development processes.[100,101] By identifying drug candidates, predicting drug interactions, and optimizing drug design, GPT can contribute to advancing medical research and improving patient outcomes.[100]

These are just a few examples of how GPT and other large language models are being utilized in the field of medicine. With continuing

progress, we anticipate to see more innovative applications that leverage NLP to improve healthcare delivery and patient outcomes.[102–104]

Accuracy of GPT for Medicine

The accuracy of GPT for medicine depends on several factors, including the quality of the training data, the specific medical task, and the fine-tuning process.[105] While GPT and similar language models have shown impressive capabilities in natural language understanding and generation, their performance in medical applications varies depending on the complexity and domain-specific nature of the tasks:

- *Training data quality:* The quality and quantity of the training data used to fine-tune the model are important determinants of the accuracy of GPT models.[106] Training data that are representative of the medical domain and cover a wide range of medical topics, specialties, and terminology are essential for achieving high accuracy.[52]
- *Task complexity:* The accuracy of GPT varies depending on the complexity of the medical task.[107] GPT may perform well on relatively simple tasks, such as medical text generation or summarization, but may not be as effective in tasks that require deep domain knowledge or specialized expertise such as clinical management.[108]
- *Domain specificity:* GPT's accuracy for medicine is affected by its ability to understand and generate medical terminology, concepts, and contexts. GPT models fine-tuned on large volumes of medical text demonstrate better accuracy for medical tasks compared with models trained on generic text data.[109]
- *Evaluation metrics:* GPT models developed for medicine are typically evaluated using standard metrics such as precision, recall, F1 score, and perplexity.[110] However, should also be evaluated clinical relevance, interpretability, and generalizability when assessing the performance of GPT models in medical applications.
- *Ethical and regulatory considerations:* Besides accuracy, ethical considerations, such as patient privacy, algorithm bias, and regulatory compliance, also play a crucial role in determining the suitability of GPT for medical applications.[111,112]

Overall, while GPT and similar language models have demonstrated promising capabilities in medicine, the accuracy is not guaranteed and varies depending on the specific task and application. It's essential to carefully evaluate the performance of GPT models in medical settings before deploying these in clinical practice. Interdisciplinary collaboration between AI researchers, healthcare professionals, and domain experts is critical for leveraging GPT effectively in medicine while ensuring patient safety and quality of care.

Alternatives to GPT

There are several alternatives to GPT for NLP tasks, each with its own strengths and weaknesses.[79] Here are some notable alternatives:

- *Bidirectional Encoder Represention from Transformers:* BERT is another widely used transformer-based model developed by Google. Unlike GPT, which is trained in a left-to-right autoregressive manner, BERT is trained bidirectionally, allowing it to capture context from both directions. BERT is known for its effectiveness in various NLP tasks, including question answering, sentiment analysis, and named entity recognition.[113]
- *XLNet:* XLNet is a transformer-based model that extends BERT's pre-training approach by leveraging permutation-based language modeling. XLNet can achieve state-of-the-art performance on several benchmark NLP tasks by considering all possible permutations of the input sequence during training, allowing it to capture bidirectional context more effectively.
- *Transformer-XL:* Transformer-XL is a variant of the above transformer model. It introduces a novel architecture that addresses the limitation of the fixed-length context window in traditional transformers by allowing for longer-term dependency modeling. Transformer-XL is particularly useful for tasks requiring long-range context understanding, such as language modeling and document summarization.
- *Robustly-optimized BERT approach (RoBERTa):* Robustly-optimized BERT approach is a variant of BERT developed by Facebook AI. It improves upon BERT's pre-training objectives and training strategies to achieve better performance on downstream NLP tasks. Robustly-optimized BERT approach adopts larger batch sizes, longer training sequences, and dynamically changing masking patterns during pre-training, leading to improved robustness and generalization.
- *A little BERT (ALBERT):* A little BERT is a lightweight variant of BERT developed by Google Research that achieves performance that is comparable to BERT with fewer parameters. It introduces parameter-sharing techniques and factorized embedding parameterization to reduce model size and computational cost while maintaining high performance on various NLP tasks.
- *T5 (Text-to-text Transfer Transformer):* T5 is a transformer-based model developed by Google that frames all NLP tasks as text-to-text tasks, allowing for unified training and evaluation procedures. T5 achieves state-of-the-art performance on a wide range of NLP benchmarks by leveraging large-scale pre-training and fine-tuning on task-specific data.

These alternatives to GPT offer different approaches to modeling and training transformer-based architectures for NLP tasks. Depending on the specific requirements of a task or application, researchers and practitioners may choose one of these models based on factors such as performance, efficiency, model size, and computational resources available.

GPT in Medical Records

The program can be used to assist in correcting medical notes, particularly in tasks such as proofreading, grammar correction, and ensuring adherence to medical terminology and conventions.[114] Here's how GPT can be applied in correcting medical notes:

- *Grammar correction:* GPT can help identify grammatical errors, punctuation mistakes, and spelling errors in medical notes. It can suggest corrections and improvements to ensure that the notes adhere to proper grammar and writing conventions.[115] Many of the newer GPT models also include automated summary tools of frequently seen findings, the so-called "smart phrases," to make the reports more comprehensive with higher levels of detail.[116]
- *Language consistency:* GPT can assist in maintaining consistency in language and terminology throughout medical notes. It can help ensure that medical terms, abbreviations, and acronyms are used consistently and correctly across different sections of the notes.[19]

- *Clarity and readability:* GPT can help improve the clarity and readability of medical notes by suggesting revisions to modify/replace linguistically unusual phrasings, convoluted sentences, or ambiguous language.[117] It can help streamline the writing style to ensure that the notes are easier to understand for other healthcare professionals.
- *Medical terminology:* GPT can assist in accurate use of medical terminology and terminology specific to different medical specialties.[19] It can help identify incorrect or outdated terminology and suggest appropriate replacements based on current medical standards.
- *Formatting and structure:* GPT can help ensure that medical notes follow the appropriate formatting and structure guidelines.[118] It can assist in organizing information, formatting headings and subheadings, and ensuring a logical, coherent structure of the notes.
- *Quality assurance:* GPT can aid in quality assurance by flagging potential inconsistencies, errors, or omissions in medical notes.[119,120] It can help reviewers identify areas that may require further clarification or revision to ensure the accuracy and completeness of the notes.

Overall, GPT can be valuable for correcting medical notes, but it should be used as a supplement to human expertise and judgment. Healthcare professionals should critically evaluate the suggestions and feedback generated by GPT and ensure that the corrected notes adhere to relevant medical guidelines, standards, and best practices.

GPT in Education and Research

Use of GPT to Query Databases Such as PubMed

GPT can potentially be used to assist in querying large databases but there are some considerations to keep in mind:[121]

- *Natural language interface (NLI):* GPT could be employed as part of a NLI for querying databases.[122] Users could input their queries in natural language, and GPT could help parse and interpret those queries to generate more structured search queries that are compatible with the database's search interface.
- *Query expansion and refinement:* GPT could assist in refining and expanding search queries based on contextual information provided by the user.[123] For example, if a user provides a vague or ambiguous query, GPT could help clarify the user's intent and suggest additional terms or concepts to include in the search.[124]
- *Summarization of results:* After retrieving search results from PubMed or other databases, GPT could assist in summarizing and presenting the key findings or insights in a more digestible format.[125] This could include generating concise summaries of research articles, identifying relevant studies, or highlighting important keywords or concepts.
- *Contextual understanding:* GPT's ability to understand context could be leveraged to improve search relevance and accuracy.[126] For example, it could utilize previous search history, user preferences, or the specific domain of interest to tailor search results more effectively.

To summarize, GPT can potentially assist in various aspects of database querying, but it is important to note that the actual querying and retrieval of data from databases like PubMed typically utilizes more specialized tools and techniques. PubMed provides its own search interface and application programming interface (API) keys for accessing its database, and many researchers often use tools like Python with libraries such as Biopython or other specialized search engines.[127–129] Overall, even though GPT can augment the querying process by providing a NLI and assisting in query refinement and result summarization, it would typically be used in conjunction with other tools and techniques for more efficient and effective database querying.

GPT to Develop Medical Manuscripts

The GPT can provide meaningful summaries with various types of images and appendices. However, the development of full manuscripts still needs work.[130]

GPT to Review Medical Manuscripts

GPT can be used to assist in reviewing manuscripts, particularly in tasks such as summarization, language correction, and providing feedback on the clarity and coherence of writing.[131] Here's how GPT can be applied in manuscript review:

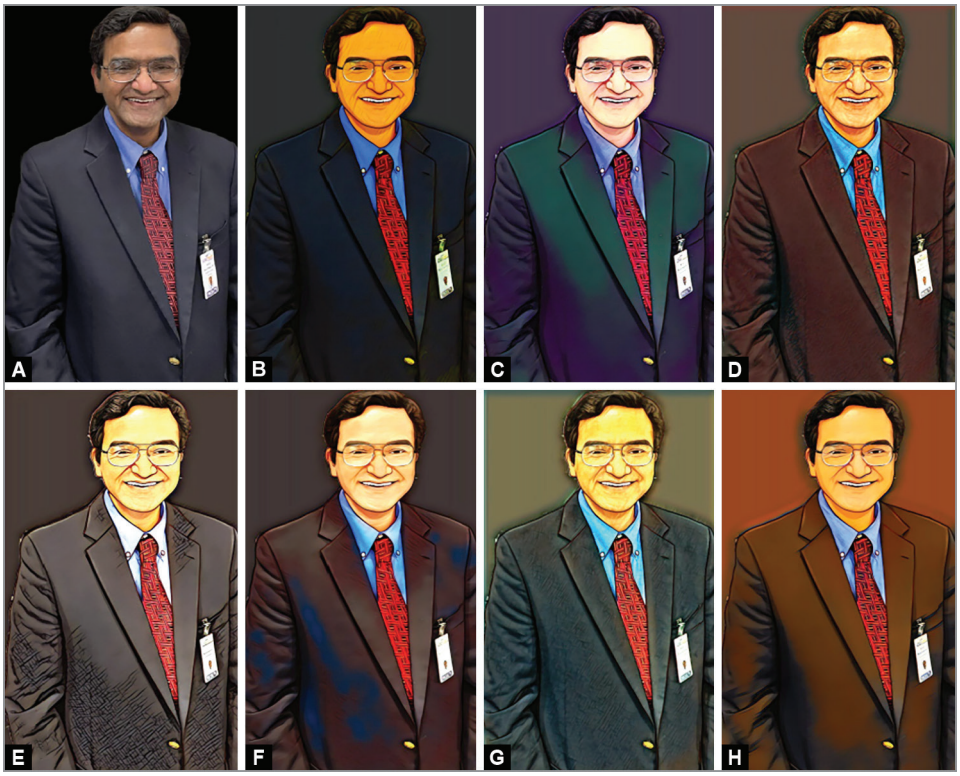
- *Summarization:* GPT can generate concise summaries of manuscripts, highlighting key findings and contributions. Reviewers can use these summaries for understanding the key points of the manuscript and provide feedback on its overall coherence and structure.[132]
- *Language correction:* GPT can help identify grammatical errors, typos, and awkward phrasings in manuscripts. Reviewers can use GPT to suggest corrections and improvements to the writing style, ensuring clarity and readability.[132]
- *Feedback generation:* GPT can generate feedback on various aspects of the manuscript, such as the strength of the arguments, the relevance of the literature cited, and the validity of the methodology. Reviewers can use GPT-generated feedback as a starting point for providing detailed critiques and suggestions for improvement.[126]
- *Plagiarism detection:* While not a primary function of GPT, it can assist in identifying potential instances of plagiarism by comparing text passages in the manuscript with existing literature and databases. Reviewers can use GPT to flag suspicious similarities and recommend further investigation.[133]
- *Reviewer assistance:* GPT can aid reviewers by providing additional context or background information for the manuscript. Reviewers can use GPT to look up relevant references, definitions, or explanations to enhance their understanding of the subject matter.[126]

Thus, GPT can be a valuable tool in manuscript review, but it should be viewed as a supplement to human expertise and judgment rather than a replacement. Reviewers should critically evaluate the suggestions and feedback generated by GPT based on their own expertise in the field. They should also be aware of the limitations and biases of these models.

Customized versions of GPT or similar language models can be developed for specific needs, using ML, NLP, and data engineering. Additional computing resources such as GPUs or TPUs might be needed to effectively train large-scale models.

GPT to Make Images for Medical Manuscripts

GPTs are designed primarily for NLP tasks, such as text generation and understanding. However, newer generative models with embedded DL can be tailored for image generation. An example is shown in Figure 2; there are several possible versions of a photographic image (one of the two authors).[134,135]



Figs 2A to H: Newer generative models with embedded deep-learning can be tailored for image generation. The images above show. (A) A photograph of one of the authors (Dr. Maheshwari) that has been modified to make (B–H) A series of simplified cartoon ("toon") "avatars" using an AI algorithm

- *Generative adversarial networks (GANs):* These DL models are comprised of two neural networks, a generator and a discriminator, which are trained simultaneously.[136] The generator can learn to produce realistic images from random noise, while the discriminator learns to distinguish between real and fake images. Generative adversarial networks can generate high-quality images across various domains.[137] Artificial intelligence has been used to generate chatbots, which can use algorithms with AI, ML, NLU, and NLP to simulate a human conversation with text messages in a chat window. These windows can produce text, images, sounds, software, and other digital media.
- *Variational autoencoders (VAEs)* are another type of generative models that can learn and generate new data points by capturing the distribution of the input data. Variational autoencoders can be trained to encode input data into a lower-dimensional latent space and then decode it back into the original space. These can be used for tasks like image generation and reconstruction.[138]
- *Autoregressive models:* GPT itself is an autoregressive model for text generation, but similar architectures can be applied to image generation tasks.[8] Models such as PixelRNN and PixelCNN can generate images that show pixel-by-pixel congruity with previous versions.[139,140]

As shown in Figures 3 to 5, current image generators can produce interesting images but there is still room for improvement. Figure 3 shows output images of the two principal authors of this article. Panel A shows an image that resembles Dr. Maheshwari but the infant seems to show congenital anomalies. In panel B, most observers did not identify the image of the physician with Dr. Huisman. Figure 4 shows the typical clinical setting of two physicians attending to a newborn baby. However, there are multiple incorrect background details and what appear to be structural abnormalities in the baby. In Figure 5, the output function failed to illustrate the requested germinal matrix hemorrhage correctly; the figure showed a whirled red color that faintly resembled an acute hemorrhage.

GPT to Tabulate Data for Medical Manuscripts

GPT tools are not specifically designed to create visualizations like bar diagrams or pie charts as these typically require manipulation of numerical data. These graphics are easier prepared using specialized software tools such as:

- *Python-based libraries:* Python is a general-purpose programming language; the design philosophy emphasizes code readability. It is a dynamically typed, garbage-collected program that can support multiple programming paradigms, including structured, object-oriented and functional programming.[141–143]
  - *Matplotlib* is a widely used library that can be used for creating static, interactive, and animated visualizations. It can generate bar plots, pie charts, line plots, and scatter plots.[144]
  - *Seaborn* is an advancement over Matplotlib; it provides a high-level interface for creating attractive and informative statistical graphics. These advanced visualizations can support options for further customization.[144]
  - *Plotly* provides interactive plots and dashboards. It supports many chart types, including bar charts, pie charts, line charts, and scatter plots. Plotly can also be used in conjunction with *Dash* for building interactive web applications.[145,146]
- *ggplot2* is a plotting system for the R programming language inspired by the Grammar of Graphics.[147] It is a powerful framework for creating statistical graphics such as bar plots, pie charts, and histograms.[148]

Figs 3A and B: Current image generators can produce interesting images but there is still room for improvement. This figure shows output images of the two principal authors of this article, produced by ChatOn powered by the Chat GPT image generator (AIBY, Florida, USA; https://aiby.com). (A) Image created using the input function: "Create an image of Dr. Akhil Maheshwari as a young neonatologist." The image shows features identifiable with those in his photograph. However, the infant in the image shows "malformed/bent" lower extremities; (B) Another image created using the input function: "Create an image of Dr. Thierry A.G.M. Huisman as a young pediatric neuroradiologist" shows an expert with a stethoscope around his neck. The screen shows soft organs of the chest and upper abdomen with an unusual anatomy. A surgical lamp can be seen above the imaging equipment. Many observers did not identify the expert in the image as resembling Dr. Huisman

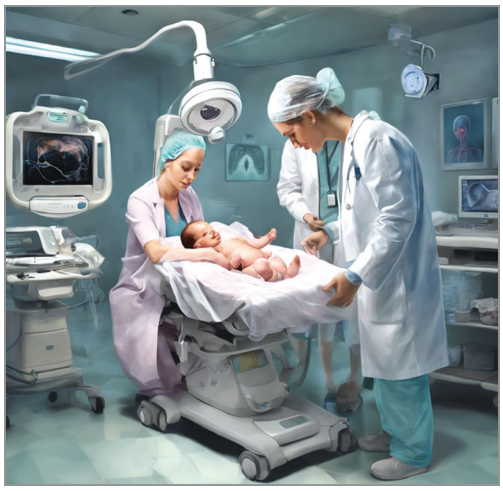


Fig. 4: Output images of a neonatologist and radiologist produced by ChatOn powered by the Chat GPT image generator (AIBY, Florida, USA; https://aiby.com). The input function was "Create an image of a neonatologist and pediatric radiologist." The figure correctly shows the typical clinical setting of two physicians attending to a newborn baby. However, multiple incorrect background details including a "malformed" chest imaging and a "holographic" bony upper chest and skull are seen. Looking at the baby, it almost seems that there might be a hemangioma on the dorsum of the nose. The eyeball appears red, and the ears look 'low-set'. The face seems to show swelling below the zygomatic arch. The abdomen looks a bit distended. In addition, the upper and lower extremities of the newborn seem malformed with subcutaneous edema and syndactyly. The left foot seems to show a hemangioma or a subcutaneous hematoma. So many artifacts!

- *Business intelligence (BI) tools like Tableau and Power BI* offer interfaces for creating visualizations such as bar charts, pie charts, heatmaps, and dashboards. These tools can be customized and help connecting to data sources directly.[149]

Fig. 5: ChatOn powered by Chat GPT image generator (AIBY, Florida, USA, https://aiby.com) output images of a germinal matrix hemorrhage. We used an input function "Create an image of a germinal matrix hemorrhage in a newborn." The output function failed to illustrate a germinal matrix hemorrhage correctly; the figure shows a whirled red color faintly suggesting an acute hemorrhage

GPT can be useful in creating visualizations such as bar diagrams or pie charts, and generating textual descriptions and/or explanations of data visualizations.

GPT for Language Translation

GPT-based models can be used for text generation and summarization, answering of questions, and language translation.[150] Some transformer-based models have been specifically tailored for language translation. The GPT transformer models have been used in Google's transformer-based translation models.[151]

Models like BERT and its variants can be fine-tuned for translation tasks. Models like T5 can be trained in a "translation

mode" to perform translation tasks. Generally, GPT can generate text and understand context well, for translation tasks; specialized models can be even more effective.

GPT to Tabulate Data for Medical Manuscripts

GPT models can be tailored to assist in certain aspects related to tabulating data, even though these are not specifically designed for tabulating data or manipulating structured data formats like tables.[152] These can be useful for:

- *Data summarization:* These can summarize textual data such as in descriptions or explanations of tabulated data to present key points or trends.
- *Data interpretation:* These models can help interpret textual descriptions of data as in identifying important features or insights and conveying those in natural language.
- *Natural language interface:* The GPT models can be used in NLI for interacting with tabular data. Users might be able to ask questions in natural language about the data, and then GPT could help parse and interpret those queries to retrieve relevant information from the dataset.

However, if the primary goal is to create or manipulate tables from raw data, other tools and techniques might be more suitable:

- *Spreadsheet software:* Tools like Microsoft Excel, Google Sheets, or specialized data analysis software provide powerful features for tabulating and manipulating structured data.
- *Data processing libraries:* Programming languages like Python offer libraries such as Pandas[153] which can help generate functions for creating, modifying, and summarizing tabular data.
- *Business intelligence software like Tableau, Power BI, or Looker* are designed specifically for data visualization and analysis, using interactive dashboards and tabular data sources.[154]

Even though GPT might not be the most suitable tool for direct tabulation or statistical analysis of data to determine whether the observed differences or relationships are likely to be real or simply due to random chance.[155] The actual statistical analysis would need statistical software or programming languages such as R, Python with libraries like NumPy, SciPy, or statsmodels, or dedicated statistical software packages like SPSS or SAS.[156,157] Then, GPT applications can be used to query data, where an NLI could be used to parse the retrieved information, summarize/interpret the results of data analysis, identify patterns, and convey those in natural language.

Conclusions

Artificial intelligence, particularly GPT, is emerging as an important tool for developing the infrastructure for processing needs and information systems; operating costs; biases in models; and evaluation metrics. Further work is needed for the development of operational factors that drive the adoption of AI in the US healthcare system, such as ensuring compliance with the health insurance portability and accountability act, team-building/collaboration with healthcare providers, and ensuring continued development and training for the use of AI tools so that correct questions can be asked. We will need teams that include healthcare practitioners, AI developers, clinicians, and decision makers, which can develop a deep understanding of the use of the powerful AI tools integrated into hospital systems and healthcare. Recent developments in analysis of electrocardiograms, electroencephalograms, data from genetics, and prediction of chronic behavioral and other conditions holds promise for newborn medicine.

We all know that there will be challenges in protection of privacy in handling data, bias in algorithms, and in regulatory compliance. A well-designed and critical expert review board will be important for preventing AI-generated systematic errors. Continued efforts will be needed to understand and streamline AI. However, if the medical community hesitates today in overseeing this juggernaut, the inclusion (or not) of AI in medicine might not stop—it might just gradually get extrapolated into patient care from other organizations/industry for cost reasons, not because of justification based on actual clinical data. If we do not get involved in this process to oversee the development/incorporation of AI in newborn medicine, the questions in making decisions will just change from who, to which, when, and how. Maybe this will not be the most appropriate scenario. Hence, we should embrace and participate in the development and regulation of AI. These are valuable tools that can be developed for accurate analysis of large and complex datasets, likely in a more accurate fashion than human observers alone.

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REVIEW ARTICLE

Intracranial Hemorrhage in Neonates: Causes, Diagnosis, and Management

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Abstract

The incidence of symptomatic intracranial hemorrhage (ICH) in newborn infants may be up to 1:2,000 spontaneous births, 1:850 vacuum extractions, and 1:650 forceps-assisted deliveries. Intracranial hemorrhage is frequently associated with adverse neurodevelopmental outcomes in neonates as the perinatal period is a crucial window for brain development. In term neonates, ICH usually occurs during labor due to mechanical injury. On the other hand, preterm infants frequently develop ICH due to hemodynamic instability and fragility of the germinal matrix (GM) vasculature. Based on the location of the hemorrhage, ICH is usually described as epidural, subdural, subarachnoid, intraventricular, and parenchymal bleeds. The cause of neonatal ICH is multifactorial and includes hemorrhage related to prematurity, hemorrhagic stroke, infection, vascular malformations, bleeding disorders, and genetic causes. Iatrogenic coagulopathy during cardiopulmonary bypass/extracorporeal membrane oxygenation (ECMO) can also be a cause. Most patients can be managed without surgical intervention. Some symptomatic infants may need neurosurgical procedure(s) such as external ventricular drainage and/or ventriculoperitoneal shunt(s). The neurodevelopmental outcomes vary according to the maturation of the brain, etiology, place, and extent of the hemorrhage. Clinically concerning complications may include developmental delay, leukomalacia, convulsion, cerebral palsy, and other neurological disorders. In this article, we have reviewed the types, etiology, severity, and clinical outcomes of neonatal ICH.

Keywords: Epidural, Germinal matrix vasculature, Hemorrhagic stroke, Infant, Infection, Intraventricular, Newborn, Parenchymal, Subdural, Subarachnoid.

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Key Points

1. Intracranial hemorrhage is a frequently noted finding in neonates. Severe hemorrhages can result in devastating neurodevelopmental outcomes as the neonatal period is a critical window for brain development.
2. The causes of ICH differ in preterm and term infants. Term neonates tend to develop ICH due to mechanical injury during labor. In preterm infants, ICH may reflect hemodynamic instability, coagulopathy, and/or vascular fragility.
3. The neurodevelopmental outcomes vary according to the maturation of the brain, etiology, place, and extent of the hemorrhage.
4. Most patients can be managed without surgical intervention. Some symptomatic infants may need neurosurgical procedure(s) with ventricular drainage.
5. Neurodevelopmental outcomes of ICH in infants vary according to the maturation of the brain, etiology, place, and extent of the hemorrhage. Developmental delay, cerebral palsy, seizures, and movement disorders are frequently seen.

Introduction

Intracranial hemorrhage is a leading cause of adverse neurological outcomes in infants as it affects the developing brain during a crucial period of structural–functional maturation.[1,2] In term neonates, ICH occurs mainly during labor due to mechanical injury, whereas in preterm infants, it likely results from hemodynamic instability and fragility of the germinal matrix (GM) vasculature.[3,4] Based on the location, ICH is usually described in epidural, subdural, subarachnoid, intraventricular, and parenchymal categories.[5] The etiopathogenesis of neonatal ICH remains unclear, and it could well be multifactorial with contributions from vascular immaturity, ischemia (hemorrhagic stroke), infection, vascular malformations, the still-evolving coagulation system, and genetics.[6] In critically ill infants, there could also be iatrogenic factors such as thoracic overinflation in ventilated infants and extracorporeal membrane oxygenation (ECMO) applied in those with severe cardiorespiratory failure.[3,7] Usage of anticoagulant agents for the prevention

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of thrombus formation in the circuit, and disturbance of cerebral autoregulation secondary to fluctuations in the systemic pressure may predispose to ICH.[8,9]

The neurodevelopmental outcomes of infants with ICH vary according to the maturation of their brain, and the etiology, place, and extent of the hemorrhage.[1] There can be complications such as ventriculomegaly due to adhesions along the Sylvian aqueduct, outlets of the 4th ventricle, or hemosiderosis with obstruction of the pachionic granulations.[10,11] Most are managed without surgical intervention.[10,12–14] Some require neurosurgical procedure(s) such as external ventricular drainage or ventriculoperitoneal (VP) shunt.[15] There might be complications including developmental delay, leukomalacia, seizures, cerebral palsy, and other neurological disorders.[16] The seizures can be subclinical, so electroencephalographic monitoring should be considered in all cases with large ICH.[17] In this article, we have reviewed the types, etiology, severity, and clinical outcomes of neonatal ICH.

Subdural and Epidural Hemorrhage

During vaginal deliveries, vertical molding of the skull predisposes to stretching and tearing of bridging veins including dural sinuses along may produce subdural hemorrhage (SDH).[3,18] Epidural hemorrhage (EH) occurs in neonates mainly after birth-related head trauma with damage to the meningeal artery(-ies) and consequent bleeding into the epidural space.[3,16] Most cases result from biomechanical stress related to a relatively-large fetal cranium, breech presentation, rigid maternal pelvis, frontal-occipital elongation, very rapid or prolonged labor, or instrumental deliveries.[19,20] SDHs are seen in up to 8% of all term deliveries; EHs occur less frequently (<2%).[21,22]

Clinical Presentation

Large hematomas may present with signs of brainstem compression such as opisthotonos, fixed pupils, and apnea.[3] These infants may present with anemia, and signs of increased intracranial pressure (ICP) such as wide-open sutures and bulging fontanelle(s).[23] Hematomas over the cerebral convexity may present with seizures.[24] EHs can be associated with large cephalohematomas or skull fractures.[25] Most small EHs and SDHs remain asymptomatic.[3]

Neonates with SDHs/EHs should be closely monitored and have serial imaging to exclude other brain injuries and the progression of these bleeds.[26] Some EHs can show both venous and arterial injuries.[27] However, the middle meningeal artery is less susceptible to injury than in adults as it is more mobile and usually does not get trapped in osseous grooves close to skull fracture(s).[28] Small skull hemorrhages are frequently seen after vaginal delivery but these typically resolve without any intervention or clinical sequelae.[29] The size of these hemorrhages is not a major determinant of neurological outcomes in these infants.[30]

Diagnosis

Magnetic resonance imaging (MRI) is the best tool for diagnosis of SDH or EH.[31] Computed tomography (CT) can be considered if the patient is hemodynamically unstable or an MRI cannot be obtained urgently. Lumbar puncture (LP) is contraindicated in cases with suspected large hematomas because of the risk of acute brain herniation due to the loss of cerebrospinal fluid.[32] An LP should be considered only after neuroimaging has been done.

Management and Prognosis

Most cases of SDH need only supportive management, including initial stabilization with volume replacement and respiratory support as needed; surgical intervention is usually not needed.[33] Only infants with very large SDHs with acute pressure changes and brainstem dysfunction sometimes require surgical evacuation.[34] Laboratory investigations to rule out bleeding abnormalities and/or sepsis should be considered in these infants.

Infants with non-surgical SDH and EH have an excellent prognosis.[33] Those requiring aspiration of the hematoma also do well if the procedure is performed in a timely fashion; many of these procedures can now be guided by interventional radiology if no other parenchymal pathology is notable. These patients should be followed for the development of hydrocephalus.[35]

Subarachnoid Hemorrhage (SAH)

Subarachnoid hemorrhage usually occurs because of the rupture of the leptomeningeal vessels or bridging veins of the subarachnoid space.[3] These bleeds usually occur due to injury to pial arteries in the subarachnoid or the subpial space, which rupture into the adjacent subarachnoid space.[36] In some cases, SAH may result from the redistribution of intraventricular blood after a GM hemorrhage.[37]

Clinical Presentation

Neonates with severe SAH may present with lethargy and/or seizures.[38] Very mild SAH may be silent. In some cases, SAH may trigger arterial vasospasm and cause ischemic injury in the brain structures perfused by these vessels.[39] Such vasospasm can be examined by duplex sonography or digital subtraction angiography.[40]

Diagnosis

Magnetic resonance imaging is preferred over CT to confirm the diagnosis of SAH as there is no radiation and it is more sensitive for excluding other parenchymal pathologies.[41] Cranial ultrasound (CUS) is less sensitive than either for detection of small SAHs and should be used only if the patient is not stable for transport for MRI or CT.[42] The image through the mastoid fontanel is preferred for excluding subarachnoid hemorrhages within the basal and peri-mesencephalic cisterns.[19] Magnetic resonance angiography (MRA) can help evaluate the degree of vasospasm and may also exclude vascular anomalies such as arteriovenous malformations or aneurysms.[43]

Management and Prognosis

Management of SAH includes symptomatic support, if needed, usage of anti-seizure medications.[44] In severe hemorrhage, blood transfusion, cardiovascular support, and neurosurgical intervention should be considered. Furthermore, moderate-to-severe SAH can be associated with hydrocephalus; serial head circumference measurements and follow-up cUS scans should be done in these neonates.[45] Transcranial Doppler and continuous intravenous milrinone infusion may be helpful in the diagnostic approaches and treatment of cerebral vasospasm.[46]

Intraparenchymal Hemorrhage (IPH)

Etiology and Pathogenesis

The term intraparenchymal hemorrhage (IPH) refers to bleeding into the cerebral or cerebellar parenchyma.[47] Cerebral hemorrhages can be either: (a) primary, which are seen less frequently and are usually related to ruptured aneurysms or arteriovenous malformations; and (b) secondary, which may occur due to venous infarction in large GM hemorrhages-intraventricular hemorrhages (GM-IVHs) in preterm

infants, or in IPHs seen in regions affected by hypoxic-ischemic injury. Other causes of IPH may include the extension from large SAHs, SDHs, or due to coagulation disorders, significant trauma, or dural sinus thromboses.

Intracerebellar hemorrhage happens mainly in preterm neonates.[48] Some cases show these lesions as an extension of large SAHs or SDHs in the posterior fossa.

Clinical Presentation of IPH

Clinical presentation depends on the location and size of the IPHs. In term neonates, the clinical manifestation may include irritability, lethargy, focal neurological signs, such as asymmetry of the movements/tone, and seizures. Most preterm neonates tend to have very minimal clinical manifestations.[47]

Diagnosis

Cranial US through the mastoid and posterior fontanelles is a good, convenient tool to detect these bleeds. The best tool for diagnosis of ICH is MRI with magnetic resonance venography/angiography (MRA/MRV) to determine sinus venous thrombosis, lack of flow distal to an arterial embolus, or vascular anomalies.[49]

Management and Prognosis

Small hemorrhages require observation and symptomatic therapy. Large IPHs may need surgical management. It is essential to rule out dural sinus thrombosis and infection because these may be associated with further progressive injury affecting neurological outcomes.[49]

The prognosis depends on the size and location of the IPH. Small IPH may have minimal long-term complications, while large ones may result in motor deficits, feeding problems, severe neurodevelopmental impairment (NDI), and seizures.[50]

In term infants, cerebellar hemorrhage is usually a relatively benign event, although hypotonia, ataxia, nystagmus, and mild cognitive dysfunction may occur.[51] In preterm neonates, large cerebellar hemorrhages may result in severe cognitive and motor disability. Cerebellar hemorrhages with subsequent loss of cerebellar tissue have been linked to autism, behavioral disorders, and developmental delay later in life.[52] However, there may be minor or no neurological deficit in small cerebellar hemorrhages in both term and preterm neonates.[53]

Pathogenesis of GMH-IVH in Preterm Neonates

Intracerebral hemorrhages in premature infants typically begin in the GM.[4] This is a highly vascularized neuroepithelial zone with metabolically active, proliferating neuroblasts and glia.[6] Germinal matrix is prominent along the full extent of the lateral ventricles in the fetal brain beginning at 7–8 weeks and peaks around 24 weeks' gestation. It then begins to involute and almost disappears by 36–37 weeks.[54] In extremely premature infants, the hemorrhage can be seen in adjoining regions all around the lateral ventricles. With advancing gestation, the region around the caudothalamic groove persists the longest during gestation and consequently, most GMH occur in this region in mid-gestation infants.[55,56]

The pathogenesis of these hemorrhages is complex and likely multifactorial.[57,58] The technological and scientific advances in neonatal intensive care have improved the survival of extremely preterm neonates and hence, by extension, led to a relative increase in the number of preterm neonates at high risk of developing GM-IVH.[59] The incidence of these hemorrhages is inversely related to gestational age and most commonly occurs in neonates of ≤32 weeks' gestation. The incidence range of GM-IVH has been reported at 5–52% (Asia-5–36%, North America up to 22%, and Europe 5–52%).[60] Mild GV-IVHs constitute about 60% and 25% are severe.[61] Nearly, half of all GM-IVHs occur in the first 6 hours, and the occurrence becomes very uncommon after the 5th postnatal day.[62]

Germinal matrix hemorrhage-intraventricular hemorrhage can be restricted to the GM, involve lateral cerebral ventricle(s), or cause periventricular hemorrhagic infarction (PVHI).[63] Most affected infants are asymptomatic. The neurodevelopmental outcomes are determined by the underlying etiology, maturity of the brain, site, and extension of the hemorrhage. Abnormal neurodevelopmental outcomes such as post hemorrhagic hydrocephalus (PHH), seizures, cerebral palsy, and impaired cognitive, hearing, and visual impairment may occur. No optimal treatment exists; potential interventions currently under evaluation include stem cell treatment and endoscopic removal of clots.[64] Our current understanding of the pathogenesis of these hemorrhages is summarized below:

(a) Fragility of the Cerebral Vasculature

Germinal matrix contains an immature, extensive vascular rete, a network of fragile, irregular vessels that are not supported by a robust-looking basement membrane; the endothelium contains only a few tight junctions; and the surrounding astrocytes contain lesser-than-usual glial fibrillary acidic protein in the end-feet. These structural deficiencies make the GM vasculature more fragile, and consequently, increase the risk of hemorrhage.[54] The high vascularity in the GM increases the risk of hemorrhage in these regions as compared with the lesser vascularity regions in other parts of the brain. Furthermore, this fine capillary network drains into the deep venous system, which forms a terminal vein that deviates in a *U*-turn and drains into the internal vein circulation. These flow patterns increase the risk of GM-IVH even more.[65]

The etiopathogenesis of GM-IVH is still being elucidated. It is likely multifactorial; the three most important risk factors are prematurity, fragility of GM vasculature, and fluctuations in cerebral blood flow (CBF).[56,66,67] Increased expression of several factors during hypoxia and hypotension, such as cyclo-oxygenase 2 (COX-2), prostaglandins (PGs), epidermal growth factor receptor, and inflammatory modulators such as transforming growth factor, interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF) is likely to be important.[6,68–70] These mediators may disrupt tight junctions, modulate the blood–brain barrier, and activate microglia. Microglial activation can stimulate the release of reactive oxygen species (ROS), which can damage the endothelium, alter hemostasis, and increase anaerobic metabolism.[71] This feed-forward loop may increase the risk of periventricular parenchymal infarction.[72–74] Hemorrhagic events can also alter vascular lumina and impair brain perfusion. Venous stasis within the periventricular white matter can lead to parenchymal venous infarction.[75] Coagulation or platelet disorders may also predispose to hemorrhage.[54]

Clinically, low-birth weight, low Apgar scores, and the presence of hypercapnia, acidosis, hypoxemia, infection, and systemic hypotension have been associated with GM-IVH.[76,77] Bleeding in the GM can disrupt the ependyma leading to the filling of the cerebral ventricles with blood. Antenatal steroid therapy in women at risk of premature delivery is protective. Factors that likely increase the risk of severe IVH include 5-minute Apgar scores <7, extremely low gestational age, need for intubation, and vasopressors within the first 24 hours after birth.[78] The pathogenesis of IVH and IPH

in term neonates include hypoxic-ischemic encephalopathy (HIE),[79] traumatic delivery, platelet/coagulation abnormalities,[80] sinovenous thrombosis,[81] rupture of vascular malformation, and mutations in collagen genes.[82]

(b) Autoregulation of CBF

In mature infant, cerebral brain vessels maintain a stable blood flow despite changes in systemic blood pressures (BPs). In contrast, this autoregulation of CBF is mostly unpredictable and transient in premature infants.[4,83] There is a "pressure-passive" dependence of CBF on systemic BPs in infants born at lower gestational ages, with low-birth weights, and who have fluctuations in the systolic and diastolic blood flow velocity.[83,84]

Unstable CBF can enhance the risk of GMH.[85] Factors associated with fluctuations in CBF velocity include systemic hypotension, irritability, and asynchrony between spontaneous and ventilator breaths. Hemodynamically significant patent *ductus arteriosus* (PDA) can also increase the variability in CBF.[86] Hypoglycemia, hypoxia, and hypercarbia can also cause cerebral vasodilatation and have been correlated with the development of GMH.[87,88]

Unstable BPs increase the risk of GM-IVH,[89] especially when the initial low blood pressure (BP) readings are followed by high, fluctuating BPs.[90] Very low-birth weight (VLBW) neonates show pressure-passive cerebral perfusion in up to 20% of the time. In extremely low-birth weight (ELBW) infants, this pressure passivity might be seen in more than 50% of the time.[91] Even minor steps of routine clinical care such as tracheal suctioning, diaper changes, changing position/posture;[89,92] and rapid infusion of intravenous fluids can alter CBF.[93] These deficiencies in CBF autoregulation can prolong ischemic and hyperperfusion phases of brain injury and consequently, increase the risk of GM-IVH.[94] In critically ill neonates, pulmonary hypoxia, hypercarbia, bradycardia, acidosis, apnea, persistent patency of the *ductus arteriosus*, and changing thoracic distension with high-pressure ventilation can destabilize the systemic and cerebral hemodynamics, cause ischemic alterations in cerebral perfusion, and have been associated with GM-IVH.[83,89,95,96] These changes can also contribute to reperfusion following cerebral ischemia.[97]

(c) Disorders of Hemostasis due to Immature Coagulation and Platelet Function

The role of thrombocytopenia in the development of GMH in neonates has been reported.[98] However, other studies found no correlation. Studies on the severity of the thrombocytopenia and its association with GMH have been limited with varying results.[99,100] However, low gestation age and birth weight are known to affect platelet function and hence, it is quite plausible that platelet dysfunction and related coagulation disorders may contribute to the risk of GM-IVH in preterm neonates.[98,101] Thrombocyte hyporeactivity together with fragility of the GM and hemodynamic instability may contribute to the risk of GMH in preterm neonates. Studies on adhesion, aggregation, and activation of the thrombocytes in preterm neonates have shown functional improvement of platelets after 4–10 postnatal days.[102,103]

(d) Genetic Factors

Genetic risk factors include prothrombin gene mutations, methylenetetrahydrofolate reductase polymorphism, and factor V Leiden gene mutations.[104,105] Screening for polymorphisms or mutations should be considered in neonates with an atypical presentation of PVHI.[106]

Table 1: GMH grading based on the computed tomography (CT)

Grade I	Germinal matrix hemorrhage
Grade II	Hemorrhage extent to lateral ventricle without dilatation
Grade III	Ventricle hemorrhage with ventricle dilatation
Grade IV	Intraparenchymal hemorrhage

Table 2: GMH grading based on cranial sonography[88]

Grade I	Germinal matrix hemorrhage
Grade II	Hemorrhage extent to lateral ventricle without dilatation and or hemorrhage occupying less than 50% of the ventricle
Grade III	Ventricle hemorrhage with ventricle dilatation
Grade IV	Also, called an intraparenchymal hemorrhage

(e) Mode of Delivery

Some studies reported that elective cesarean section is associated with a decrease in the risk of severe grades of GMH in preterm neonates when presenting with preterm labor. However, recent data showed no correlation. Therefore, the mode of delivery could be decided based on the obstetrical indications.[107]

Clinical Presentation

Approximately, 50% of GMH are asymptomatic and are detectable only during routine screening by the cranial US.[108] Infants with symptoms are more likely to have a severe grade of GM-IVH. Symptomatic infants may present with acidosis, hyper/hypoglycemia, and sudden reduction in hematocrit level. Clinical examinations may reveal lethargy, tense fontanelle, respiratory distress, apnea, temperature instability, unexplained pallor, and convulsions. Uncommonly, progression can be fast with progress to stupor, coma, decerebrate posturing, and death. Infants with a severe type of GMH are more likely to have clinically detectable convulsions[109] and inappropriate antidiuretic hormone (ADH) release.[110]

Grading of GM-IVH

The severity of GM-IVH is graded based on localization, the extent of bleeding, and the presence of acute ventricular dilatation. GM-IVH can be mild or severe, unilateral or bilateral, and can also be classified based on localization, the extent of bleeding, and the presence of acute ventricular dilatation. Mild GM-IVH includes grades I and II, while severe hemorrhages include grade III and PVHI (previously graded as GMH grade IV).[111] Hemorrhages restricted to the subependymal zone are classified as grade I. Extension of bleeding into the non-distended lateral ventricle(s), where the hemorrhage occupies <50% of the ventricular(s) diameter is classified as grade II. Grade III hemorrhages occupy >50% of the ventricular diameter. Periventricular hemorrhagic infarction[112] involves compression of the terminal vein by the GM hemorrhage and consequent congestion of the draining medullary veins. These events predispose to ischemia, infarction, and then to hemorrhagic changes in the periventricular white matter.[113]

Grading of GMH was first described by Papile et al.[114] and presented in Table 1 and later modified by Volpe.[88] The information in Table 2 is routinely used in clinical practice.

Diagnosis of GM-IVH

Cranial US is a widely used, non-invasive, and easily accessible diagnostic tool to diagnose/monitor GM-IVH. It is performed using

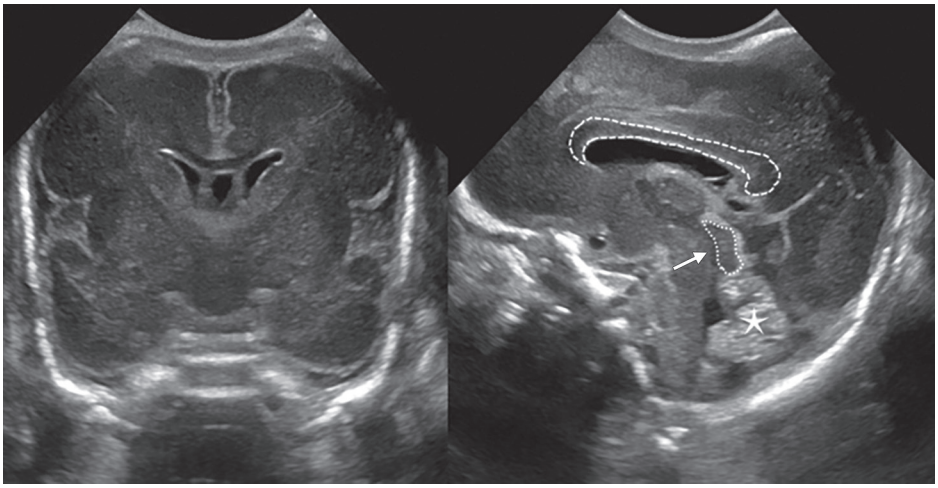


Fig. 1: Coronal and sagittal ultrasound of the normal brain through the anterior fontanel of a preterm 28-weeks' gestational age newborn. The surface of both hemispheres appears smooth, the Sylvian fissures are wide open, the cavum septum pellucidum is present, all findings are compatible with prematurity. On the midsagittal image, the corpus callosum (outlined) as well as the tectal plate (outlined) are easily identified. The Sylvian aqueduct (arrow) is seen anterior to the tectal plate. Within the posterior fossa the brainstem and hyperechogenic vermis (asterisk) are noted

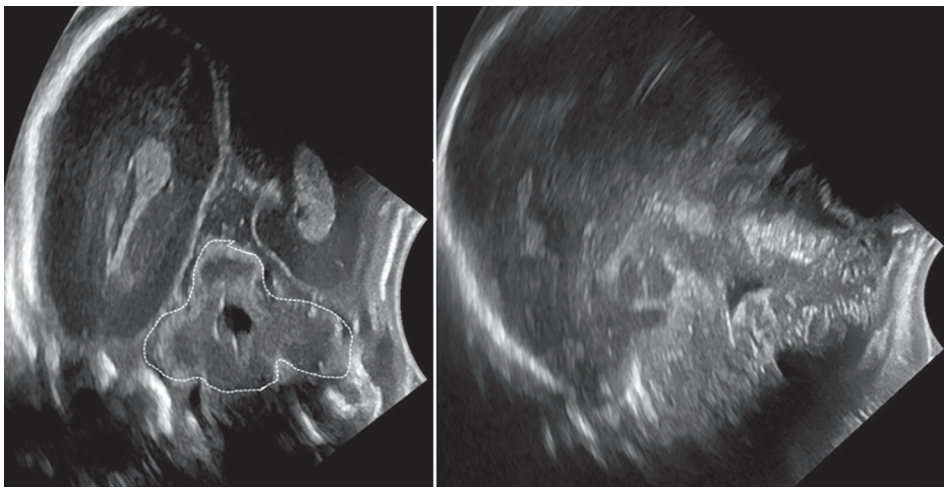
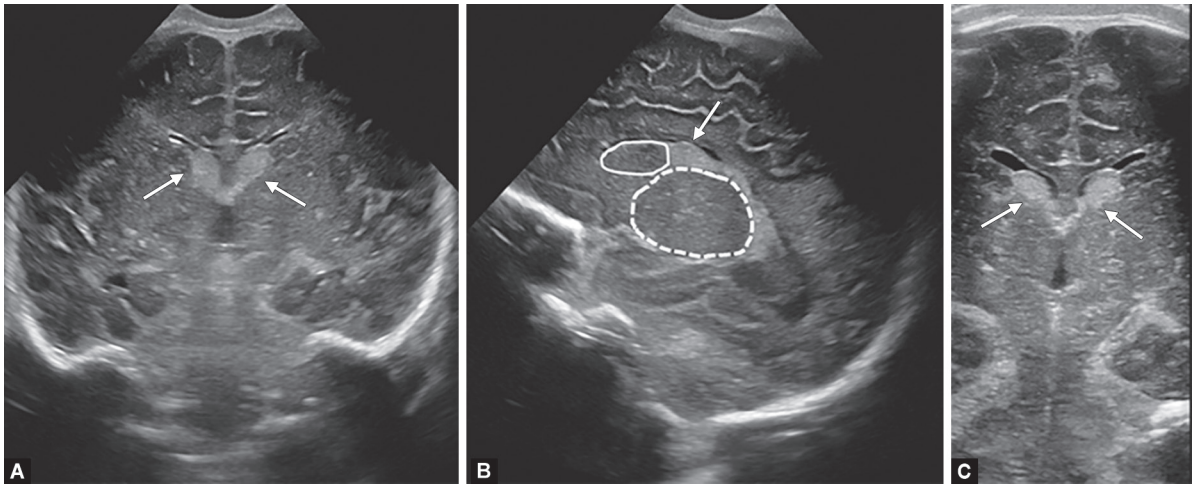


Fig. 2: Mastoid views of the normal posterior fossa in two newborns [left at 27 weeks' gestational (outlined) and right at 35 weeks' GA]. The progressing foliation of the cerebellum is noted, smooth at 27 weeks' gestation and progressively complex at 35 weeks' gestation. The fourth ventricle is filled with hypoechogenic CSF

the cranial fontanels as sonographic windows for assessing the ventricular system and periventricular white matter. All preterm infants <32 weeks' gestation and/or those born VLBW should be considered for GM-IVH screening.[115] Infants born at ≥32 weeks are considered for screening if they need critical care, have sepsis, necrotizing enterocolitis (NEC), abnormal neurological manifestations, and require major surgical intervention(s). The cranial US should include descriptions of findings on both left and right sides in parasagittal and coronal views; the location, size, and extension of the lesions should be determined.[116] The anterior fontanelle is the most frequently described site for the cranial US, although the mastoid and posterior fontanelles can be useful.[115] Grade I GMH images show focal hyperechogenic, rounded/nodular lesions in the caudothalamic groove. Grade II bleeds are similarly hyperechogenic but with additional blood products within non-distended ventricles. Grade III GM-IVH shows blood clots within the GM and enlarged ventricles. PVHI shows focal enlarged GMH(s) at the level of caudothalamic notches and notable hyperechogenicity of the periventricular white matter within the distribution of the venous drainage[117] (Figs 1 to 7).

The timing of screening is usually based on institutional protocols. As most cases of GMH occur in the 1st week after birth, the American Academy of Neurology (2020) recommends performing the initial cUS at 7–14 days after birth and a repeat scan at 36–40 corrected gestational age.[56,67] However, it is essential to consider that GMH may progress and the grade may change over the period, justifying the need for cUS screening for infants with abnormal sonographic findings adjusted according to the clinical presentation.[118] Cranial US is limited to GM hemorrhages >5 mm; smaller GMHs are better detected by CT and MRI. MRI is superior to cUS at detecting small GMHs <5 mm, white matter lesions, and cystic and hemorrhagic abnormalities. However, GMH lesions <5 mm usually do not alter outcomes, resolve and do not need an MRI study to confirm. MRI could be considered for infants whose cranial US



Figs 3A to C: Coronal (A), Sagittal; (B) and high-resolution coronal; (C) Ultrasound images of newborn with bilateral grade I GM-IVH in the region of the caudothalamic grooves (arrows). The groove between head of the caudate nucleus (outlined by the solid line) and the thalamus (outlined by the dashed line) harbor the germinal matrix hemorrhage. The ventricles are of normal size

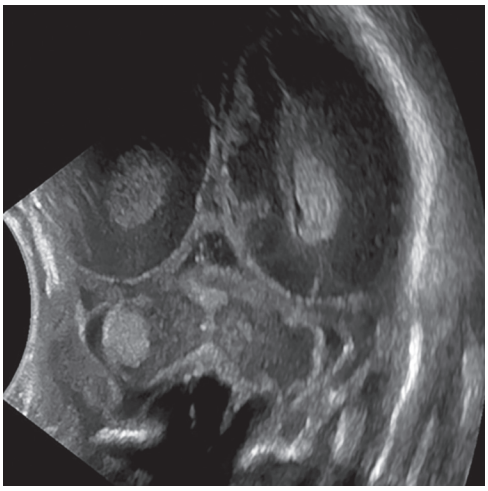


Fig. 4: Coronal view of the posterior fossa through the mastoid fontanel show a focal hyperechogenic hemorrhage in the GM of the right cerebellar hemisphere. The choroid plexus is physiologic large within the occipital horn of the supratentorial lateral ventricles in this premature newborn

reveals severe GMH-PVH, periventricular leukomalacia (PVL), post hemorrhagic ventricular dilatation (PHVD), and other abnormalities associated with the risk of white matter infarction.[119]

Management of GMH-IVH

We still do not have a specific therapy for GM-IVH.[97] Therefore, we need to focus on preventing these hemorrhages. A multi-pronged approach, with steps during the pre-, peri-, and postnatal periods is needed.[120] The most important way to prevent GM-IVH will be to prevent preterm delivery, as the premature brain has high levels of vascular fragility and poor regulation of CBF.[111] Preterm deliveries can be prevented in some cases by using tocolytics and cervical cerclage.[121] Avoidance of tobacco and treatment of bacterial vaginosis may have some effect.[122] Head vibrations during neonatal transportation could increase the risk of hemorrhage, although there have been some reassuring advancements in the last few years.[123] Hence, it might be safer to conduct high-risk deliveries in a tertiary unit.[123]

Antenatal Steroids

Treatment of pregnant women with steroids (betamethasone or dexamethasone) prior to delivery can reduce the risk of GM-IVH through stabilization of GM vasculature; these changes are likely achieved through suppression of vascular endothelial growth factor and increased transforming growth factor-β levels.[57] Furthermore, administration of steroids to birth interval of 24 hours prior to birth to 7 days then after has been shown to reduce the risk of hemorrhage in preterm neonates.[124]

DCC can prevent GM-IVH.[125] It might optimize the cardiac preload following placental transfusion and consequently, increase CBF.[126] The American Academy of Pediatrics (2020) recommends at least a 30–60-second delay prior to clamping the cord.[127]

Volume Guarantee Ventilation

Volume targeted/guarantee ventilation can achieve nearly stable tidal volumes through automatic weaning of peak inspiratory pressures while improving lung compliance.[128] Such an e-targeted mode can limit the episodes of hypocarbia that may predispose to GMH.[129]

Pharmacologic Prophylaxis

Indomethacin is a prostaglandin inhibitor, a drug that inhibits free radical formation and stimulates the maturation of the GM vasculature.[130] In ELBW neonates, prophylactic administration of 3–6 doses of indomethacin after birth can reduce the incidence of high-grade GM-IVH.[131,132] However, a reduction in NDI has not been consistently documented (aOR 1.1, 95% CI, 0.8–1.4).[133] Numerous studies have suggested that prophylactic indomethacin may have a better therapeutic effect on the incidence of GM-IVH in carefully chosen high-risk target groups of infants.[134,135] The authors developed a predictive model for severe GM-IVH based on clinical characteristics that would encourage targeted prophylactic indomethacin therapy in high-risk infants. However, the conducted studies did not support selective prophylactic indomethacin treatment to improve the NDI in ELBW infants at high risk for severe GMH.[136,137] The optimal timing and broad applicability is still controversial. Considering such contradictory evidence regarding the benefits and a lack of conclusive improvement in developmental outcomes, and a concern for side effects, this drug is not universally

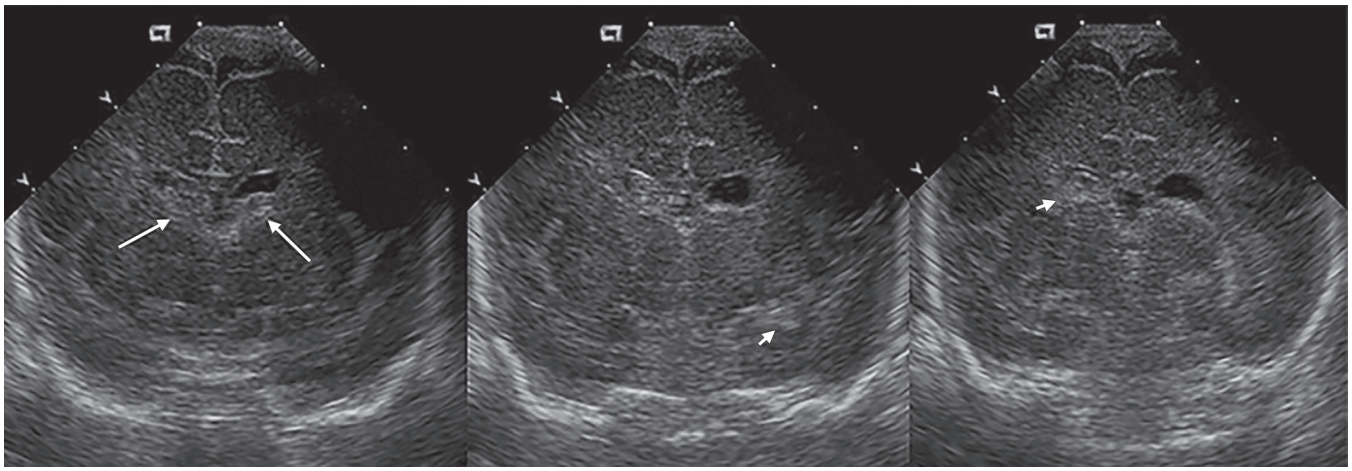
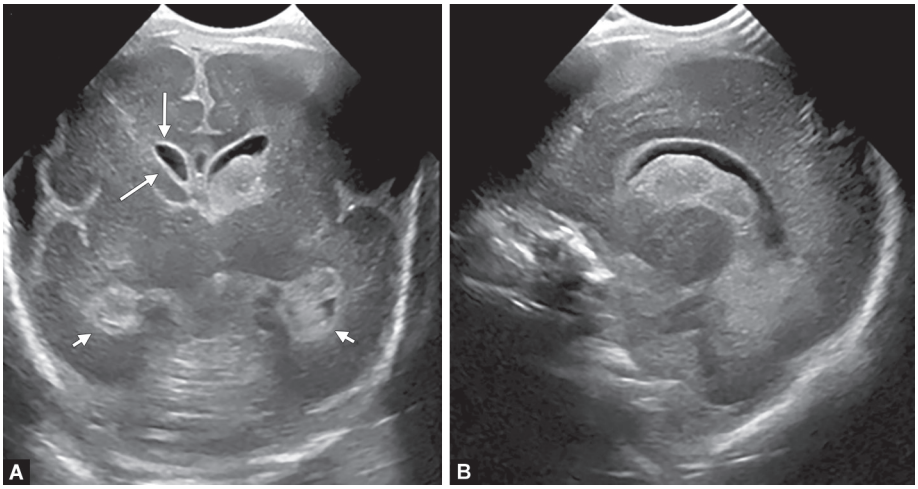


Fig. 5: Coronal ultrasound images through the anterior fontanel show a bilateral grade II GMH located within the caudothalamic grooves (long arrows) with additional hyperechogenic blood products within the temporal horn of the left lateral ventricle as well as on top of the choroid plexus within the right lateral ventricle (short arrows) in a 2-day-old, 29-weeks' gestation infant



Figs 6A and B: Coronal and sagittal ultrasound images acquired through the anterior fontanel in a 1-week-old preterm newborn show a mid-sized GM-IVH within the left caudothalamic groove. Blood products are also noted within the temporal horns bilaterally (short arrows). The ventricles are moderately widened. Constellation of findings are compatible with a grade III GM-IVH. The ependymal lining appears hyperechogenic (long arrows) secondary to the intraventricular blood products

accepted. Pharmacological drugs like vitamin K, phenobarbitone, and vitamin E have shone some promise.[138] However, further studies are also needed here to demonstrate the safety and evidence of the benefit of these agents.

Postnatal prevention of GM-IVH should be aimed toward avoiding risk factors of hemorrhage. Stabilization of respiratory status, BP, fluid and nutritional support, assisted ventilation, control of seizures, and timely correction of acidosis could prevent the progression of GM-IVH.[57] Some of the most promising strategies are summarized in Table 3.

Long-term follow-up includes neurologic and developmental follow-up.

Supportive Management of GM-IVH

Supportive care includes maintaining stable cerebral perfusion by maintaining normal blood volume and BP.[97] Correction of anemia, thrombocytopenia, or coagulation disturbances should be considered.[139] Transplantation of the allogeneic mesenchymal stem cells (MSCs) is a promising intervention as documented to reduce brain injury and PHH following GMH, although more trials are needed to evaluate the efficacy.[140]

Clinical Outcomes and Prognosis

The prognosis of cases with GMH depends on the severity of bleeding, parenchymal injury, occurrence of seizure(s), and the need/type/timing of intervention.[141] Improving the quality of life of the patients should be targeted through appropriate management and follow-up.

Neurologic complications like PVHIs, PVL, PVHD, cerebral palsy, convulsions, and cognitive disabilities are more prominent in infants with severe GM-IVH, although these can sometimes be associated also with low-grade GMH cases.[142,143] Approximately, 50–80% of premature neonates with severe GMH develop severe developmental disabilities and require special education in school.[144] The pathogenesis of the two major complications of GMH such as PVHI and PHVD are discussed below.

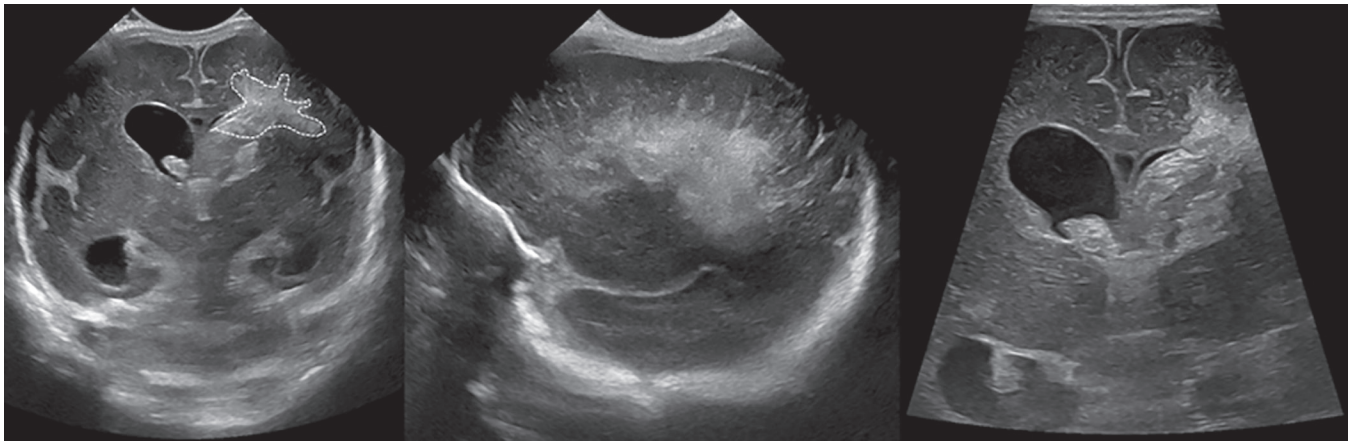


Fig. 7: Coronal and sagittal and high-resolution coronal ultrasound images acquired through the anterior fontanel show a left sided GM-IVH with adjacent fan shaped hyperechogenicity within the adjacent periventricular white matter (outlined by a dashed line). The area of white matter hyperechogenicity matches the area of white matter that drains over the intramedullary veins into the subependymal deep venous system which is obstructed/compressed by the GM-IVH. In the sagittal view, the dilated or partially thrombosed intramedullary veins are reality identified along the periphery of the hyperechogenic area. The ventricles are dilated; additional blood clots are noted within the right lateral ventricle. Constellation of findings are consistent with a PVHI previously known as a grade IV GM-IVH

Table 3: Strategies for prevention of GM-IVH

Prenatal	*Perinatal*	*Postnatal*
Prevention of preterm delivery[111]	Delivery at a tertiary neonatal intensive care unit	Prevent conditions that interfere with autoregulation:
Corticosteroids (World Health Organization 2015)	Delayed cord clamping	Hypo/hypercarbia
		Hypoxia
		Acidosis
		Prevent conditions that overcome autoregulatory abilities: hypertension
		Prevent conditions that contribute to rapid fluctuations of cerebral blood flow:
		Avoidance inter-hospital transportation
		Minimize vigorous handling, stimulation
		Pharmacologic prophylaxis (Indomethacin)
		Avoid unnecessary frequent suction, rapid volume expansion, ventilatory asynchrony
		Prevention and treatment sepsis
		Correction of the bleeding disorders

Post Hemorrhagic Ventricular Dilatation (PHVD)

Post hemorrhagic ventricular dilatation is a frequent complication seen in 1–3 weeks following a severe hemorrhage.[120] The incidence of PHH in mild GMH may reach 1–4%, while in severe types of GMH up to 30–50%.[58,145] It is usually a transient, spontaneously recovering disorder that can be diagnosed by cUS. Around 30% of PHVD may develop progressive hydrocephalus, and 15% of these cases require surgical intervention.[58,142]

The primary cause of PHVD is the formation of fibrin during hemorrhage, which causes obstruction in the acute period and platelet activation in the chronic period that evokes/accentuates inflammation.[88] Most cases presented with a communicating hydrocephalus due to obliteration of the arachnoid villi by microthrombi and consequently, altered cerebrospinal fluid (CSF) reabsorption.[14] However, non-communicating hydrocephalus can also occur due to obstruction of the Sylvian aqueduct or foramen of Monro by a blood clot or due to subependymal scarring.[14] Early diagnosis by serial cranial US screenings and timely intervention can minimize the severity of the PHVD.[120]

The results of serial cranial US should be followed.[56] Based on the Fenton growth chart (2003),[146] HC should normally increase by 1 mm per day in neonates from 26 to 32 weeks' gestation and by 0.7 mm in the 32–40 postnatal weeks.[146] A persistent increase of ≥2 mm/day or 14 mm in a week is abnormal.[147] Besides the rapidly increasing HC, other findings include bulging fontanelle, widely separated sutures, apnea, hypo-/hypertonia, irritability, and altered consciousness.[148]

Management of PVHD is targeted at preventing secondary injury due to increased ICP.[149] At present, a VP shunt is accepted as the most-effective surgical intervention in PVHD.[150] However, the insertion of a shunt may have to be deferred in infants who are too small or sick.[151] In these patients, the ICP can be controlled by applying a ventricular-subgaleal shunt or ventricular reservoir.[152,153] Many other methods including repeated lumbar punctures, drug therapy (acetazolamide/furosemide), choroid plexus coagulation, and intravenous fibrinolytic therapy have been tried but not found to be as beneficial as VP shunts in minimizing neurologic injury.[147,154] Furthermore, acetazolamide and furosemide often predispose to

electrolyte disturbance and nephrocalcinosis,[155,156] and might also independently cause long-term neurologic abnormalities.[157] The most frequently seen complications of VP shunts are infection and obstruction.[158]

Periventricular Hemorrhagic Infarction (PVHI)

Periventricular hemorrhagic infarction has been considered as GM-IVH grade IV due to the extension of a large grade III hemorrhage.[159] However, further studies have shown it can often be a separate and an asymmetric/unilateral lesion. PVHI mainly includes frontal and parietal areas and can evolve into a porencephalic cyst.[65] The outcomes of the PVHI depend on the site of the lesion; approximately half of all infants with a large unilateral infarction may develop contralateral hemiparesis; those with bilateral PVHI may develop spastic quadriparesis.[160] Other clinical findings include epilepsy, cerebral palsy, visual disturbance, and cognitive dysfunctions.[161]

Follow-up of Survivors of Neonates with GM-IVH

Neonates with a history of GM-IVH are at risk for cognitive and/or motor deficits.[143] Therefore, outpatient follow-up should be considered to identify associated morbidities and those at risk should be provided appropriate management through a comprehensive neuro-rehabilitation program.[162]

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REVIEW ARTICLE

Utility of Point-of-care Ultrasound in Hypoxic-ischemic Brain Injury in Neonates

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Abstract

Background: Perinatal asphyxia and resulting hypoxic-ischemic encephalopathy (HIE) remain a significant cause of neonatal morbidity and mortality. This review focuses on the utilization of bedside cranial ultrasound in HIE to guide appropriate therapy, monitor disease progress, provide prognostic information, and help identify relevant research areas.

Methods: A comprehensive literature search was conducted to review recognized patterns of HIE seen on ultrasound. Further efforts were focused on understanding the clinical relevance of these changes in the management of such infants and the prediction of long-term neurodevelopmental outcomes.

Results: We reviewed cranial sonographic changes in asphyxiated neonates. Dynamic changes are observed across various time frames; hyperechogenicity of the thalamus, basal ganglia, and the altered appearance of the posterior limb of the internal capsule (PLIC) are frequently seen in acute and subacute insults. Also, a resistive index of 0.55 or less in cerebral Doppler studies within the first 72 hours of life is associated with adverse short- and long-term outcomes and increased mortality.

Conclusion: Bedside cranial ultrasound is a useful screening tool for the diagnosis and monitoring of neonates with HIE. However, further studies are needed to improve our understanding of sonographic findings as predictors of adverse neurodevelopmental outcomes and mortality in affected neonates.

Keywords: Basal ganglia, Birth asphyxia, Cerebral Doppler, Cranial ultrasound, Echogenicity, Four-column sign, Hypoxic-ischemic encephalopathy, Neonates, Periventricular leukomalacia, PLIC sign.

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Key Points

- Cranial ultrasonography (USG) is a valuable screening tool in the diagnosis and management of asphyxiated neonates.
- Serial USG can identify the evolution, pattern, timing, and severity of injury.
- Near-total asphyxia with extensive grey and white matter involvement is associated with increased neurological morbidity and mortality.
- Resistive index values on cerebral Doppler study before initiation of therapeutic hypothermia can serve as an important marker of long-term prognosis.
- We need a better understanding of the progression of HIE in neonates, focusing on its diagnostic and prognostic implications, and identifying relevant research areas.

Introduction

Perinatal asphyxia and consequent hypoxic-ischemic encephalopathy (HIE) is a frequently seen pathology associated with considerable short- and long-term neurodevelopmental morbidities and mortality.[1,2] Neuroimaging, including cranial ultrasonography (USG) and magnetic resonance imaging (MRI), are important tools for confirming the diagnosis, assessing the severity of the injury, guiding clinical decisions, and predicting the likelihood of adverse outcomes. Magnetic resonance imaging with diffusion-weighted imaging and proton-spectroscopy can help predict adverse outcomes in HIE, but it has limitations as an imaging

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modality including its cost, need for sedation, and limitations of portability of the equipment.[3,4]

Point-of-care ultrasound (POCUS) is increasingly being recognized as a useful tool in the management of HIE[5] the equipment is widely available, is inexpensive and can be used for sequential evaluation of the progression of encephalopathy. If the care provider has a reasonable grasp of neuroanatomy seen through the acoustic window, cranial USG can help outline diverse pathologies including grey- and white-matter ischemic injury, intracranial bleeding, and any malformations. Additionally, Doppler studies can help in real-time assessment of perfusion and the evolution of the injury.[6–8] These can also serve as pivotal screening tools prior to commencing therapeutic hypothermia (TH).[9,10] In this article, we have reviewed the utility of cranial USG in the diagnosis, monitoring, management, and prognostication of HIE.

Technique and Normal Views

A brief summary of the technical needs in the sonographic assessment of HIE is provided below:

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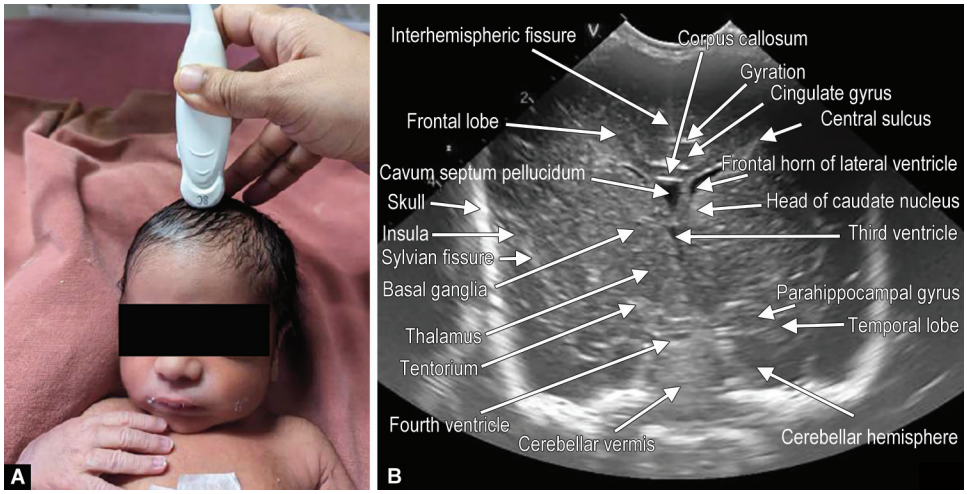
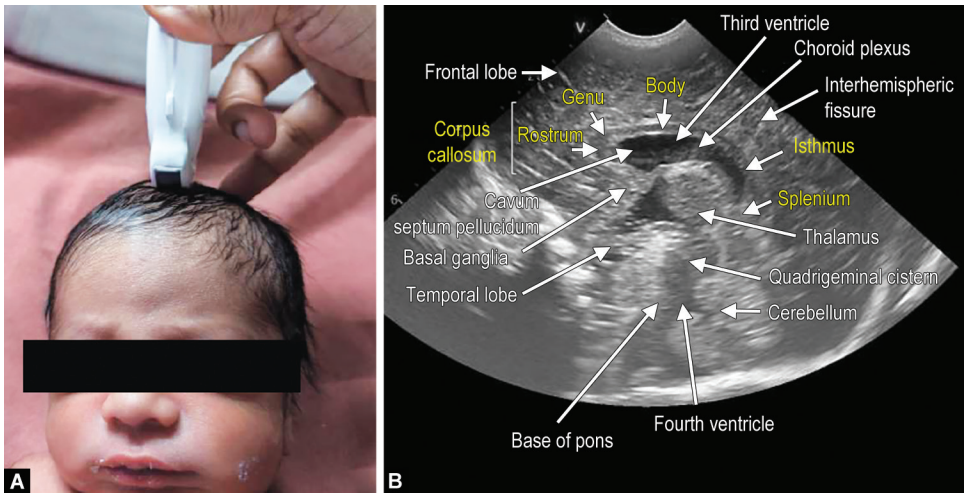
Transducer

A multi-frequency (5–10 MHz) convex or linear array transducer is useful. The lower-frequency transducer enables visualization of deeper structures including the deep grey matter, temporal lobes, and the posterior fossa, whereas the higher frequencies can improve the resolution for visualizing the more superficial cortex



Figs 1A and B: Anterior fontanel coronal and sagittal views. (A) Probe in coronal plane; (B) Mid-ventricle view showing various parts. The normal echogenicity of the brain parenchyma, including that of grey and white matter are notable



Figs 2A and B: Anterior fontanel sagittal view. (A) Probe in sagittal plane; (B) Midline sagittal view showing various parts. Parts of the corpus callosum shown in yellow font

and underlying subcortical white matter.[11,12] In addition to standard cranial USG views through the anterior fontanel, ancillary acoustic windows such as the mastoid fontanels for supratentorial structures and the temporal window for a transverse view of the brainstem area can improve diagnostic accuracy.[11] Cine clips providing real-time evaluation are more useful than static images for appreciating subtle changes in echogenicity (Figs 1 to 4).[13]

Normal Pattern of Echogenicity on Cranial USG

The white matter normally shows a loosely packed, low-level granular echogenicity. It becomes less echogenic as it merges with anechoic grey matter. This normal pattern of regional echogenicity progressively increases from grey matter, thalamus, and descending corticospinal tracts, to the choroid plexus (Figs 1 to 4).

Abnormalities on Grey-scale Cranial USG in Asphyxiated Neonates

Sequential assessment using cranial USG can provide a pictorial representation of the pattern, evolution, and severity of brain injury. In terms of pathophysiology, the acute phase of HIE is marked by anaerobic metabolism, depletion of high-energy metabolites, cytotoxic edema, and neuronal apoptotic cell death, followed by ongoing inflammation, and secondary energy failure. In contrast, the chronic phase includes reparative changes and reorganization that may continue for months.[14–16] Cerebral edema, neuronal necrosis, gliosis, infarcts, hemorrhages, hypermyelination, and calcification may manifest as diffuse or patchy echogenicity on cranial USG, depending on neuropathological patterns of injury.[17] Typical findings suggestive of near-total asphyxia become more apparent after the first 24–48 hours following the onset of HIE, but the variability of such findings depends on the severity of the injury, the presence of coexisting complications, and the onset of insult.[17]

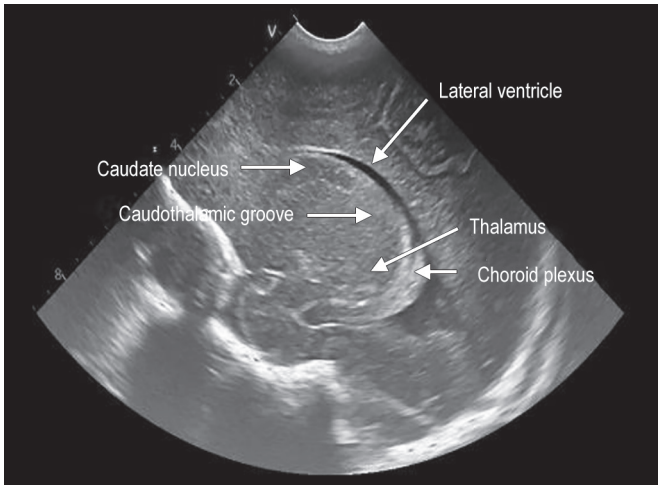
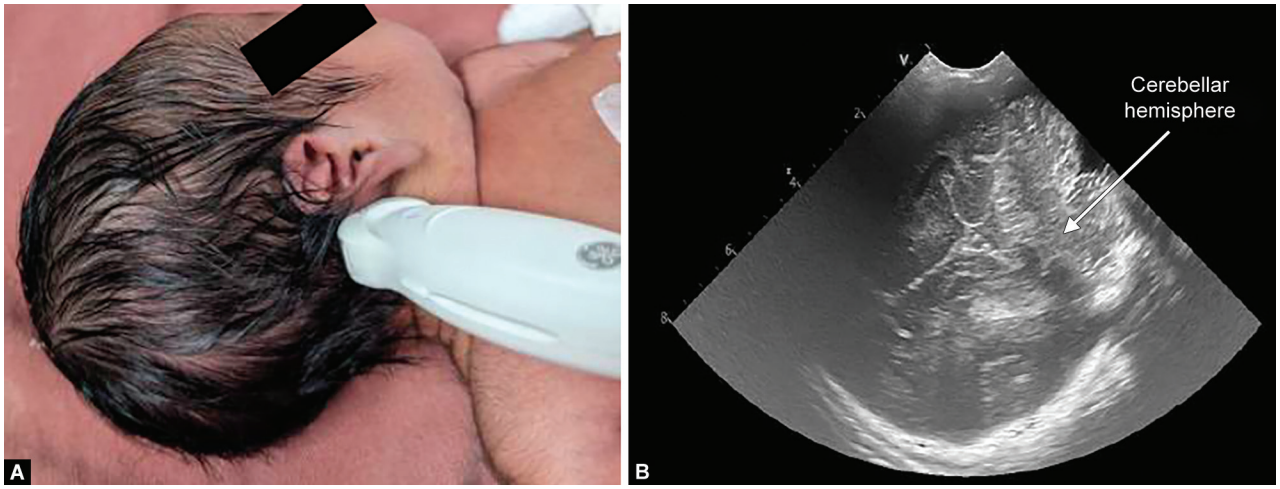


Fig. 3: Anterior fontanel parasagittal view showing caudothalamic groove, thalamus, and the choroid plexus

Evolution and Pattern of Asphyxia-induced Brain Injury

Changes in Acute and Subacute Phase

- Increased white matter echogenicity
  Depending on the severity of the injury, diffuse or patchy echogenicity in periventricular and subcortical regions is associated with similar or slightly less prominent echogenicity in the choroid plexus.[13,18] Severe subcortical white matter hyperechogenicity appears as *'tramlines'* due to hypoechoic signals of cortex in between, best seen in sagittal views (Fig. 5).[18] Primary white matter injury manifests within a context of both partial and sustained hypoxia.[17]
- Loss of grey-white matter differentiation
  In less severe cases, grey-white matter differentiation may be accentuated due to enhanced white matter echogenicity compared with the cortical grey matter.[19] However, parenchymal edema in more severe injury shows a loss of the anatomical landmarks of the brain such as sulci and interhemispheric and sylvian fissures (Fig. 6).[13,18]
- Compression of brain structures due to parenchymal edema
  Cerebral edema may be seen within 24–48 hours following injury due to ongoing intrapartum sentinel events. The resultant parenchymal compressive changes appear as slit-like ventricles, effacement of cerebral sulci, narrowing of intrahemispheric fissures, and basal cisterns (Fig. 6).[17] However, one must bear in mind that ventricles may appear small in size in some normal infants in the first 36 hours of life. Consequently, caution is advised in the interpretation of these observations.[20]
- Hyperechogenicity of deep grey matter



Figs 4A and B: Axial view through the mastoid fontanel; please note the position of the probe in the mastoid area to visualize the cerebellar hemisphere

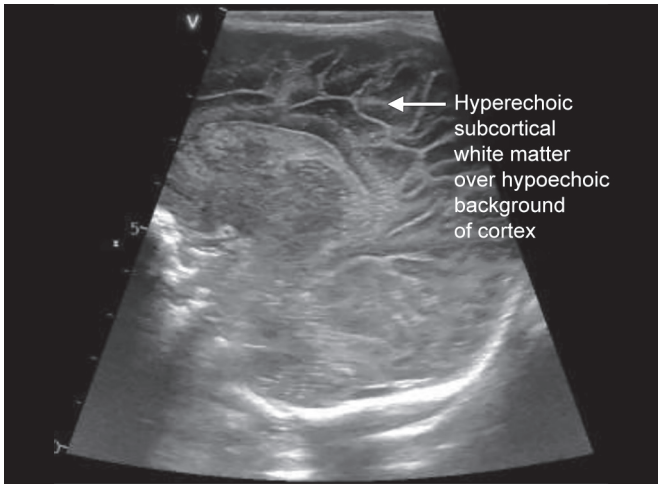


Fig. 5: Tramline appearance in parasagittal view. Hyperechoic subcortical white matter superimposed over the hypoechoic signals of the cortex viewed as forming '*tramlines*'. Differentiation of the grey and white matter can be noted throughout the entire brain both in anterior and posterior distributions

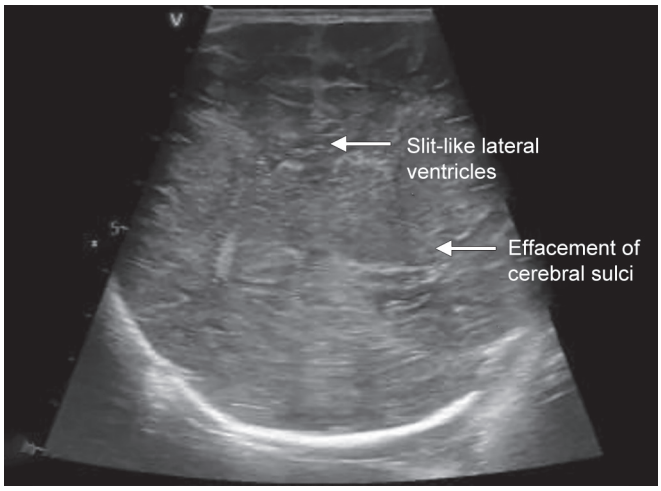


Fig. 6: Cerebral edema with poorly distinguished grey-white matter. Both lateral ventricles show a slit-like appearance due to parenchymal edema and consequent compression. There is effacement of cerebral sulci and narrowing of intrahemispheric fissures

A central, unilateral or bilateral, pattern of injury could be seen as focal or diffuse hyperechogenicity of the thalamus and putamen (Figs 7 and 8). This is usually described as the *'four-column sign'* in the coronal view, with echogenic thalamus and basal ganglia on each side, giving an appearance of four pillars parallel to each other, thereby enhancing the visibility of the hypoechoic crescentic posterior limb of internal capsule (often referred to as *PLIC sign*; Fig. 8).[18] This pattern often implies severe HIE following near-total asphyxia, due to sentinel events such as placental abruption or cord prolapse.[17,21]

- Cerebellar involvement
  A hyperechogenic cerebellum is best seen in axial view. This is one of the least recognized patterns of injury in neonates and represents severe insult. Cerebellar USG is a niche area of research that requires more rigorous evaluation; these results could help understand the extent of disease injury.[17,22]
- Hemorrhages
  Term infants may develop intraventricular hemorrhages originating in the choroid plexus. In contrast, preterm infants typically show germinal matrix and/or parenchymal hemorrhages.[21]

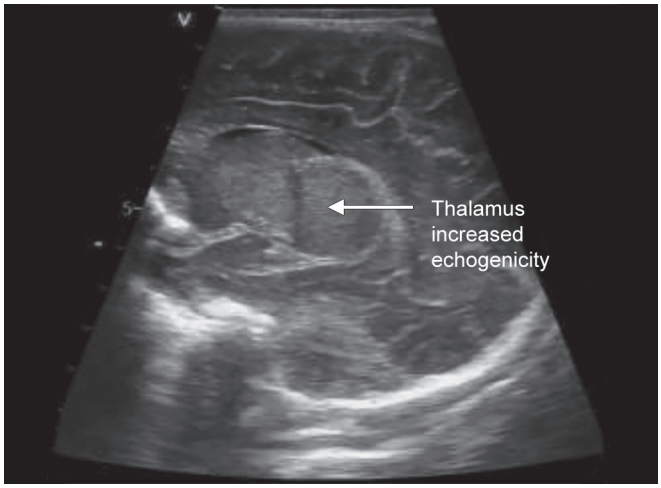


Fig. 7: Parasagittal view from a 7-day-old asphyxiated neonate showing a hyperechoic thalamus representing grey matter injury

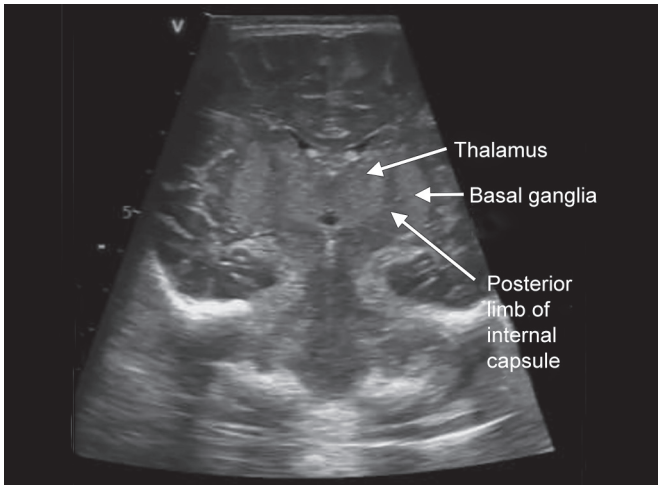


Fig. 8: Coronal view from a severely asphyxiated acute neonate showing the 'four-column sign with involvement of the posterior limb of the internal capsule (PLIC sign). Due to the acute insult, the thalami and basal ganglia on both sides appear hyperechogenic and are visualized as four pillars separated by a hypoechoic internal capsule

Distinct Patterns of Hypoxic-ischemic Injury

Myers described four distinct patterns, which are likely related to variations in the cause, timing, site, and severity of insults across diverse clinical situations (Table 1).[23]

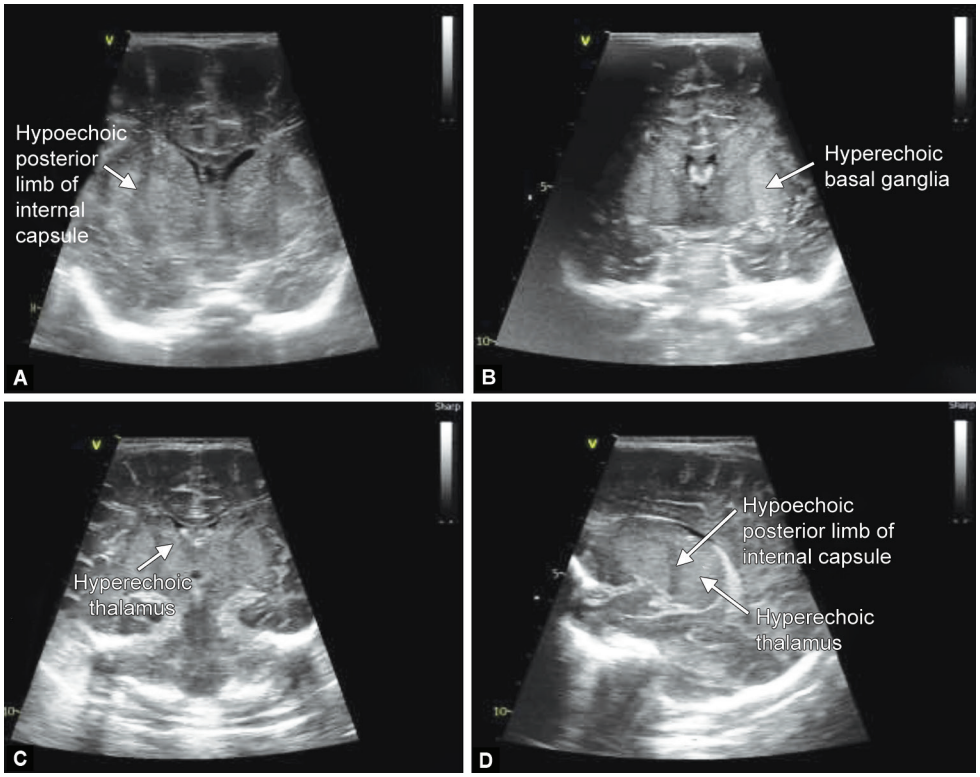
Changes during the Chronic Phase of Injury

In a few weeks after the initial hypoxic insult, generalized atrophy of affected regions is seen. These changes result in volume loss of central grey matter and white matter with sonographic findings of *exvacuo ventriculomegaly* and *widening of subarachnoid space*.[17]

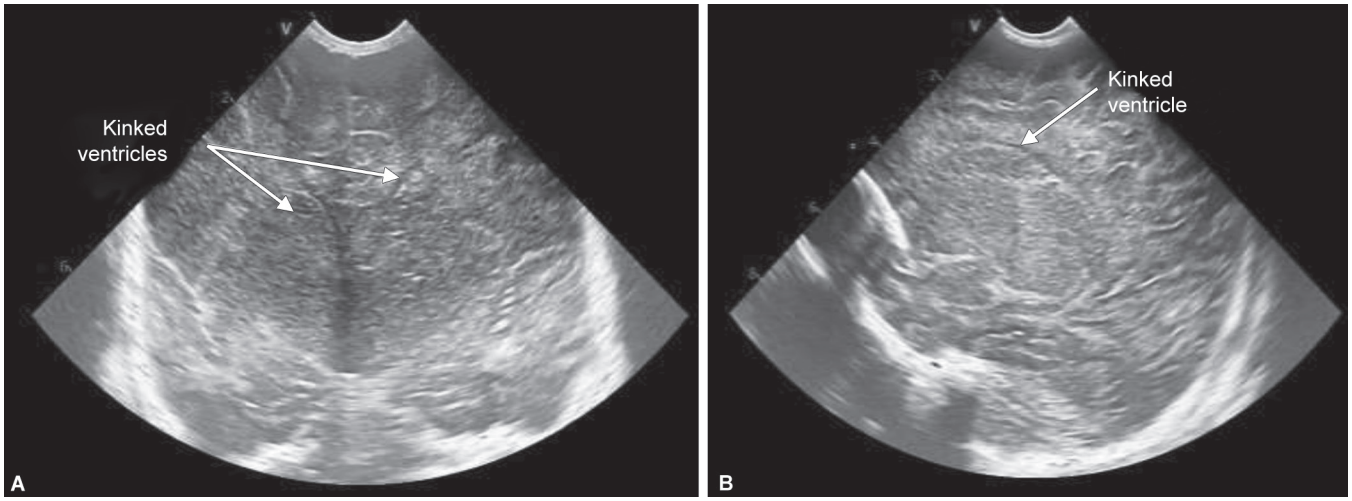
Table 1: Various patterns of brain injury in neonates with hypoxic insult[23]

Pattern of injury	*Severity of injury*	*Specific USG findings*
1. Near-total asphyxia	– Severe compromise in fetal blood flow	– Areas involved basal ganglia, thalamus sparing the internal capsule, the brainstem, and the cerebellum.[27,28]
	– High mortality or survival with disability.[24,25]	– Extensive grey and white matter regions of hyperechogenicity on CUS (Fig. 9).
	– Can be unilateral/bilateral/focal.	
	– More pronounced after 24–48 hours.	
	– Brainstem involvement is an independent risk factor for death in the neonatal period.[26]	
2. Watershed injury	– Seen in cases of partial prolonged asphyxia.[29]	– Wedge-shaped region of hyperechogenicity at border zones.
	– Cortical hypoperfusion manifests at the outer edges of major arterial perfusion territories.[30,31]	– Watershed zones include area of frontal lobe, near the posterior horn, in the parafalcine region in the subcortical white matter, and in parieto-occipital region.
	– Milder clinical signs than near-total asphyxia and less severe outcome.[32]	– Cortical injury may appear as parenchymal edema (Fig. 10).
	– MRI is superior to USG for the extent of injury.[24]	
3. Primary white matter injury	– Denotes partial asphyxia with sustained hypoxia.	– Subcortical and periventricular white matter hyperechogenicity.
	– Internal capsule involvement, commonly precedes global developmental delay, visual impairment, and seizures.	– Increased corticomedullary differentiation on CUS (Fig. 11).
4. Concurrent partial and near-total asphyxia	– Worst prognosis as compared with other pattern of injury.	– Most affected area – Basal ganglia.
	– Bilateral involvement and higher echogenicity predict high risk of mortality and poor long-term neurodevelopmental outcomes.[33,34]	– Other concurrent injury – Watershed cortical involvement, focal infarctions, or global injury.

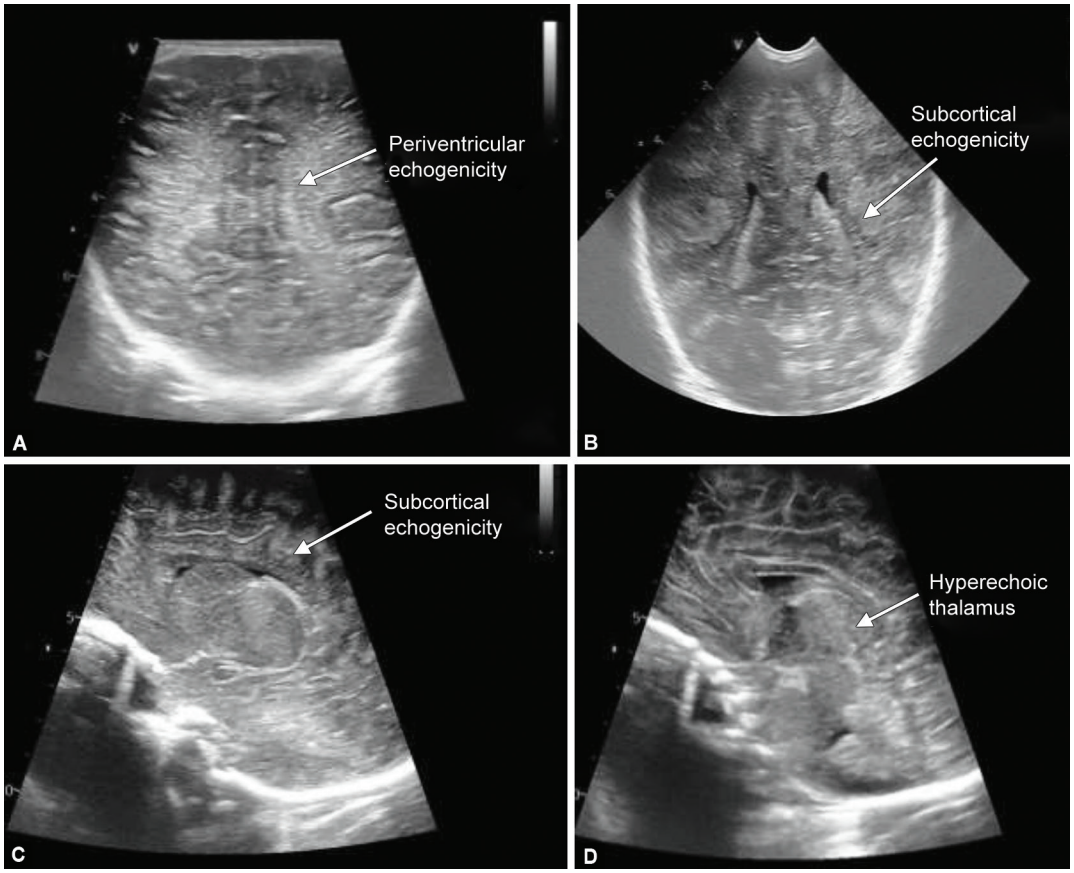
*CUS, cranial ultrasound; MRI, magnetic resonance imaging; USG, ultrasonography



Figs 9A to D: Central pattern of injury. Full-term neonate with history of cord prolapse with images obtained through anterior fontanel obtained after 4 hours of insult coronal (A–C) and parasagittal view (D), note the bilateral symmetrical increased echogenicity in the thalamus and basal ganglia representing ischemic injury along with a hypoechoic internal capsule



Figs 10A and B: Partial prolonged insult: (A) Cranial ultrasound images through anterior fontanel on coronal; (B) Parasagittal view, obtained within 24 hours of birth showing gross cerebral edema with slit-like ventricles



Figs 11A to D: (A and B) Subcortical and periventricular echogenicity in a full-term neonate. The cranial ultrasound performed at 36 hours of life with severe hypoxic-ischemic injury, coronal view; (C) Midline sagittal view; (D) Parasagittal view

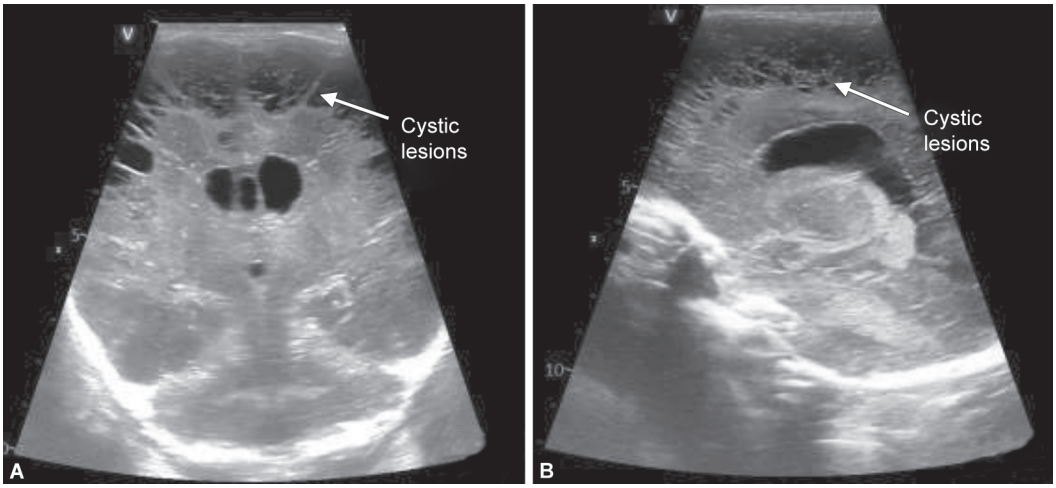
As the brain injury progresses, cortical necrosis and cystic changes in the injured brain regions might be seen.[3] Cysts may be seen after ≥10 days following hypoxic insult to the brain (Fig. 12).[35,36]

Absence of Abnormal Findings in HIE Infants on Cranial USG

A normal cranial USG does not exclude brain injury. Advanced imaging modalities such as contrast-enhanced ultrasound or diffusion-weighted MRI can help detect subtle abnormalities that may not be apparent on conventional imaging.

Time Frame of Hypoxic Changes on Cranial USG

Hypoxic-ischemic encephalopathy is a dynamic brain injury, and therefore, relying on imaging at a solitary time point may fail to fully capture the extent of cerebral damage. In the initial phases, cerebral edema might exhibit minimal severity, and



Figs 12A and B: Chronic changes on ultrasound: (A) Cranial ultrasound through anterior fontanel of a 24-day-old term neonate with a severe asphyxiated insult at birth both coronal; and (B) Parasagittal view. Note the exvacuo hydrocephalous due to cortical atrophy and the visual cyst along the cortical area

cranial USG may be unremarkable for 24–48 hours post-insult. Hyperechogenicity of the thalamus and basal ganglia and the appearance of PLIC sign may take 48–72 hours to develop. In cases with a near total pattern of injury, loss of grey-white matter differentiation and appearance of slit-like ventricles may take 48–72 hours to appear on cranial USG. If the insult is remote from the time of delivery, edema may have already developed and resolved by the time of birth.[17,22]

Pattern of Cranial USG in Preterm Hypoxic Insult

The anatomical area and pattern of acute ischemic insult differ between preterm and term infants, secondary to differences in the maturity of cerebral vessels. The periventricular white matter in the preterm brain is particularly susceptible to injury from ischemia, owing to the coexistence of immature premyelinating oligodendrocytes and watershed zones.[37]

Periventricular leukomalacia (PVL) is seen most frequently in preterm infants born at ≤33 weeks' gestation with a birth weight of <1500 g.[38] Cranial USG typically reveals the most pronounced bilateral diffuse and uneven sonographic enhancement in the periventricular white matter, which is almost equal to the intensity of choroid plexus.[39] Three to four weeks after the initial insult, cranial USG may show cysts of varying sizes within the previously hyperechoic regions with atrophic changes in the surrounding parenchyma.[39] It is important to emphasize that unlike in term neonates, diffuse echogenicity of the basal ganglia and thalami is a common normal finding observed in over 90% of preterm infants, particularly those born before 32 weeks' gestation.[40] This demands caution in the interpretation of the findings (Fig. 13).

Therapeutic Hypothermia and Imaging

Therapeutic hypothermia is a widely accepted modality for improving neurodevelopmental outcomes and reducing the severity of injury on imaging in neonates with asphyxiated insult.[41,42] Crucially, ultrasound performed before initiation of therapeutic hypothermia can help assess alternative brain pathologies mimicking HIE. Additionally, it may identify relative contraindications to therapeutic hypothermia; including focal hemorrhage, arterial stroke, metabolic disorders, infections, or brain malformations. Therapeutic hypothermia reduces the secondary energy failure and hence represents the delay in the MRI changes such as pseudonormalization of diffusion restriction, which is deferred for several days following therapeutic hypothermia.[43] Specific changes in cranial USG in neonates undergoing therapeutic hypothermia remain a potential area of research.

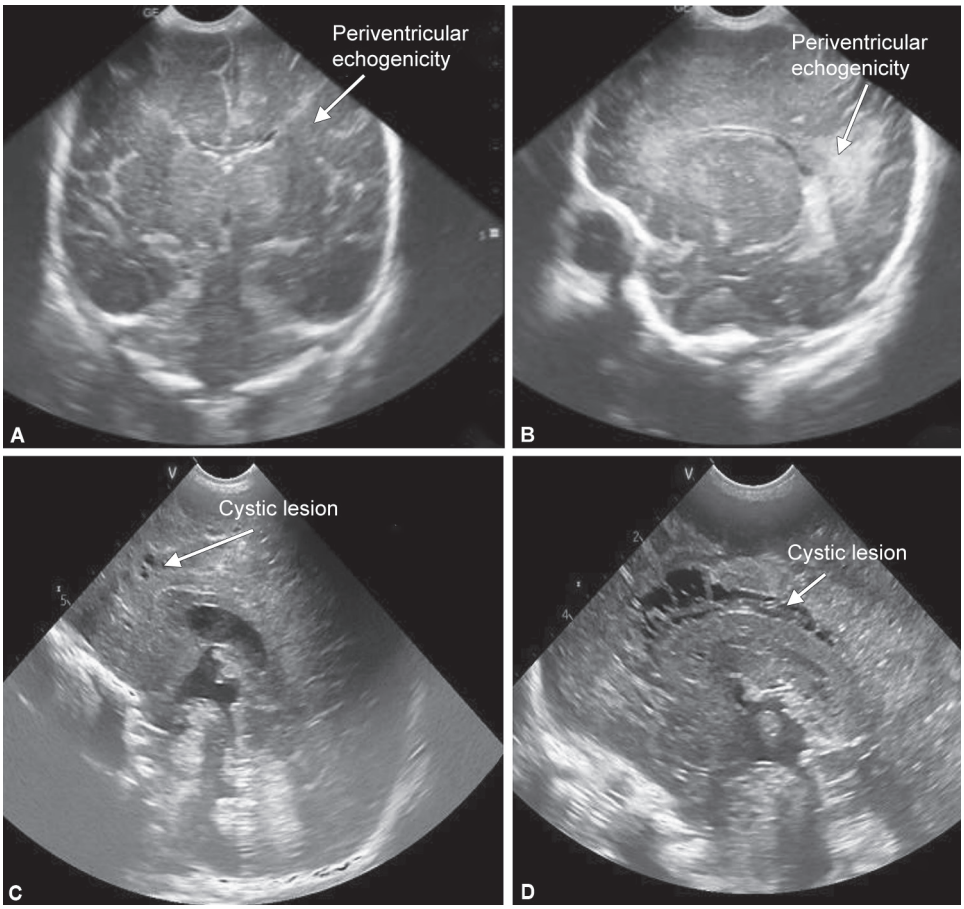
Cerebral Doppler Changes in Hypoxic Insults

Hypoxic-ischemic insults to the fetal and neonatal brain can alter cerebral blood flow (CBF).[44–46] This phenomenon could serve as a protective mechanism aimed at preventing additional injury, or it may signify the repercussions of existing brain damage.[45] Vascular hemodynamics are affected by many factors including alteration in intracranial pressure, partial pressure of carbon dioxide (pCO_2), prostaglandins, nitric oxide, free radicals, and temperature, in addition to alterations in cardiac output.[47–49]

After a hypoxic insult, the autoregulatory mechanism causes CBF to decrease, which is reflected by an increasing resistive index (RI) of cerebral vessels. If not treated with therapeutic hypothermia, the brain often shows hyperemia for hours to days with an accompanying drop in RI.[50,51] Therapeutic hypothermia can interrupt this cycle and limit this hyperemic period.[52,53]

Changes in the RI have been associated with prognostic implications. Although many of the hitherto-reported studies show differences in results, RI ≤ 0.55 within the initial 72 hours following birth has a strong predictive value for adverse outcomes, including death or severe disability (Fig. 14).[54–58] Even though abnormal RI prior to the initiation of cooling is associated with poor outcomes, its accuracy decreases during therapeutic hypothermia.[53] This might be attributed to relative vasoconstriction in the cerebral circulation or altered metabolic demand during the period of cooling.[59–61] Elstad et al. demonstrated that therapeutic hypothermia significantly reduced the positive predictive value of a low RI value and an unfavorable outcome from around 84% to only 60%.[59] However, this predictive value returned to the same range following rewarming.[60] Interestingly, an RI of >1 may be associated with brain death.[62]

A normal RI in the early stages of injury, within the first 6–12 hours, can be misleading as these patients may still show substantial disability or even mortality. This discrepancy may stem from the confounding influence of factors such as elevated intracranial



Figs 13A to D: Periventricular echogenicity (A: Coronal view, B: Parasagittal view) observed in 28-week neonate. Subsequently, the neonate developed a cystic lesion demarcating the ongoing changes as a result of hypoxic injury in the frontotemporal area (C and D: Sagittal view)

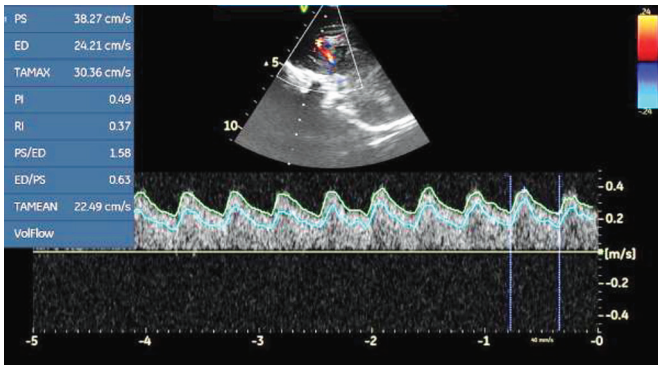


Fig. 14: Cerebral Doppler: Term infant with a history of severe perinatal asphyxia. Ultrasound examination performed on day 1 showed a sagittal view PWD in ACA showing increased EDV and decreased RI (0.37) in early asphyxia

ACA, anterior cerebral artery; EDV, end-diastolic velocity; PWD, pulse wave Doppler; RI, resistive index

pressure, patent ductus arteriosus, cardiac dysfunction, or the natural transition of the injured brain from a reduced cerebral blood flow soon after insult to subsequent hyperemia.[54,55]

Rath et al. systematically reviewed 26 studies and evaluated the importance of Doppler parameters separately in precooling and cooling eras in predicting long-term outcomes following perinatal asphyxia.[63] They concluded that cerebral Doppler may be useful in predicting death or disability in infants with HIE who are not cooled, or if performed prior to cooling. Although no individual clinical sign or investigation is good at predicting neurological outcomes and the sensitivity of abnormal RI is relatively poor, its specificity resembles that of MRI, EEG, and aEEG.[63,64]

HIE Scores Based on Cranial USG

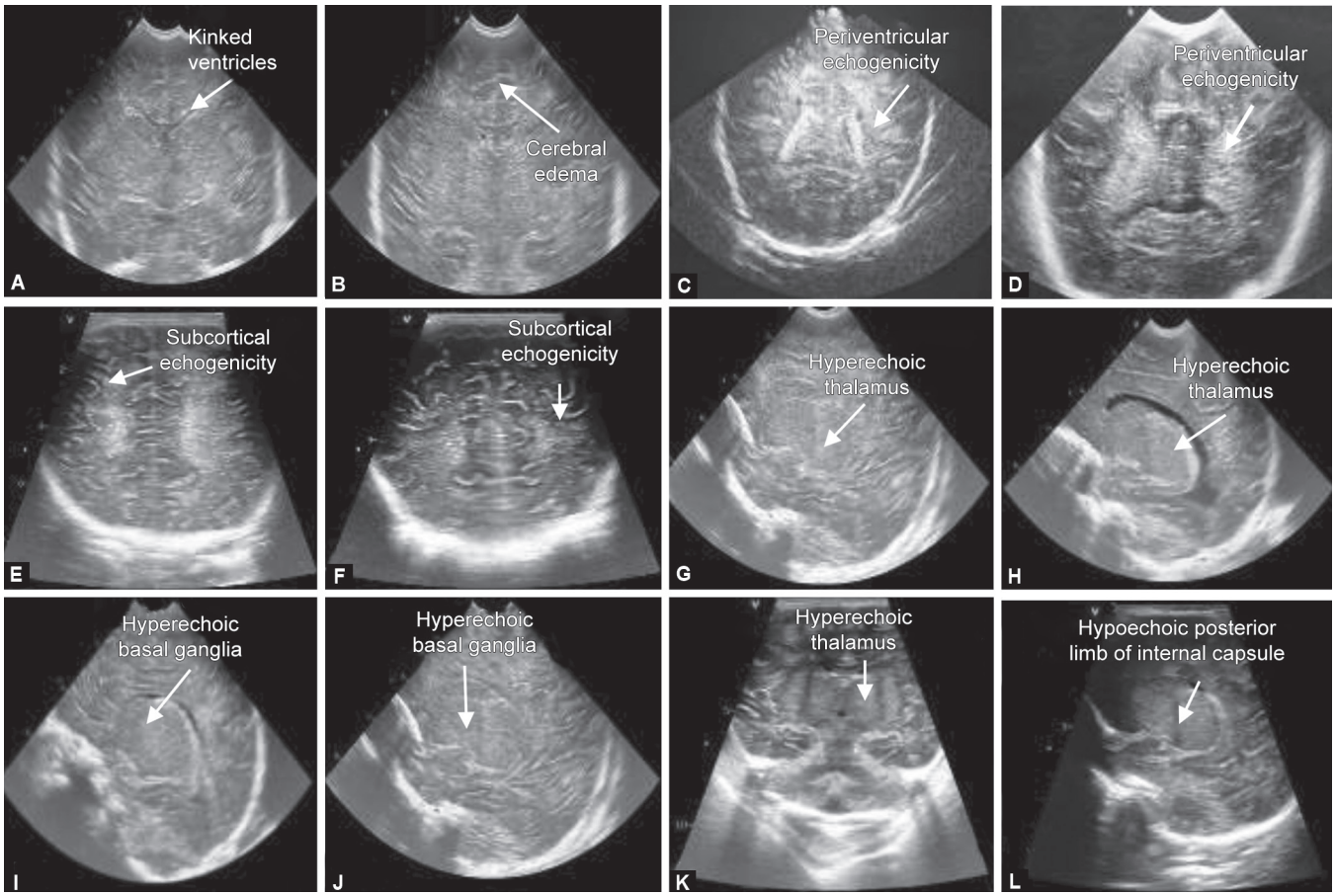
Composite cranial USG scores seem to be valuable as predictors of outcomes in sick asphyxiated neonates especially where transportation, affordability, and availability of MRI is challenging.[65–67] Four cranial USG scoring systems were compared. The first classified CUS findings into 8 grades based on pattern and severity of grey/white matter involvement. A second by Swarte et al. defined 6 patterns using a combination of a deep grey matter and a subcortical white matter injury score.[26,68] Another scoring system tried to identify early brain injury including a basal ganglia and thalami score and a white matter score.[65] However, none of the above-mentioned scores has been validated.

A recent cranial USG scoring study by Annink et al. (Table 2) performed between day 3 and 7 after birth included composite scores of white matter and deep grey matter involvement, each consisting of multiple separate items.[18] This scoring system was validated with a cut-off of ≥3 to consider the need for additional future neuroprotective strategies and/or redirection of care (Fig. 15). However, the inter-rater variability was still moderate. The subjectivity could be improvised with structured training.

Table 2: Cranial ultrasound scoring systems for neonates with HIE[18]

Item	*Normal-mildly abnormal (0)*	*Moderately abnormal (1)*	*Severely abnormal (2)*
White matter involvement (0–6 points)			
Impaired grey/white matter differentiation and/or slit-like ventricles	Normal differentiation between grey and white matter and open ventricles	Reduced differentiation between grey and white matter and/or slit-like ventricles	No differentiation between grey and white matter and slit-like ventricles
Periventricular WM hyperechogenicity	Normal echogenicity or minor hyperechogenicity	Moderate or focal hyperechogenicity, not as white as choroid plexus	Severe and diffuse hyperechogenicity, as white as choroid plexus
Subcortical WM hyperechogenicity	Normal echogenicity or minor hyperechogenicity	Focal hyperechogenicity of the subcortical WM Moderate differentiation of white and (subcortical) grey matter	Clear "tramlines" sign; hyperechogenicity of subcortical WM almost similar to sulci with the reduced signal intensity of cortex in between
Grey matter involvement (0–6 points)			
Thalamus hyperechogenicity	Normal echogenicity or minor hyperechogenicity	Moderate or focal hyperechogenicity of thalamus	Hyperechogenicity is severe and diffuse
Putamen hyperechogenicity	Normal echogenicity or minor hyperechogenicity	Moderate or focal hyperechogenicity of putamen	Hyperechogenicity is severe and diffuse
	Absent (0)	Present (1)	
Four-column sign	Normal echogenicity to minor hyperechogenicity	On the coronal plane, there is a four-column sign caused by moderate or severe bilateral hyperechogenicity of the thalamus and putamen.	
PLIC visibility	PLIC is not visible as a hypoechogenic line between the putamen and thalamus	PLIC is clearly visible as a hypoechogenic line between the hyperechogenic putamen and thalamus	

PLIC, posterior limb of internal capsule; WM, white matter



Figs 15A to L: Scoring HIE images on ultrasound **(**A) Moderate cerebral edema (1 point); (B) Severe cerebral edema (2 points); (C) Moderate periventricular white matter hyperechogenicity (1 point); (D) Severe periventricular white matter hyperechogenicity (2 points); (E) Moderate subcortical white matter hyperechogenicity (1 point); (F) Severe subcortical white matter hyperechogenicity (2 points); (G) Moderately hyperechogenic thalamus (1 point); (H) Severely hyperechogenic thalamus (2 points); (I) Moderately hyperechogenic putamen (1 point); (J) Severely hyperechogenic putamen (2 points); (K) Four-column sign (1 point); (L) Visibility of the PLIC (1 point)

Mimickers of HIE

Neonatal encephalopathy (NE) has varied etiology. Hence, it is important to consider conditions that may mimic HIE. It is equally important to consider that HIE can co-exist with other causes of NE. Often there can be similarities in various presentations, and targeted investigation guided by clinical suspicion can differentiate various states. Table 3 delineates several conditions that could mimic HIE with the differentiating clinical-radiological factors.

Correlation between Cranial USG and MRI

Cranial USG lacks the sensitivity for defining the full extent of cerebral lesions, even in severe encephalopathy, and particularly

Table 3: Diseased states that may mimic HIE along with the differentiated findings both clinically and radiologically

Disease state	*Relevant clinical history*	*Differentiating radiological features*
Perinatal asphyxia	– Perinatal risk factors. – Encephalopathy soon after birth. – Associated hemodynamic instability. – Seizures mostly within 24 hour of birth.	– Bilateral watershed area, white matter, deep grey matter injury, basal ganglia, thalamus, brainstem injury. – Abnormal PLIC – a good predictor of motor outcome.
Vascular injury[69–73] a. Arterial ischemic stroke b. CSVT	– Perinatal risk factor – Uncommon. – Encephalopathy not after birth. – Usually not associated with hemodynamic instability. – Seizures can be present, not usually soon after birth.	– Focal ischemia in an arterial distribution. – May show IVH and/or intraparenchymal hemorrhage, hydrocephalous, thrombosis on venogram.
Cerebral vascular malformation[74–77]	– Perinatal risk – Uncommon. – Hemodynamic instability, associated with vein of Galen malformation or hemorrhage. – Seizures may be present if the lesion is close to cortex or complicated with hemorrhage.	– Cranial Doppler represents flow turbulence across the malformation.
Subgaleal hemorrhage[78,79]	– Perinatal risk factors associated. – Encephalopathy – unusual in the early phase. – Can present with hypovolemic shock.	– Difficult to differentiate on USG.
Infections- Meningitis/ Meningoencephalitis/ Encephalitis[80–84]	– Clinical features of sepsis. – History suggestive of chorioamnionitis. – Blood and CSF culture PCR.	– Hydrocephalous, cerebral abscess, subdural effusion. – White matter injury, frontal and temporal lobe involved in HSV infection. – Diffuse echogenicity periventricular and deep white matter in parechovirus/enterovirus. – Infarction secondary to bacterial infections.
Metabolic derangements – Hypoglycemia	– Propensity of risk factor to develop hypoglycemia. – Can be associated with seizures.	– Hyperechogenicity of posterior subcortical white matter and overlying cortex with sparing of the central grey matter.
Syndromes[85] • Prader–Willi Syndrome • Aicardi–Goutieres syndrome • Congenital central hypoventilation syndrome	– Dysmorphism, organomegaly, hematological abnormality, variable presentation from birth till early infancy.	– Polymicrogyria – Prader Willi. – Multiple white matter abnormalities, hypothalamus, posterior thalamus, midbrain, caudal raphe, locus coeruleus, lateral medulla, parabrachial pons, cerebellum, insular, and cingulate cortex changes in Congenital central hypoventilation syndrome. – Frontotemporal white matter changes, basal ganglia calcification in Aicardi syndrome.
Neuromuscular disorder[86–90]	– Presents with hypotonia immediately or soon after birth. – Facial or bulbar weakness related to dysfunction of the lower cranial nerves out of proportion to appendicular weakness is more suggestive of neuromuscular etiology.	– Absence of acute brain injury on imaging. – EMG/NCS can help localize symptoms to the nerve, muscle or neuromuscular junction.

(Contd...)

Table 3: *(Contd...)*

Disease state	*Relevant clinical history*	*Differentiating radiological features*
Brain malformation[91–98] • Joubert syndrome. • Dandy–Walker malformation.	– Antenatal USG suggestive. – Can be symptomatic at birth or thereafter.	Specific features: – Molar Tooth appearance – Joubert syndrome. – Hypoplasia of the cerebellar vermis and dilatation of the fourth ventricle, with variable degree of posterior fossa enlargement and hydrocephalus.
Metabolic diseases		
	Overlapping features of HIE	*Differentiating factors*
• Sulphite oxidase deficiency.[99–101]	Basal ganglia involvement Loss of grey-white matter differentiation	Cystic encephalomalacia, corpus callosum hypoplasia, ventriculomegaly
• Molybdenum cofactor deficiency.[102]	Diffuse parenchymal hyperechogenicity	Calcifications in the basal ganglia, white matter cysts, and later cerebral atrophy
• Zellweger syndrome.[103,104]	Clinical picture overlaps HIE	Subependymal cysts, ventricular enlargement, lenticulostriate vasculopathy, and gyral malformations
• Nonketotic hyperglycinemia (NKH).[105,106]	–Involvement of brainstem	Hypoplasia of corpus callosum
• Maple syrup urine disease.[107]	Diffuse cerebral edema Presentation after 4–7 days of life	White matter and central grey matter hyperechogenicity with corresponding white matter tract disease
	*Metabolic diseases require detail evaluation based on MRI and MRS	

CSF, cerebrospinal fluid; CSVT, cerebral sinovenous thrombosis; EMG, electromyography; HIE, hypoxic-ischemic encephalopathy; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NCS, nerve conduction study; PCR, polymerase chain reaction; PLIC, posterior limb of internal capsule; USG, ultrasound

in the first 24 hours after birth.[108,109] Because of the delay in the evolution of cranial USG abnormalities by a minimum of 48 hours, detection of pronounced abnormalities on postnatal day 1 may assist in identifying established severe HIE originating before the onset of labour.[110] Mahantesh et al. elaborated on the limited accuracy of duplex ultrasound in mild HIE, with increasing precision of 77% in moderate and 100% in severely asphyxiated neonates with distinguishingly raised RI.[111]

Aun et al. reported the diagnostic accuracy of USG as 78.9% in comparison to MRI, with 92.3 and 40% of positive- and negative-predictive values, respectively.[112] The advent of recent advances in MRI sequences, such as diffusion-weighted, susceptibility-weighted imaging, and metabolic sequencing, allow for better tissue characterization. These sequences can reveal subtle abnormalities and provide insights into brain injuries especially in mild to moderate cases with white matter injury that may not be as apparent on cranial USG.

In conjunction with the middle cerebral artery Doppler, cranial USG shows higher predictive accuracy and differentiation between the severity grades of HIE. However, predictive accuracy is relatively low for abnormal neurologic outcomes at 18 months.[113] There is also some disagreement over the value of early USG compared with more definitive MRI after rewarming.[10] Moreover, USG can help predict the neurodevelopmental outcomes at early school age in full-term neonates with asphyxia. Moderate hypoxic-ischemic brain changes detected in cranial USG were associated with hearing disorders, cerebellar dysfunction, epilepsy, and a lower Working Memory Index in children at an early school age.[7]

Long-term Implications of the Cranial USG

The prognosis of a neonate with hypoxic insult depends on multiple factors including the severity, extent and timing of the insult, gestational age, other associated comorbidities and metabolic derangements, congenital malformation, infection, hyperbilirubinemia, developmentally supportive and family participatory care, along with quality of follow-up.

Studies based on the topographic pattern of brain injury have indicated that term infants experiencing predominant damage to the basal ganglia and thalamus tend to have unfavorable neurological outcomes.[114,108] Involvement of the cortex and basal ganglia within the first 24 hours of life, along with severe EEG abnormalities, can predict a poor outcome. This may indicate either a particularly severe insult or that the injury occurred before the onset of labour.[68,115] Guan et al. concluded in their study of 158 neonates with hypoxic insult (54-mild HIE, 60-moderate, and 44-severe HIE) that abnormal ultrasound findings of brain parenchyma were found in 46.3% of neonates with mild HIE, 96.7% with moderate and 100% of neonates with severe HIE.[116] Almost all neonates with severe HIE also had decreased cerebral artery blood flow velocity and increased RI of cerebral arteries. Of the 104 neonates with moderate or severe HIE, follow-up cranial USG revealed cystic parenchymal lesions in 11.5%, progressive ventricular dilatation and brain atrophy in 11.5%, mild ventricular dilatation in 14.4%, and leukoencephalomalacia in 1.9% neonates. On the other hand, cranial USG findings in neonates with mild HIE returned to normal during the follow-up, consistent with the clinical course, and most of the lesions in those with moderate HIE also returned to normal. Neonates with severe HIE followed up to 12 months had sequelae such as ventricular expansion, brain atrophy, and nervous system symptoms.[116]

In another study, Robertson et al. found the onset of CNS abnormalities to be closely associated with the severity of HIE and neurological dysfunction at 3.5 years of age.[117] In conclusion, cranial USG features such as the size of lateral ventricles, altered brain parenchymal echogenicity and cerebral blood flow parameters are useful for the early diagnosis of HIE and help predict outcome.

Limitations

Being a nonhazardous, low-cost, and noninvasive intervention, cranial USG has evoked interest for clinical use. However, there are limitations as it is an operator-dependent tool with a learning curve. Furthermore, its sensitivity for subtle-mild changes is operator-dependent. There is a need for predictive tools with combination of USG and clinical parameters that could help assess severity of changes and prognosticate long-term neurological outcomes.

Conclusion

Cranial USG is potentially a valuable screening tool in both the diagnosis and management of neonatal encephalopathy. Serial high-resolution cranial USG with Doppler evaluations can help in real-time assessment of clinically important changes in HIE. This may also help predict disability in infants with hypoxic brain damage before cooling. Further research is needed to assess its value in predicting long-term neurological outcomes.

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REVIEW ARTICLE

Abnormalities of Corpus Callosum and Other Interhemispheric Commissures

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Abstract

The two neocortical cerebral hemispheres are connected by white matter tracts such as the corpus callosum (CC), and the anterior and the hippocampal commissures. Complete agenesis of the CC is seen in about 7 persons per 1,000; the incidence in patients with developmental delay can be as high as 3%. In addition, many patients show a paucity, not complete absence, of commissural axons due to altered development. Others may develop secondary destruction of the CC following infarction, hemorrhage, trauma, and in some metabolic diseases. One notable structural feature in these patients with agenesis or hypogenesis of the CC are the Probst bundles (PBs), which are longitudinal, rostrocaudally oriented coiled white matter fascicles running alongside the lateral ventricles into the tapetum. The presence or absence of these PBs can affect the clinical presentation and outcome of these patients. Many patients with agenesis of the CC manifest with seizures within the first weeks of life. Others present with developmental delay and a multitude of neurological manifestations. The etiopathogenesis of agenesis of the CC is unknown and is still being investigated. These commissural defects can also be seen as a part of several genetic associations such as Aicardi syndrome, Andermann syndrome, Mowat-Wilson syndrome, and XLAG (X-linked lissencephaly with ambiguous genitalia). As of now, no specific treatment is known for any of these conditions. Careful clinical and genetic evaluation of these patients is necessary for symptomatic management and for counseling the families. In this article, we present our clinical/imaging experience and have combined it with an extensive search of the databases PubMed, EMBASE, and Scopus. To avoid bias, keywords were identified from discussions in our group and from PubMed's Medical Subject Heading (MeSH) thesaurus.

Keywords: Axonal projections, Body, Commissural, Chorioallantoic placenta, Cortical layers eutherian mammals, Genu, Pyramidal neurons, Rostrum, White matter tracts.

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Keypoints

- The two neocortical cerebral hemispheres are connected by several white matter commissures. The corpus callosum (CC) is the largest. The anterior and the hippocampal commissures are other well-described connections.
- Agenesis of the CC and other commissures may be seen in up to 7 per 1000 persons. In infants with developmental delay, the incidence may be as high as 3%.
- Altered development of CC and other commissures may present with seizures, delayed development, or be a part of multiorgan syndromic conditions. Many remain asymptomatic.
- One notable structural feature in patients with agenesis or hypogenesis of the CC is the presence of the so-called Probst bundles (PBs), which are longitudinal, rostrocaudally oriented coiled white matter fascicles running alongside the lateral ventricles into the tapetum. The presence or absence of these PBs can affect the clinical presentation and outcome of these patients.
- Treatment is limited to supportive measures for functional deficiencies. Genetic evaluation can help in counseling the families.

Introduction

In eutherian mammals, the ones with a chorioallantoic placenta, the neocortical parts of the two cerebral hemispheres are connected by several white matter tracts, such as the CC, and the anterior and hippocampal commissures.[1,2] The CC is the primary, largest commissural region[3–6] that is largely composed of axonal projections from cortical layers 2 and 3 (80%) and 5 (20%) pyramidal neurons, making both homotopic (symmetrical) and heterotopic (asymmetrical; 75%) connections.[7,8] Anterior-to-posterior, the CC shows 5 structural segments, the rostrum, genu, body, isthmus, and the splenium (Fig. 1).[9–12] There is also an anterior commissure that connects the amygdaloid nuclei, and a hippocampal commissure (psalterium), a conduit between the fornices (Fig. 1).[13–17]

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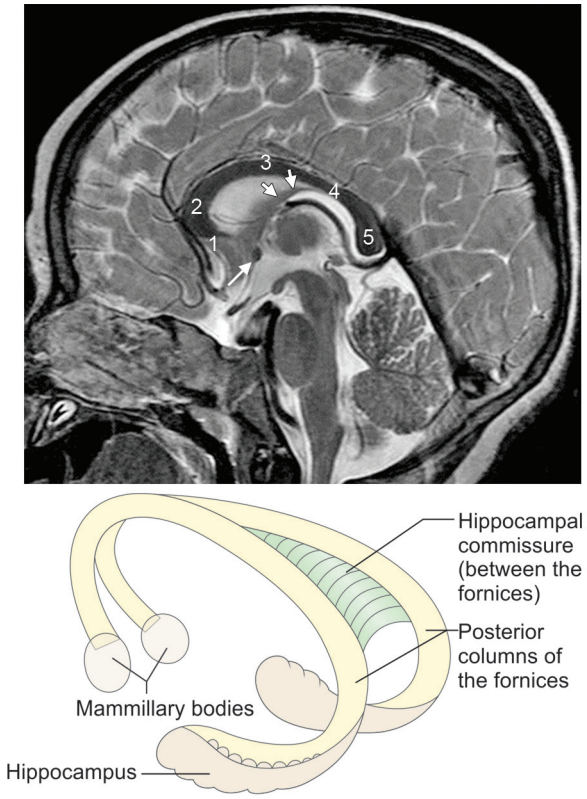


Fig. 1: Sagittal T2-weighted MRI of the normal midline anatomy and the major commissures. A graphic below the MR image summarizes the site and structure of the minor commissures. The corpus callosum (CC), the largest commissure of the human brain, is a C-shaped hypointense structure that can be subdivided into five parts, the rostrum (1), the genu (2), the trunk (3), isthmus (4), and the splenium (5). The anterior commissure (arrow) is an ovoid T2-hypointense well-demarcated structure along the superior–anterior wall of the third ventricle. The body of the fornix (small arrows) is seen along the undersurface of the CC. The hippocampi are connected by the so-called hippocampal commissure, where transversely oriented decussating white matter fibers connect the bodies of the fornix in the midline. The graphic below the MR scan summarizes the structure of the fornix, a bundle of nerve fibers located underneath the CC, and the location of the anterior and the hippocampal commissures. The fornix is a major output tract of the hippocampus and is attached to the inner surface of the CC; it bifurcates at the level of the anterior commissure. The post-commissural fibers project to the mammillary bodies

The structure of these tracts is largely conserved but some variations may be seen in the shape, thickness, and orientation in up to 10% subjects (Fig. 2).[18] Some changes may also be seen with age and gender.[19,20] There might be abnormalities ranging from complete agenesis of these commissures to localized structural defects (Fig. 3). In this article, we have reviewed currently available data on the epidemiology of these defects, the spectrum of structural abnormalities, clinical manifestations, genetics, and guidelines for management.

Epidemiology

Complete agenesis of the CC has been seen in up to 7 infants per 1,000 live births.[21,22] The incidence in those with developmental delay may be as high as 3%.[22,23] About 25% of all patients with agenesis of the CC have other idiopathic anomalies, and another 25% have chromosomal, monogenic, or teratogenic syndromes.[24–27] Inherited conditions may include complete or partial chromosomal anomalies, autosomal dominant, autosomal recessive, or X-linked monogenic disorders, and these could develop *de novo* in some cases.[23] In about half of all patients, agenesis of the CC has been believed to be an isolated anomaly or in conditions limited to the central nervous system (CNS).[24]

Structural Abnormalities

Many patients show isolated, complete agenesis of the CC (Figs 4 to 11). The widely spaced lateral ventricles due to the agenesis of the CC has been described as the "racing car sign" (Fig. 5E). Appearances on axial magnetic resonance imaging (MRI) or computed tomography (CT) are reminiscent of a Formula One car seen from above.

Others may have associated abnormalities in other midline structures or adjacent parts of the forebrain.[28,29] The subcallosal sling, the midline glial populations and pioneering axons are known to work together to guide axons across the midline, and several abnormalities may result from altered balance between guidance molecules, and/or that between chemorepellent molecules and cognate receptors.[30–33] These changes can restrict the development of commissural axons with failure of these tracts to cross the midline.

Complete agenesis of the CC can be associated with altered development of the anterior and hippocampal commissures.[34] Migrational disturbances (e.g., schizencephaly) (Fig. 11) and callosal lipomas (Figs 10 and 12) have also be seen to interfere with the normal callosal development.[35] The combined absence of multiple commissures may represent a severe form of cerebral malformation;[34] there may also be altered morphology of the cerebral commissures and associated malformations of the midline, cortical development, white matter, and of the differentiating diencephalon and rhombencephalon.[17] They may need diffusion tensor imaging studies with adequate number of subjects to assess the impact of absence/anomalous course of white matter tracts/commissures.[34] The importance of the absence/hypoplasia of the AC and/or HC along with CC agenesis on neurocognitive outcomes also needs review.[22,36]

Corpus callosum agenesis/hypogenesis can be seen in association with complex telencephalic, diencephalic, or rhombencephalic malformations in the cortex such as heterotopia (Fig. 13) or abnormal sulcation, reduced cerebral hemispheric white matter volume, non-callosal midline anomalies in the anterior or hippocampal commissures, interhemispheric cysts (Figs 7 and 8), and lipomas (Figs 10 and 12).[17] There might also be associated abnormalities of the cerebellum or brainstem.[37] Corpus callosum agenesis/hypogenesis may not be distinct disorders but might just represent a larger dysgenetic spectrum. In some infants, CC damage could also be a secondary phenomenon related to infarction, hemorrhage, trauma, and some metabolic diseases.[38]

Associated Systemic Anomalies

Commissural abnormalities are frequently associated with abnormalities in the musculoskeletal, central nervous, cardiovascular, urogenital, and digestive systems. In syndromic conditions, neurological anomalies, such as hydrocephalus, cerebellar hypoplasia, periventricular nodular heterotopia, polymicrogyria, microgyria, and lissencephaly have been seen.[25–27] Infants with hydrocephalus could have radiological markers such as altered frontal-occipital horn ratio, apparent diffusion coefficient, and cerebral blood flow indices.

Multicentric Data from the Agenesis of the CC (ACC) Network

The ACC network is a national support organization; Hetts et al.[17] analyzed 66,736 MRI examinations from the period 1985–2003

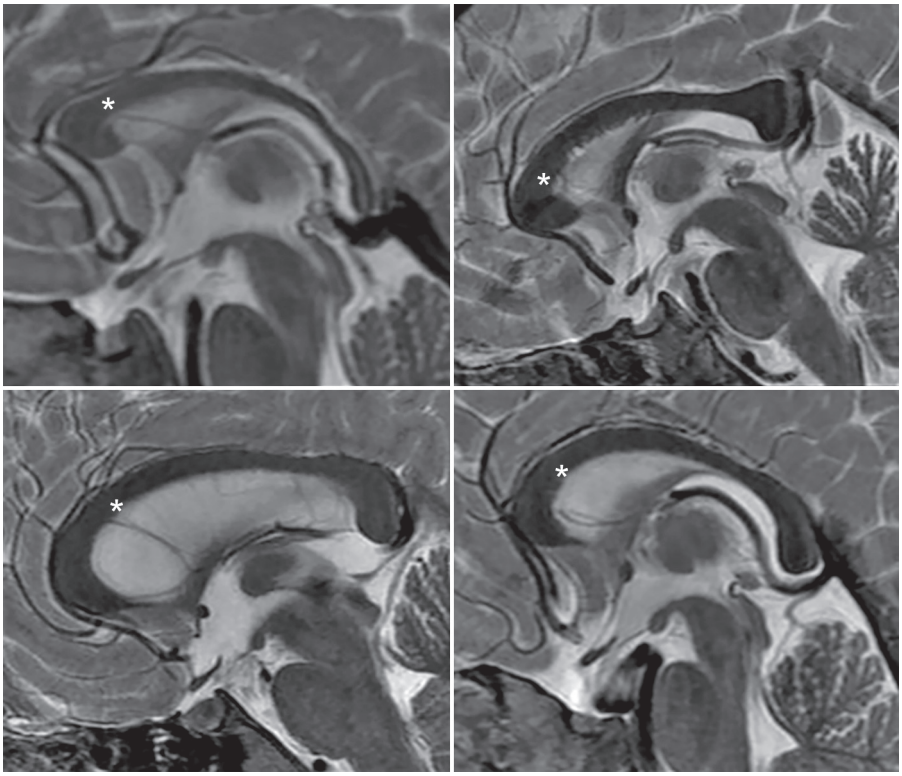


Fig. 2: Sagittal T2-weighted images of four healthy subjects demonstrate the variability in shape, thickness and orientation of the corpus callosum (CC) (marked in each image by an asterisk, *). Familiarity with this variation is essential to prevent incorrect diagnosis of a CC anomaly or pathology

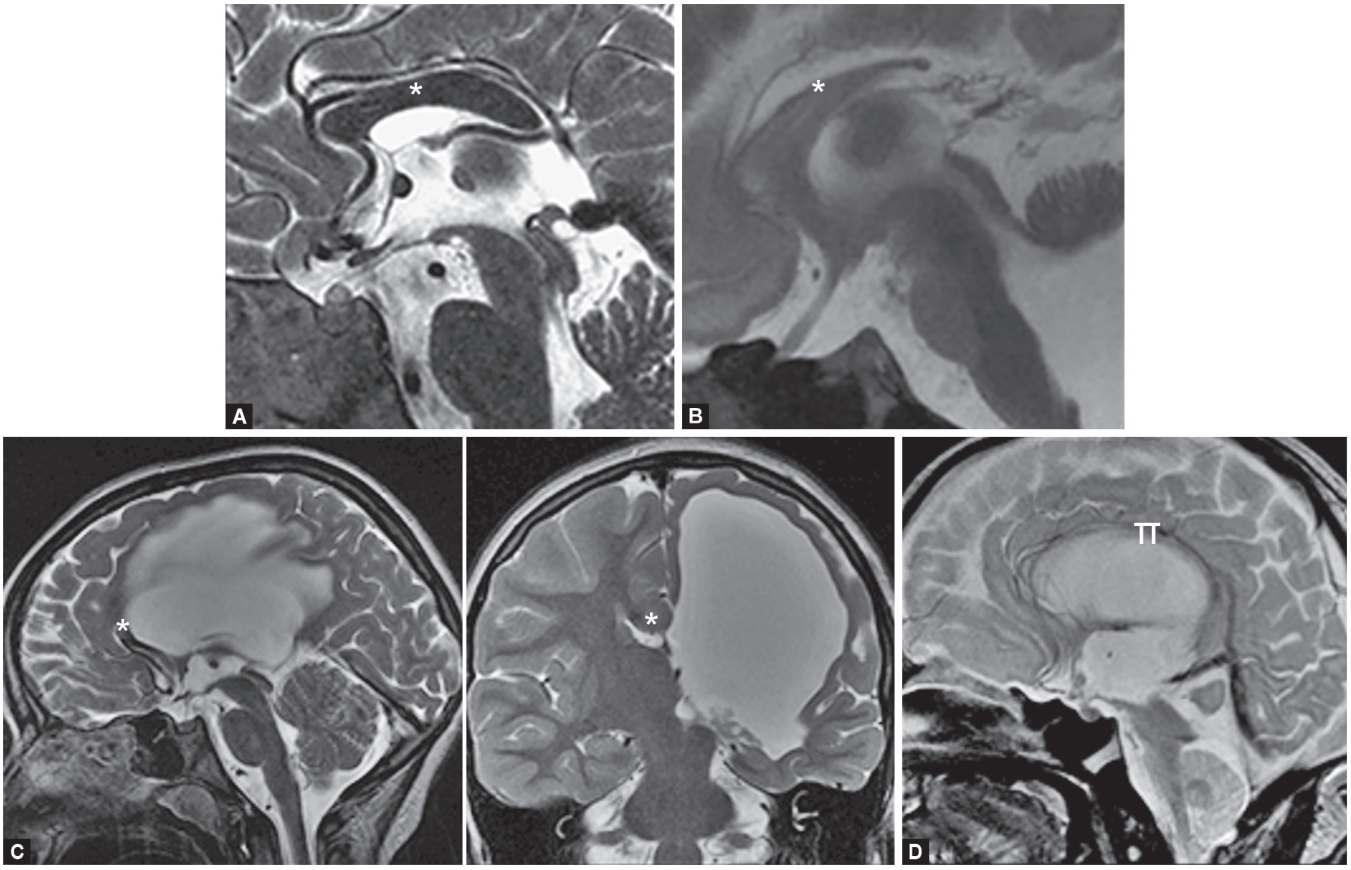
and queried these for the keywords "callosum" and "hypogenesis" or "dysgenesis" or "agenesis; 198 patients were identified. After excluding cases with incomplete records, 142 were reviewed. Their scans were evaluated for commissural anomalies, interhemispheric cysts, malformations of cortical development; altered cerebral ventricles, and anomalies of white matter such as reduced volume with its location and state of myelination. Corpus callosum agenesis or dysgenesis was seen in 167 (0.25%); 82 had agenesis and 60 had hypogenesis of the CC. After excluding patients who had normal commissures, known multiple congenital anomalies, or technically limited studies, the remaining 142 patients were studied. The mean age (± standard deviation, SD) of identification of agenesis and hypogenesis of CC was 4.0 ± 7.1 (range, 1 day-39 years) and 7.8 ± 13.7 years (range, 2 days-68 years; $p = 0.04$), respectively. There were no significant differences in gender.

Seventy-three had cortical malformations such as heterotopia and abnormal sulcations. The AC was absent in 48 and was abnormal in size in 46 (10 enlarged and 36 small). Overall, 71% of the infants with agenesis of the CC and 67% of those with hypogenesis also had AC abnormalities. The hippocampal commissure was absent in 107 and abnormal in size in 4. Cerebral ventricles were abnormal in 128 patients, white matter volume was reduced in 134, and myelination was delayed in 32. Cerebral ventricles were more frequently abnormal in patients with agenesis (96%) than in hypogenesis of CC (83%, $p < 0.01$). Patients with agenesis of CC showed abnormal olfactory sulci more frequently than those with abnormalities in other commissures (33% anterior and 15% hippocampal commissure; $p = 0.03$). The size of the *centrum semiovale* was compared with age-matched controls to assess differences in white matter. Cortical malformations, such as pachygyria, polymicrogyria, and oversulcation; the size and folial pattern of the cerebellum; and the size and location of the 4th ventricle were assessed qualitatively.

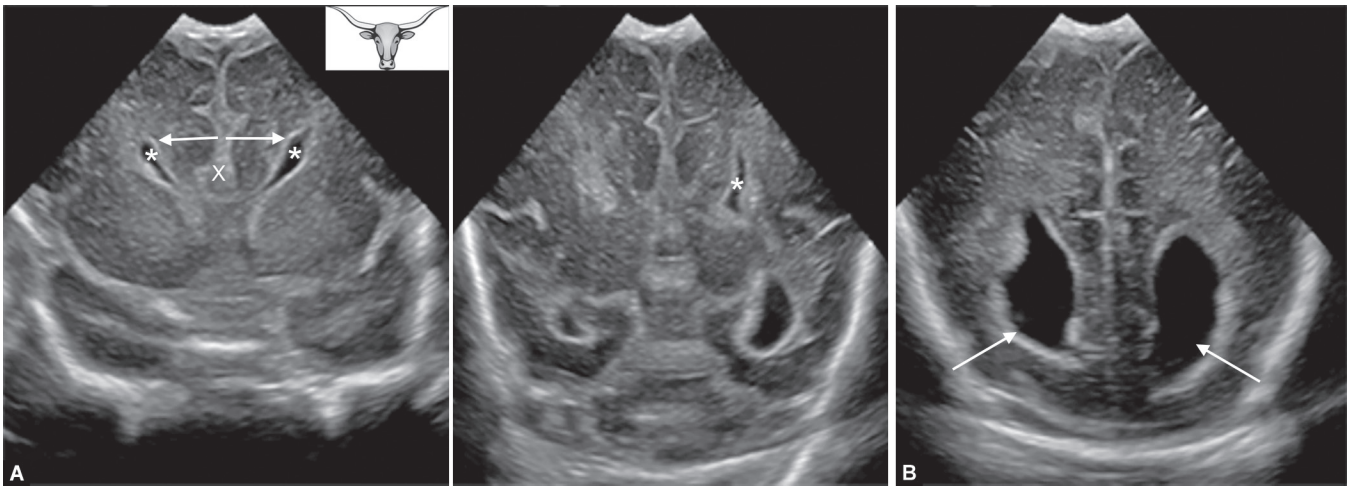
Data from one hospital in this network showed a higher frequency of abnormal ACs (78% tertiary hospital, 63% ACC Network; $p = 0.05$), cortical malformations (64% tertiary hospital, 45% ACC Network; $p = 0.027$), abnormal ventricles (82% tertiary hospital, 95% ACC Network; $p = 0.013$), moderately to markedly reduced white matter volume (76% tertiary hospital, 56% ACC Network; $p = 0.016$), abnormal (delayed or incomplete) myelination (32% tertiary hospital, 17% ACC Network; $p = 0.024$), and anomalies of the cerebellar vermis (42% tertiary hospital, 24% ACC Network; $p = 0.027$) and brainstem (34% tertiary hospital, 17% ACC Network; $p = 0.023$). Probst bundles, however, were far more common among ACC Network prospective cohort patients (66%) than among patients from one hospital (18%, $p < 0.001$).

Many patients with absent/abnormal cerebral commissures have associated abnormalities. Byrd et al.[39] performed a retro-/prospective analysis of 105 children with agenesis of the CC. Twenty-six had isolated ACC, but 8 of these 26 had Aicardi's syndrome with heterotopia, polymicrogyria, and other characteristic features. Thirty-five had interhemispheric cysts, and 31 communicated with the ventricles (type I). Four did not communicate (type II). Twenty (14%) with agenesis of the CC had interhemispheric cysts, of which 11 communicated with the ventricles and 9 did not. Interhemispheric lipomas were seen in 3% of patients in both studies.

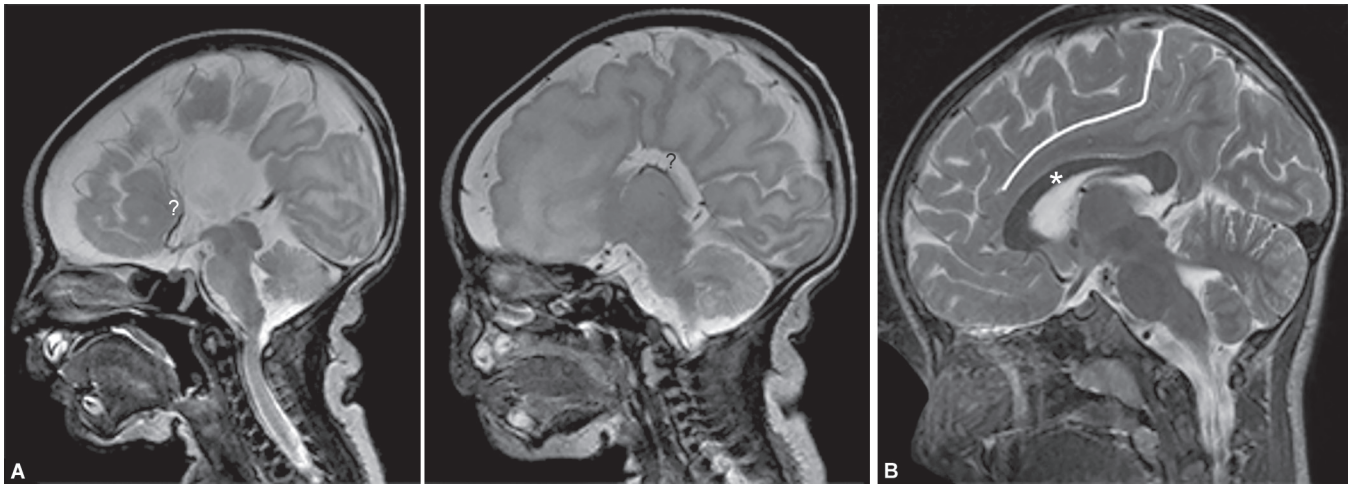
Patients with commissural anomalies frequently show malformations in cortical development.[17] In one study, gray matter heterotopias were seen in 29% of subjects with agenesis and 21% of those with hypogenesis of the CC. Barkovich and Norman[40] reported



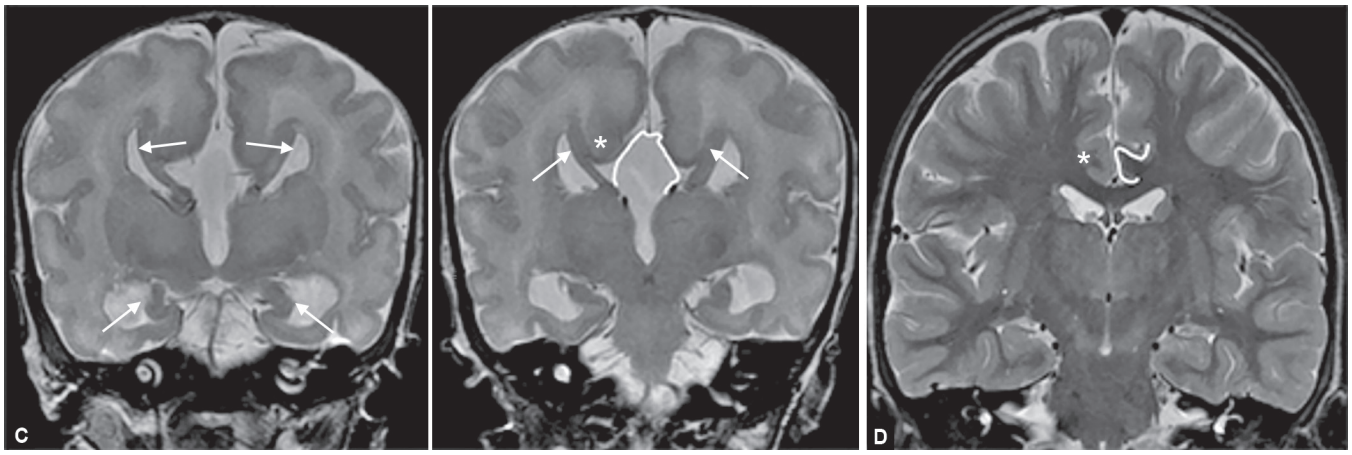
Figs 3A to D: Sagittal T2-weighted images of four infants with an abnormal shape and contour of the corpus callosum (CC) (marked by an asterisk, *). Patients in images A and B show a maldeveloped, foreshortened, and thinned corpus. Patient C has a partially destructed CC secondary to a large, chronic periventricular ischemic brain defect. Patient D shows a significantly thinned out, deformed CC (marked by a pi sign, ∏). Due to a high-grade obstructive hydrocephalus caused by an aqueductal stenosis. This patient had rhombencephalosynapsis (midline fusion of both cerebellar hemispheres, complete absence of the midline vermis). Correct differentiation between malformation, destruction, and secondary thinning/deformity due to a hydrocephalus is essential



Figs 4A and B: (A) Coronal transfontanellar ultrasound images of a neonate with complete agenesis of the corpus callosum (CC). No commissural fibers of the CC are noted to cross the interhemispheric fissure (the "X" marks the area where the missing CC would have been seen). In addition, the lateral ventricles are lateralized (marked by laterally pointing white arrows) and the anterior horns of the lateral ventricles nearly mimic a Texas longhorn configuration (shown above, horn-like appearance marked by asterisks, *); (B) Colpocephalic-widening of the occipital horns of the lateral ventricles (arrows)



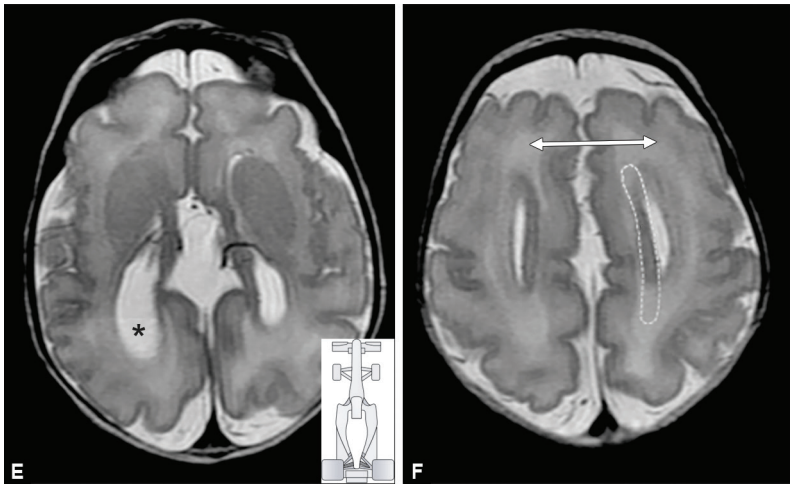
Figs 5A and B: (A) Sagittal T2-weighted MR images of a neonate with a complete agenesis of the corpus callosum (CC). The sagittal images show a complete lack of the CC with a moderately high-riding, interhemispherically extending third ventricle (absence marked by question marks, ?). The mesial hemispheric sulci appear to radiate from the third ventricle toward the periphery of the brain, no cingulate gyrus is seen in the midline; (B) For comparison, a normal midsagittal T2-weighted MR image is shown. Here, the CC can be seen (marked by an asterisk, *), marginated by the cingulate sulcus (superior contour marked by the white line)



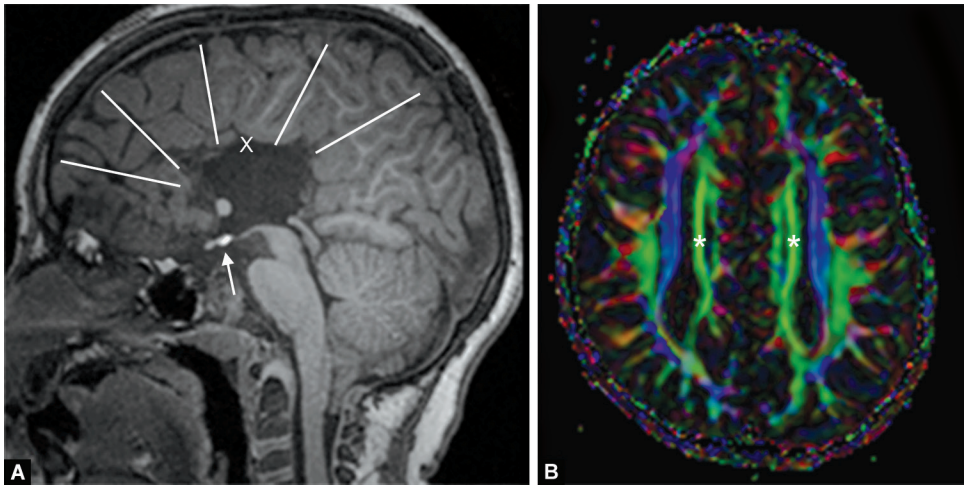
Figs 5C and D : Coronal T2-weighted coronal MR images of neonates with (C) Complete agenesis of the corpus callosum (CC). The third ventricle has a moderately high-riding, interhemispherically extending third ventricle (outlined by a white contour). The lateral ventricles are lateralized (laterally pointing wide white lines). The medial contour of the lateral ventricles is impressed by the Probst bundles (short arrows), which represents the aberrant anterior–posterior course of the white matter fibers that failed to cross the midline. The constellation of the maldeveloped midline structures result in a Texas longhorn appearance of the lateral ventricles on coronal imaging. The cingulate gyrus is not inverted (star), compared with the normal cingulate gyrus (asterisk) seen in image D. In addition, the hippocampi (arrows) are vertically orientated due to incomplete rotation; (D) A normal coronal T2-weighted MR image is displayed for comparison. The normal configuration and position of the cingulate gyrus is outlined by a white contouring

a lower frequency of 2/68 patients. Byrd et al.[39] noted 18/105 patients with "migration disorder." They documented polymicrogyria in 17 and abnormal sulcation in 35. Classic lissencephaly, cobblestone lissencephalies, polymicrogyria, schizencephaly, heterotopias, meningoceles, and other malformations (Figs 13 to 20) can be seen in conjunction with anomalies of the cerebral commissures.[17,41] Many patients with CC agenesis/hypogenesis have altered gyral patterns that do not fit into one of the classic categories (30/35 with abnormal sulcation).[22,42] In addition to the expected eversion of the cingulum and radial orientation of paramedian gyri associated with CC agenesis, sulcation abnormalities ranging from overly shallow olfactory sulci to notable hemispheric dysplasia can also be seen.[17] Abnormal sulcation, in association with commissural anomalies, could reflect a more generalized developmental disorder of the cerebral white matter.[17,43]

Most patients had decreased extracallosal white matter volumes in the supratentorial zone.[17] Only 1/81 with agenesis and 5/59 patients with hypogenesis of the CC had normal white matter volume. Reduced extracallosal white matter may represent a primary dysplasia or hypogenesis with fewer axons forming during development, or a secondary regression due to retraction of axons that cross the midline to synapse with their homologues and gain the necessary neurotrophic support. Alternatively, the number of axons in white matter tracts that did not cross midline could be similar, but these may have relatively less myelin than in normal commissures.



Figs 5E and F: Axial T2-weighted MR images of a neonate with a complete agenesis of the corpus callosum with a moderately high-riding, interhemispherically extending third ventricle. The lateral ventricles are lateralized (horizontal white line). The medial contour of the lateral ventricles is impressed by the Probst bundle (outlined in broken white line), which represents the aberrant anterior–posterior course of the white matter fibers that failed to cross the midline. The image on the left shows moderate colpocephaly (enlarged occipital horns; asterisk *) of the lateral ventricles. The appearance of the ventricles on axial imaging are infrequently referred to as the "racing car sign." The lateralized anterior horns of the lateral ventricles and the colpocephalic widened parieto-occipital horns resemble the tires of a formula 1 racing car seen from above, with small tires in the front and wide tires in the back



Figs 6A and B: (A) Sagittal T1-weighted MR, and (B) axial color-coded fractional anisotropy MR image of a neonate with complete agenesis of the corpus callosum (CC) show a complete lack of the CC with typical radiating appearance (white lines) of the cerebral sulci along the mesial brain surface. An "X" marks the expected location of the CC which is completely missing in this infant. Incidental note is made of a T1-hyperintense ectopical (neurohypophysis along the floor of the third ventricle (arrow). The color-coded FA map shows the green encoded anterior–posterior running fibers of the Probst bundle along the medial contour of the lateral ventricles (asterisks *)

Cerebral hemispheres have lateralized functions, which are particularly pronounced in humans. The CC is critical for integrating interhemispheric information; a developmental agenesis of the CC affects about 1 in 4,000 live births.[8,34] Interestingly, there is some preserved interhemispheric connectivity as seen in behavioral assessment and in resting-state functional MRI studies. These distinct functional outcomes for different ages of callosal loss were first noted by Roger Sperry, and are known as the "Sperry paradox."[44] This age-dependent plasticity may result from some compensatory rewiring through alternative routes.

Probst Bundles

One notable structural feature in these patients with agenesis or hypogenesis of the CC are the PBs, which are longitudinal, rostrocaudally oriented coiled white matter fascicles running alongside the lateral ventricles into the tapetum. These were named as the PBs, after Moriz Probst (1867–1923), an Austrian psychiatrist and neuroanatomist. The presence or absence of these PBs can affect the clinical presentation and outcome of these patients.[8,22,40,45–64] Some of these fibers show a ventromedial projection toward the fornix, where a few may cross the hippocampal commissure to the contralateral hemisphere.

Probst bundles indicate a failure of the callosally projecting neurons to extend axons across the midline due to anomalous axonal guidance in forming the CC. The inability of these axons to cross the midline results in front-to-back projections within each hemisphere, rather than connecting in the CC between the hemispheres. The inner fibers arise from the rostral pole and outer ones from the

caudal pole, and these may project in either direction. These findings have been confirmed in multiple reports at various stages of development.[8,45–60] More recently, these anomalies are detected in even more detail by MRI-based diffusion tensor imaging (Fig. 6).

Pathophysiology of PB Development

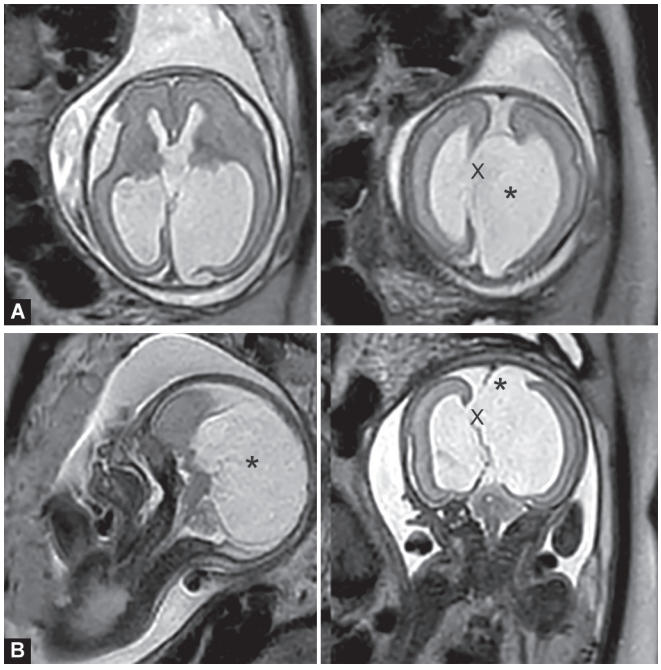
Probst bundles development is still being explored. There are two possibilities:

(a) Probst bundles may develop from mispositioning of midline glial structures.[8] In primates, callosal axons get positioned according to the guidance cues from specialized glia-rich guideposts at the midline: the indusium griseum, the glial wedge, and the midline zipper glia.[8] In agenesis of the CC with PB, these structures are frequently mispositioned; the guidance cues drives PB directionality in aberrant locations.[8,34] Midline glia frequently get situated within and around the PB structure itself. These might provide guidance signals to the axons within. However, alternative or additional mechanisms may exist.

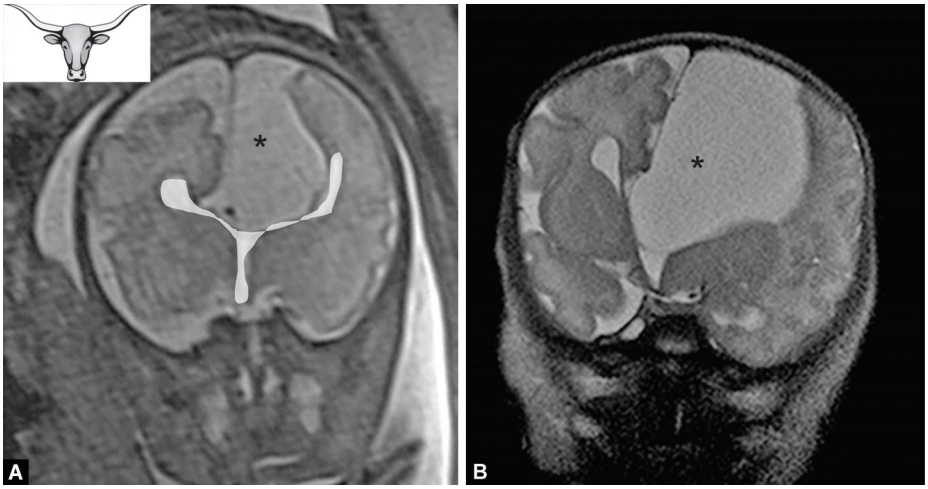
The development of interhemispheric cysts in the interhemispheric fissure that communicate with the ventricular system can disrupt the development of CC.[65] Midline lipomas are also an important cause; these form within the intradural space and may develop in the pericallosal region in the interhemispheric fissure.[66] In murine models, early surgical callosotomy conducted either embryonically, on embryonic day (E)16, or on the first postnatal day consistently produces PBs.[67] Surgical lesioning of the glial populations that contribute to remodeling of the midline seems to be the primary cause.

(b) Probst bundles might hijack axon guidance systems of other fiber tracts in neighboring regions that are spared in agenesis of the CC.[32] One mechanistic possibility is that axon guidance ligands in existing association tracts encourage axon growth and guidance along the alternative paths. In some cases, pioneering populations of axon tracts rely on guidance signals, while these signals are less necessary for follower axons. Follower axons may therefore be able to indiscriminately follow in the pre-existing tracts.

Probst bundles most likely develop along a physical scaffold and/or concentrations gradients of molecular cues.[8] The putative physical scaffolds are referred to as the cingulum bundles – these are believed to be longitudinal, bilateral tracts that bidirectionally interconnect diverse areas that might be prelimbic, anterior cingulate, retrosplenial, and occipital cortex, as well as extracortical areas, such as the hippocampus, thalamus, and brainstem.[58] Cingulum bundles are also present in agenesis of CC brains dorsomedial to the PBs. Other hypothesized longitudinal tracks include the inferior longitudinal fasciculus, interior fronto-occipital fasciculus, and the superior fronto-occipital fasciculus.[68–70]



Figs 7A and B: (A) Axial (top row), and (B) sagittal and coronal (lower row) T2-weighted fetal MRI of a fetus with a complete agenesis of the corpus callosum (CC) (an "X" marks the location where the CC is lacking) and an associated interhemispheric cerebrospinal fluid-filled cyst (marked by an asterisk, *). The cyst is located to the left of the falx



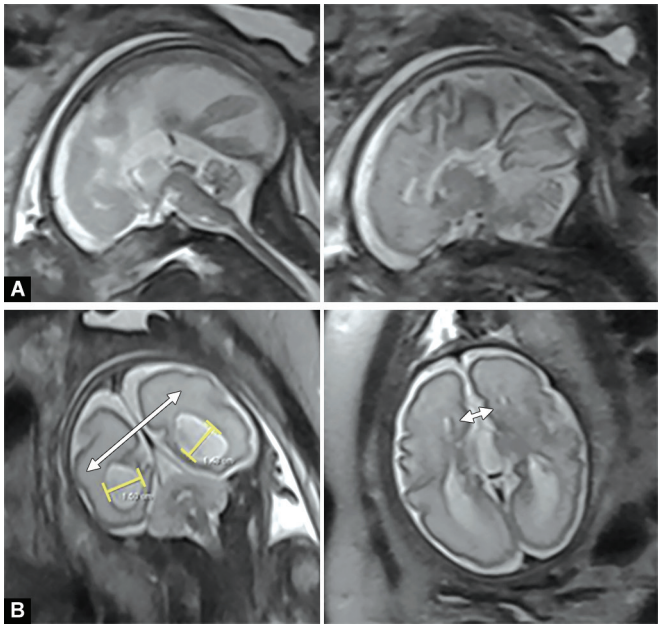
Figs 8A and B: (A) Coronal fetal and (B) matching postnatal T2-weighted MRI of a patient with complete agenesis of the corpus callosum with a large interhemispheric cyst (marked by an asterisk, *) to the left of the falx cerebri. The lateral ventricles are lateralized and show the characteristic Texas longhorn configuration (shaded in white). The cyst is located to the left of the falx

Hetts and coworkers[17] noted PBs in 66 of their patients. These tracts crossed the midline in some infants with a partial or intact CC. Interhemispheric cysts were seen in 20 (11 patients had cysts in communication with the ventricular system and 9 had cysts that did not communicate. Interhemispheric lipomas were noted in 3 patients. Anomalies of the cerebellum, brainstem, orbits, and olfactory apparatus were also evident in a few patients. Microcephaly, anomalies of the cerebellum, brainstem, orbits, and the olfactory apparatus may also be associated. There was no difference in the frequency of interhemispheric cysts, interhemispheric lipomas, abnormalities of the anterior and the hippocampal commissures, cortical malformations, and gray matter heterotopias. Similarly, the incidence of abnormal orbits, pituitary, white matter myelination, cerebellar hemispheres, cerebellar vermis, and/or structural abnormalities of the brainstem did not differ. There was no difference in the volume of extracallosal white matter.

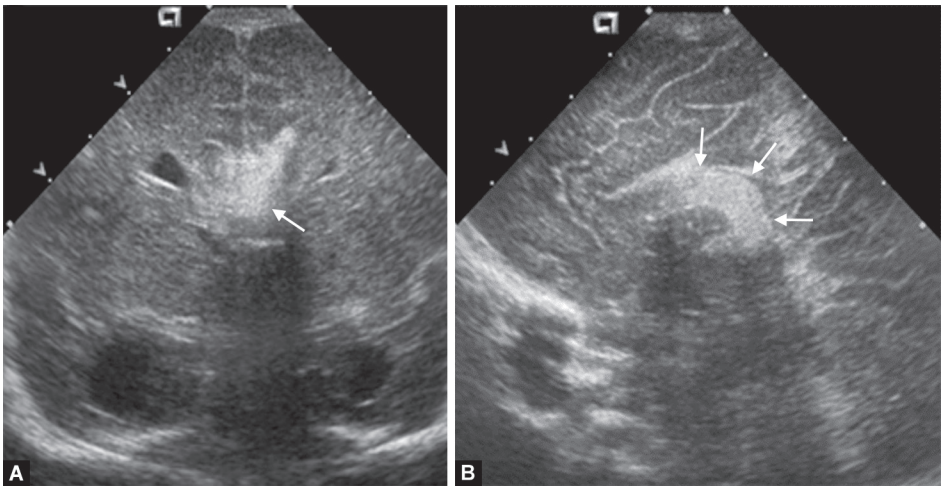
Patients with prominent PBs frequently showed altered cortical development, rhombencephalic and diencephalic anomalies, and were also seen in multiple congenital anomaly syndromes such as Aicardi's syndrome.[25] Other associated minor anomalies can also be seen. Midline anomalies such as primarily cysts, lipomas, and anomalies of the anterior or hippocampal commissures are frequently associated supratentorial abnormalities. Most patients with agenesis of CC and other midline anomalies (22/25) had PBs, but that was not the case with those with hypogenesis of CC and other midline anomalies. Rhombencephalic or diencephalic abnormalities (14/61) were less likely to be associated with PBs (53/81).

At a genetic level, PBs have been associated with nearly 115 different gene mutations in mice and humans.[8] Most PBs contain morphologically similar fibers with a predictable stereotypical orientation in specific locations of the brain.[8] These also show functional similarities with both faciliatory and detrimental functions. Unlike other developmental anomalies where aberrant axons appear pruned, PBs are preserved intact into adulthood;[8] the longitudinal ridge seems to persist as an underdeveloped CC.[71] The lateral callosal PBs indent the superomedial aspect of the lateral ventricles and may represent the axons that would have crossed the midline.[72] Probst bundles are seen about twice as frequently in patients with agenesis (59%) than in hypogenesis (30%) of the CC.[22] Byrd et al.[39] described PBs in patients with isolated agenesis of the CC. However, the histomorphology still needs to be characterized. Further studies are needed to outline the role(s) of these stereotypical ectopic tracts; plastic anatomical changes might be adaptive, maladaptive, or neutral.[8] MRI/diffusion tensor tractography[73] and neurodevelopmental follow-up are needed.

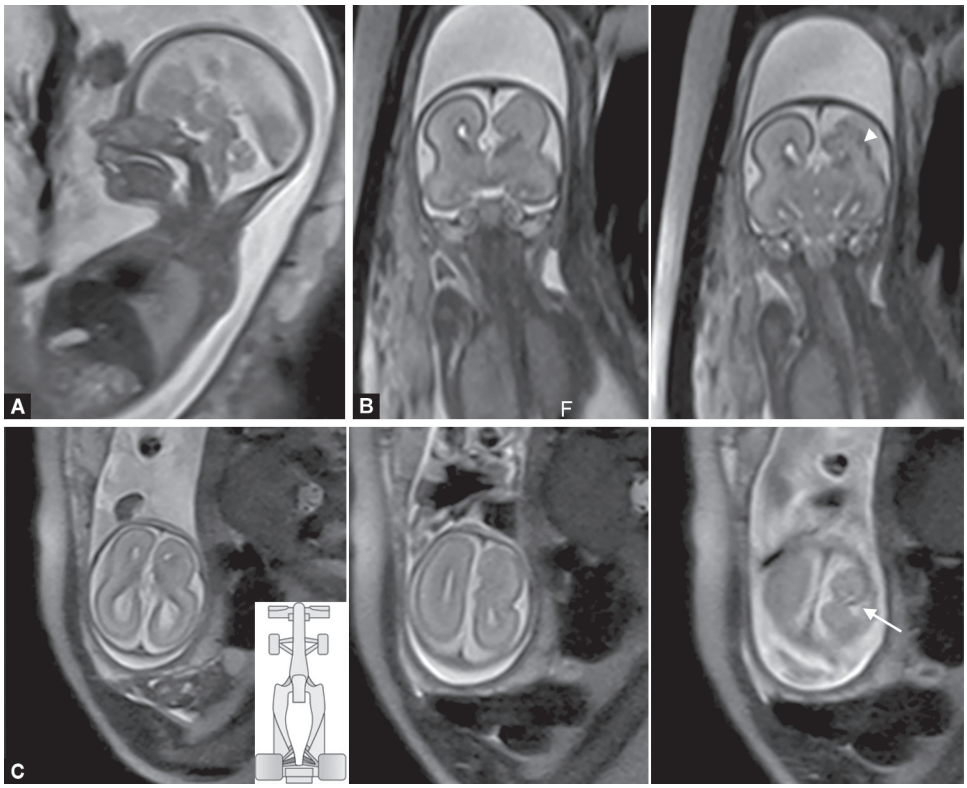
Axons composing PBs originate from neurons arising from cortical projections that resemble those in the CC in neurotypical brains.[8] In the CC, the axon density is highest at the rostral end,



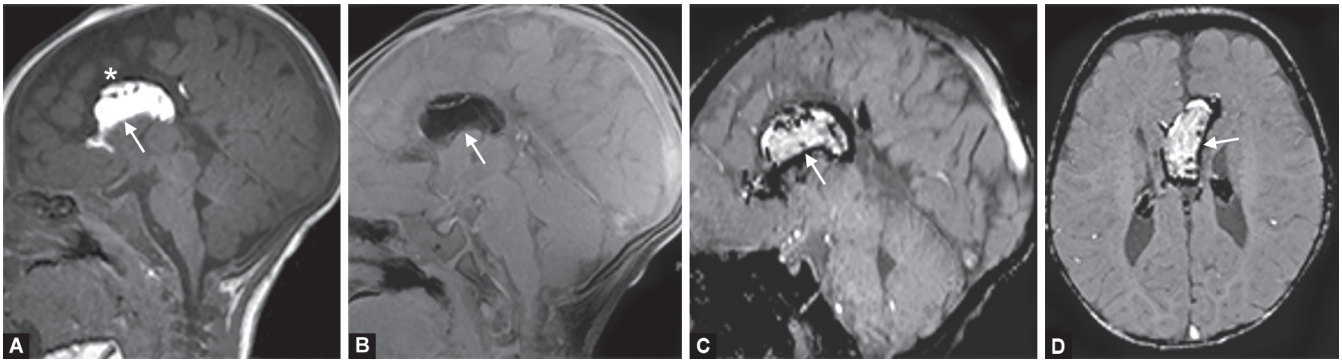
Figs 9A and B: (A) Sagittal (top row), and (B) Coronal and axial (lower row) T2-weighted fetal MRI of a fetus with a complete agenesis of the corpus callosum. The interhemispheric fissure is wide (short horizontal white line), no commissural fibers are noted crossing the midline, the lateral ventricles are lateralized (long horizontal white line) and show a parallel course, the occipital horns are colpocephaly widened (yellow lines)



Figs 10A and B: (A) Sagittal, and (B) Coronal transfontanellar ultrasound examination of a neonatal brain reveals the characteristic Texas longhorn configuration of the lateralized lateral ventricles on coronal imaging. In addition, an ill-defined midline hyperechogenicity (arrows) is noted which is following the expected course of the corpus callosum (CC) which is compatible with an interhemispheric lipoma which interfered with the normal development of the CC



Figs 11A to C: (A) Sagittal, (B) Coronal (top row); (C) Axial (lower row) T2-weighted fetal MRI of a fetus with a complex complete agenesis of the corpus callosum (CC). The axial image shows the "racing car sign." In addition to the CC agenesis, a closed lip schizencephaly is noted in the left cerebral hemisphere extending from the surface of the cerebral hemisphere toward the ipsilateral ventricle (white arrow). The adjacent cortical ribbon is malformed with extensive polymicrogyria as well as disruption of the sulcation pattern (arrowhead)



Figs 12A to D: Sagittal T1-weighted (A), Sagittal T1-weighted with fat suppression (B), Sagittal and axial T1-weighted (C and D) Gradient echo MR images of a neonatal brain with a large interhemispheric lipoma (arrows) and complete agenesis of the corpus callosum (asterisk *). The lipoma is T1-hyperintense, the signal intensity is suppressed on fat-suppressed sequences and shows a characteristic peripheral hypointense signal intensity on the gradient echo images due to the MR-related frequency shift confirming the lipomatous nature of the lesion

it tapers through the mid-callosum, and then increases again caudally at its posterior pole.[74] In contrast, the neuronal density in PBs is highest at the rostral end but it progressively decreases toward the caudal end.[8] The origin of these fibers likely decreases anteroposteriorly from the frontal, parietal, and the occipital cortex. Questions remain whether these rostrocaudal differences in brains with PBs originate in neuronal proliferation/migration during development or in cell death related to developmental pruning.[8]

The seemingly tortuous configuration of PBs might contain a consistent topographic arrangement.[8] Probst bundles seem to be orientated along the rostrocaudal axis, although the exact directionality is not always clear. During early development, axons stretch longitudinally in both a rostral and caudal direction. The longitudinal directionality of PB may be mixed in earlier developmental stages, but may get pruned later in different regions into a primarily rostral or caudal trajectory. Probst bundles may run dorsally and medially to the lateral ventricles and extend into the caudal tapetum. These patterns may cause morphological indenting of the rostral lateral ventricles and dilation of the caudal portions. The interpretation needs some caution as the appearance of PBs varies across species and might get altered with various stimuli. "PB-like" fibers have been noted as halted at the midline in arrested prenatal growth.

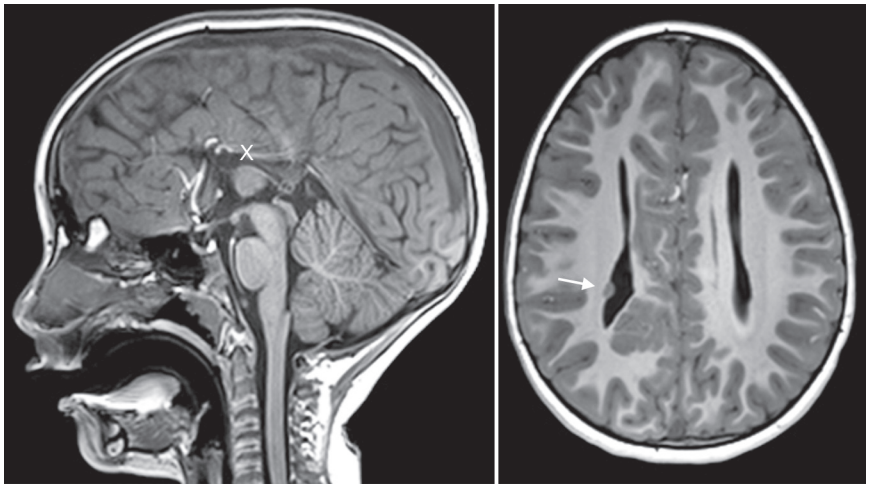
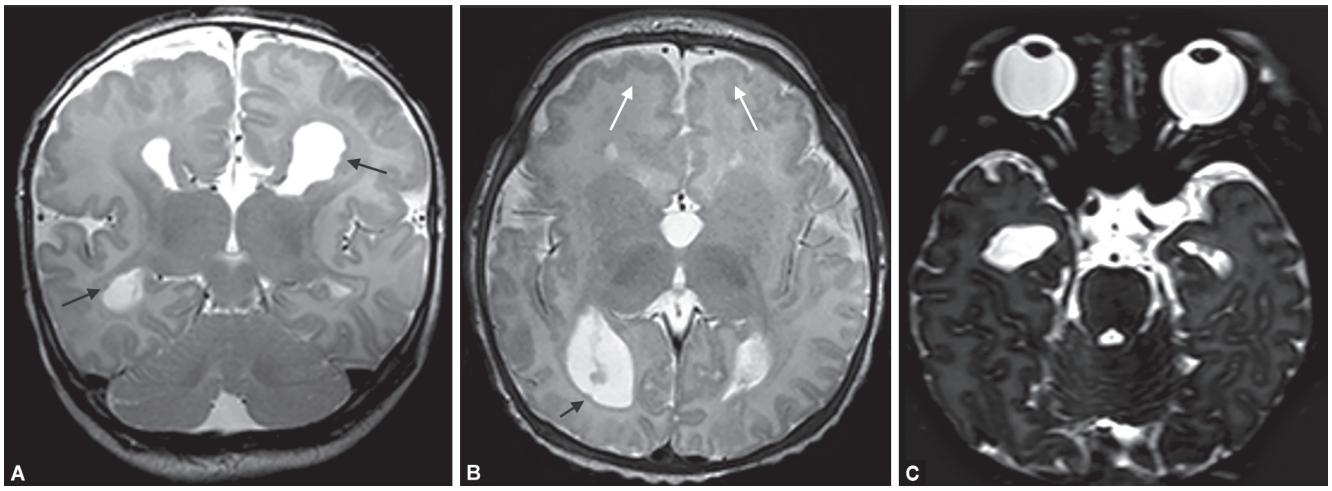


Fig. 13: Sagittal and axial T1-weighted (MR images of a child with a complete agenesis of the corpus callosum (CC) ("X"). In addition to the CC anomaly, a heterotopic gray matter nodule is seen along the right lateral ventricle (arrow)



Figs 14A to C: Coronal and axial T2-weighted (A and B), axial heavily T2-weighted high resolution (C) MR images of an infant with a complete agenesis of the corpus callosum with additional subependymal heterotopic gray matter nodules (black arrows) bilaterally as well as diffuse polymicrogyria of both frontal lobes (long arrows). The patient also had bilateral colobomas, which were consistent with the diagnosis of Aicardi syndrome

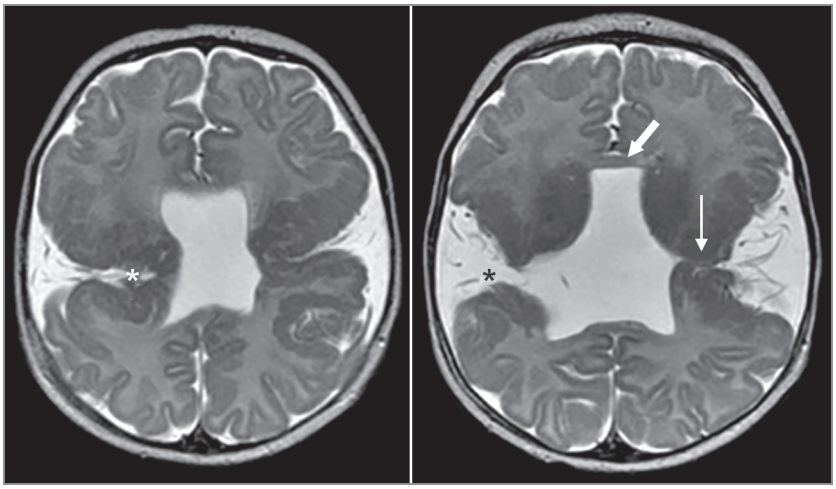
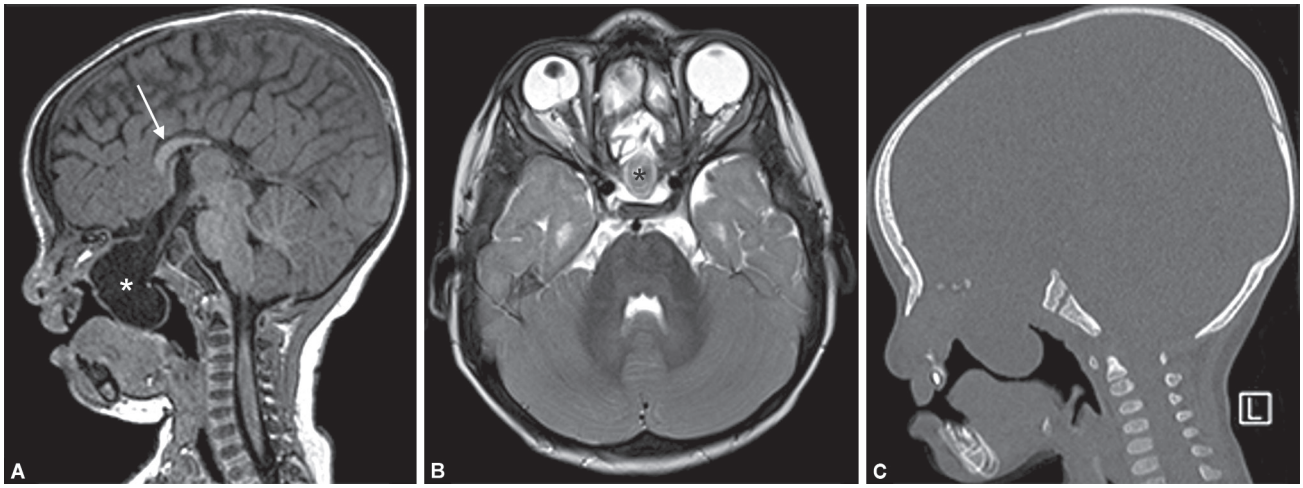
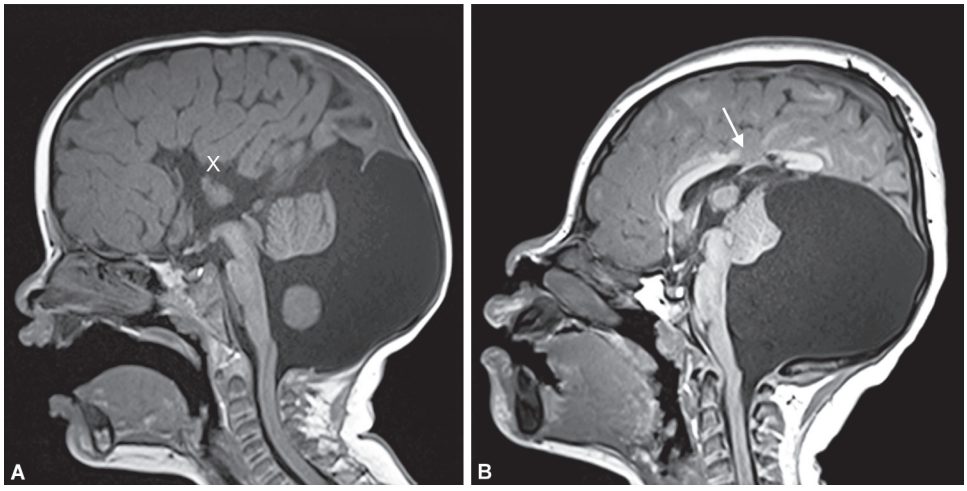


Fig. 15: Axial T2-weighted images of a patient with an open schizencephaly on the right (*) and a closed schizencephaly (arrow) on the left. The cleft is lined by a malformed cortical ribbon characterized by a combination of polymicrogyria and pachygyria. In addition, nearly complete agenesis of the corpus callosum (small thick arrow) is noted which is present in nearly 100% of cases of bilateral schizencephaly



Figs 16A to C: Sagittal T1-weighted (A), axial T2-weighted (B), MR images and a sagittal CT (C), image of a sphenoethmoid meningocele (asterisk), high-grade hypoplasia of the foreshortened corpus callosum (arrow), as well as bilateral colobomas and microphthalmia. The CT study shows the large osseous defect within the anterior skull base allowing for the meningocele to herniate into the nasopharynx



Figs 17A and B: Sagittal T1-weighted MR images of two different children with a Dandy–Walker malformation (enlarged posterior fossa due to a cystic dilatation of the fourth ventricle and upwards rotated hypoplastic vermis). (A) Child A has a complete corpus callosum (CC) agenesis (X); (B) Child B has a segmental agenesis of the trunk of the CC (arrow)

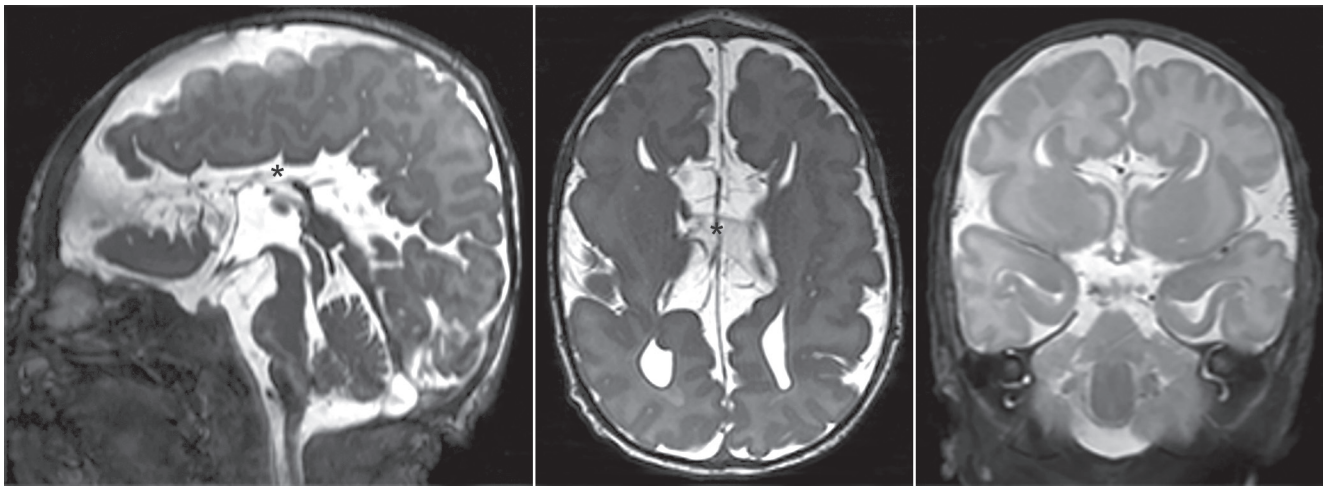


Fig. 18: Sagittal, axial and coronal T2-weighted MR images of a child with genetically confirmed Vici syndrome, which is characterized by a complete lack of the corpus callosum (asterisk *) with resultant typical appearance of the lateralized and deformed lateral ventricles. Texas longhorn configuration of the lateral ventricles on the coronal image

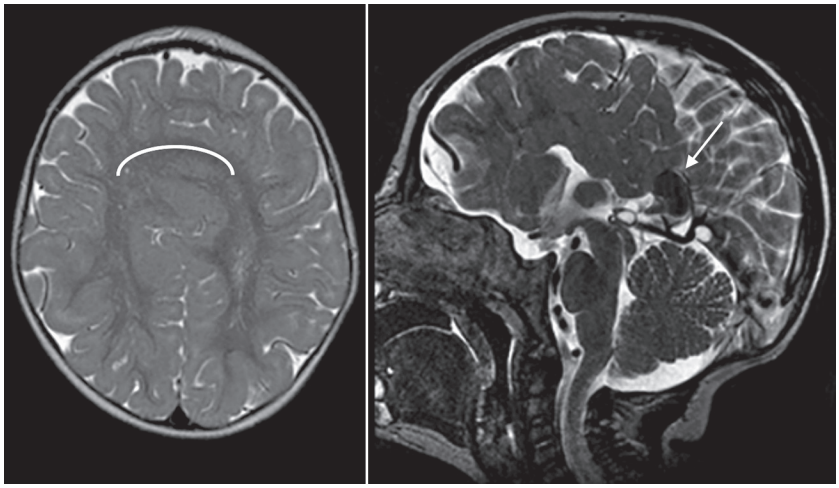


Fig. 19: Axial and sagittal T2-weighted MR images of a child with a semilobar holoprosencephaly with fusion of the frontal lobes (curved line). Only the splenium of the corpus callosum (arrow) developed, the rostrum, genu, and trunk are lacking

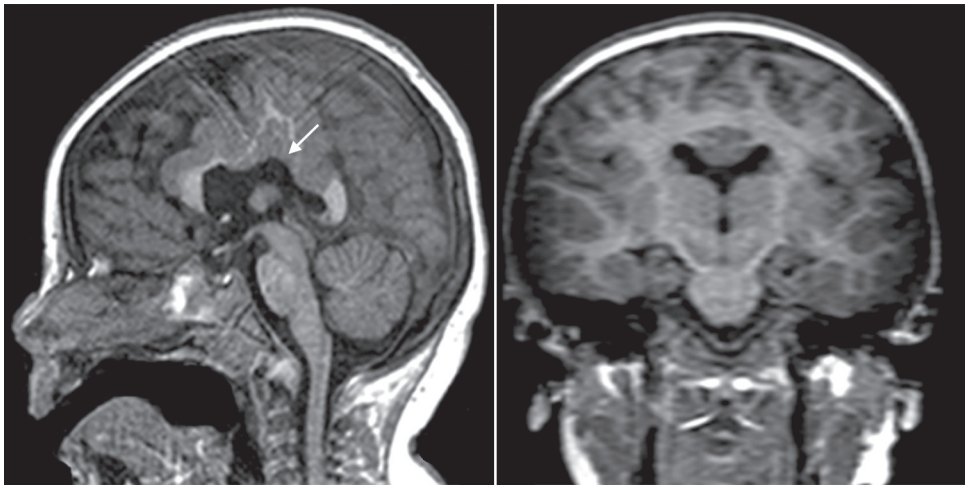


Fig. 20: Sagittal and coronal T1-weighted MR images of a child with a syntelencephaly characterized by a fusion of the brain across the region. Only the rostrum, genu, and splenium of the corpus callosum are developed; the trunk is not seen (arrow)

There are important differences in the neurons contributing to the CC or the PB, but the tracts are similar in the initial stages of development;[8,75,76] the morphological differences become more evident when callosal axons begin to traverse the midline. The CC axons cross the midline through a glia-rich permissive midline substrate but those from the PB make a sharp longitudinal turn as they approach the midline in response to cues such as disrupted midline guide-post cells, spatial and physical constraints, altered axon guidance molecules, and axon contacts with a retained/unmodeled interhemispheric fissure.[8] Corpus callosum axons may transiently bifurcate before reaching midline targets, depending on the location in the cortex.[77] The bifurcation prior to midline crossing might promote some axons to take alternative routes and differentiate to get integrated into the PB. Future studies are needed to dissect these differentiation pathways. Both form fasciculated axon tracts and share many callosal axon guidance and maturation programs.

In both tracts, spatially symmetrical bilateral activity might be necessary for normal contralateral callosal targeting. However, it is unclear if both differentiate from the same precursors. Cortical neurons in both project axons medially and rostrocaudally; these trajectories diverge as these approach the midline glia in the indusium griseum, glial wedge, and midline zipper glia, which displace the leptomeningeal fibroblasts and consequently shorten the interhemispheric fissure.[8,32] In the developing PB, the midline glia often appear malformed or mispositioned, or are functionally unable to secrete guidance cues and consequently, are not able to intercalate at the midline. The elongated axons take an ipsilateral U-turn in the same hemisphere. Some of these target ipsilateral structures such as the anterior septum. Other targets of PBs are still unknown.

Some of the PB fibers may project out of the fasciculated tract to other locations in the CNS.[8,78] However, the precise PB connectome and its degree of variability remains unclear. Current studies suggest that most PB fiber largely project to ipsilateral areas innervated by the CC.[8] Human diffusion tensor imaging studies show similar ipsilateral PB projection pattern consistent with a neurotypical CC projecting contralaterally to the frontal, parietal, occipital and temporal lobes.[8,79] The PB fibers do seem to preferentially project to more rostral frontal lobes and more

Table 1: Genes implicated in agenesis of CC in humans, organized by cellular component in which the gene is most highly expressed

	Genes involved: HGNC [Human Genome Organization (HUGO) Gene Nomenclature Committee] symbol	
Cellular component	*Manipulation produces ACC with PBs*	*Manipulation produces ACC without PBs*
Membrane	11 genes: *ATP1A3, B3GALNT2, BRCA2, DCC, DHCR7, FGFR2, OFD1, PAX6, RAC3, ROBO1, SLC12A6*	5 genes: *L1CAM, MID1, PAFAH1B1, PEX1, POMT2*
Cytoskeleton	11 genes: *ACTG1, BRCA2, DYNC1H1, HYLS1, KIF26A, KIF7, OFD1, RAC3, TUBA1A, TUBB2B, TUBB3*	6 genes: *ASPM, MID1, NDE1, PAFAH1B1, TUBA1A, TUBB3*
Cell projection	7 genes: *HYLS1, KIF7, L1CAM, OFD1, RAC3, ROBO1, TUBB3*	2 genes: *L1CAM, TUBB3*
Cell membrane	5 genes: *ATP1A3, FGFR2, RAC3, ROBO1, SLC12A6*	1 gene: *L1CAM*
Microtubule	5 genes: *DYNC1H1, KIF26A, TUBA1A, TUBB2B, TUBB3*	5 genes: *MID1, NDE1, PAFAH1B1, TUBA1A, TUBB3*
Nucleus	14 genes: *ALDH7A1, ARID1A, BRCA2, CHD7, FBXW11, FOXG1, FOXN1, KDM5B, NFIA, OFD1, PAX6, ZBTB20, ZEB1, ZEB2*	5 genes: *ARX, ASPM, CHD7, PAFAH1B1, RNF113A*

Genes with reduced expression. Listed cellular components have shown ≥5 implicated genes

paramedial cortical regions. This rostral and rostrocaudal axis of PBs may contribute to a higher rostrocaudal connectivity in absent agenesis of CC. Some of these anatomical features of PBs resemble those of the neurotypical cingulate bundle, which runs rostrocaudally over the CC to connect ipsilateral cortical hubs along the midline (regions that are also heavily connected interhemispherically by the CC), as well as extracortical regions that include the thalamus, basal forebrain, hippocampal formation, and other limbic regions.

In brains with agenesis of CC, some axons may project ventrally from the PB into the ipsilateral anterior septum. The cell bodies of origin might be in the cingulate cortex, where the first pioneering exons in the CC originate. These ectopic septal neurons in caudal regions of the brain are misplaced glutamatergic neurons and Sema3C cells.[80] Such ectopic projections to the septum have also been reported in brains with agenesis of the CC without PBs; the two structures are not necessarily always linked. Some patients with absent CC can be unexpectedly more functional than expected;[81] these tasks require bilateral integration and the PBs could contribute to other interhemispheric connections.[82]

Some PB fibers may project ventromedially to join the fornix.[83–85] The fibers cross at the level of the hippocampal commissure[86] and may maintain connectivity within cortical regions and for projecting to subcortical targets.[8] In animal models, a virtual Probstomy can alter the connections between cortical and subcortical regions.[87] Further work is needed to understand these circuits.[87]

PBs in Partial Agenesis of the CC

Probst bundles may also be seen with partial agenesis of the CC;[8] these patients have a callosal remnant along the rostro-caudal axis of the CC (partial hypogenesis) or a hypoplastic CC (thinning along the dorsoventral axis). In one study, the authors studied 113 reports of partial agenesis of the CC in experimental animals and humans and found adequate data for analysis in 43.[8] They noted 19 cases with hypogenesis of the CC, 31 with partial agenesis, and 1 who could not be classified. Of the 19 cases with hypogenesis, PBs were noted dorsal to (16/19) and ventral to (3/19) a thin callosum.[8] In these infants, the tract thinned out along its dorsocaudal axis, and can include both dorsal and ventral fibers. In the 31 infants with partial hypogenesis, PBs were seen most frequently posterior to callosal remnants (20 cases); anterior in 9, and in the mid-callosum in 2.[8]

Another type of an ectopic tract, the sigmoid bundle, has been reported in some cases of partial hypogenesis of the CC.[88] These aberrant fiber bundles asymmetrically connect the frontal lobe to the contralateral parieto-occipital cortex via the callosal remnant.[8] These tracts could possibly contribute to functional connectivity. The contribution of PBs to the sigmoid bundle is unclear.

Genetic Etiologies of Altered Development of Commissures

Genetic factors are an important cause of agenesis of the CC. Nearly, 85% of human cases have associated PBs.[8,22,34] In contrast, the specific genes have not been identified as a cause of agenesis of the CC without PBs. The formation of PBs has been associated with underexpression of several genes; there is a possibility that altered development of the midline structures may lead to agenesis of CC with PB formation. In one study, nearly all human MRIs with agenesis of CC identified disrupted midline territories.[88] About 115 unique genes have been identified in human/mouse agenesis of CC that did or did not lead to PB formation.[8] Ninety-one of these genes are known mediators in PB formation (79%); the rest have been associated with an absence of PBs. There are some differences in the genes identified in humans vs murine models.[8] There could also be other polygenic/environmental factors that influence gene expression and biological processes and/or the identification of genetic mutations that may not be involved in PB development, but can often be implicated in agenesis of CC.

Lynton and coworkers[8] used the Database for Annotation, Visualization, and Integrated Discovery (DAVID) to identify the human or mouse genes associated with or without PB formation shared common ontologies, such as the cellular component where the gene is typically enriched. These analyses did not show major differences in the cellular component ontologies of genes in either species. In both mice and humans, 3 genes showed a strong association with PB formation. The gene deleted in colorectal cancer (DCC)/Dcc, tubulin beta-3 class III (TUBB3)/Tubb3, and tubulin alpha 1a (TUBA1A)/Tuba1a.[31,89,90] Five genes were identified as associated with PB formation/absence in humans (L1 cell adhesion molecule (L1CAM), ectopic P-granules 5 autophagy tethering factor (EPG5), chromodomain helicase DNA-binding protein 7 (CHD7), TUBB3, and TUBA1A).[8,90,91] The Tables 1 and 2 have been modified based on the work of these experts.

Several genes associated with absence of CC and PBs have been associated with callosal axon-crossing in the brain midline.[8] Fibroblast growth factor 8 (Fgf8) may play an important role in an astrogliogenic program of midline tissue remodeling.[8] The transcription factors, nuclear factor I/A (Nfia) and nuclear factor

Table 2: Genes implicated in agenesis of CC in murine models, organized by cellular component in which the gene is most highly expressed

	Genes involved: HGNC [Human Genome Organization (HUGO) Gene Nomenclature Committee] symbol	
Cellular component	*Manipulation produces ACC with PBs*	*Manipulation produces ACC without PBs*
Membrane	30 genes: *App, Arhgap35, Cdk5r1, Chl1, Csf1r, Dcc, Efnb1, Efnb3, Epha5, Ephb1, Ephb2, Ephb3, Ext1, Fgfr1, Gap43, Gli3, Hs6st1, Maoa, Mapk8ip1, Marcks, Marcksl1, Msi1, Napa, Nf2, Nrp1, Plekhb1, Rac1, Scrib, Tmco1, Vasp*	8 genes: *Arhgap5, Creb1, Fzd3, Plxna1, Ptk2, Ptprs, Robo1, Vps35*
Cytoplasm	29 genes: *Actb, App, Arhgap35, Bcl11a, Cables1, Cdk5r1, Cep55, Dclk1, Dcx, Dido1, Enah, Fgfr1, Gap43, Gli3, Map1b, Mapk8ip1, Mapk8ip3, Marcks, Marcksl1, Msi1, Nf2, Nrp1, Ntn1, Plekhb1, Rac1, Scrib, Tuba1a, Tubb3, Vasp*	3 genes: *Arhgap5, Ptk2, Vps35*
Cell projection	20 genes: *App, Arhgap35, Cables1, Cdk5r1, Dclk1, Dcx, Enah, Epha5, Ephb1, Ephb2, Ephb3, Gap43, Gli3, Map1b, Mapk8ip3, Nf2, Rac1, Scrib, Tubb3, Vasp*	3 genes: *Ptk2, Ptprs, Robo1*
Cell membrane	19 genes: *App, Arhgap35, Cdk5r1, Chl1, Csf1r, Efnb1, Epha5, Ephb1, Ephb2, Ephb3, Fgfr1, Gap43, Marcksl1, Napa, Nf2, Nrp1, Rac1, Scrib, Vasp*	6 genes: *Arhgap5, Fzd3, Plxna1, Ptk2, Ptprs, Robo1*
Cytoskeleton	12 genes: *Actb, Arhgap35, Cep55, Dido1, Enah, Map1b, Marcks, Marcksl1, Nf2, Tuba1a, Tubb3, Vasp*	1 gene: *Ptk2*
Secreted	8 genes: *App, Bmp7, Chl1, Draxin, Fgf8, Ntn1, Slit2, Wnt3a*	2 genes: *Igf1, Slit1*
Synapse	5 genes: *Enah, Gap43, Map1b, Rac1, Scrib*	1 gene: *Ptprs*
Nucleus	24 genes: *Actb, App, Arhgap35, Bcl11a, Cables1, Cdk5r1, Dido1, Efnb1, Emx1, Eomes, Fezf2, Fgfr1, Gli3, Hesx1, Mapk8ip1, Msi1, Neurog2, Nf2, Nr2f1, Rac1, Rcor2, Rfx3, Tbr1, Zfp423*	8 genes: *Creb1, Emx2, Foxc1, Lhx2, Nfia, Nfib, Ptk2, Satb2*

Genes with reduced expression. Listed cellular components have shown ≥5 implicated genes

I B (Nfib) may be important upstream regulators. Probst bundles have also been seen in several other murine models,[8,22] such as those involving the secreted protein Draxin and its axon guidance receptor Dcc.[46] These show altered axon guidance system(s) involved in midline crossing and CC formation.[92] Genetic causes of absent CC with PB formation are related to changes in midline remodeling.[8] Further studies are needed.

Clinical Manifestations of Altered Development of Commissures with PBs

Agenesis of the CC may first present with seizures during infancy, beginning as early as the first few weeks after birth.[22] Many infants have feeding problems, neurodevelopmental delay, impaired hand-eye coordination, visual and/or auditory impairment, and deficits in memory acquisition.[93] Delayed acquisition of motor milestones is seen very frequently. Some patients develop hydrocephalus.[94] Some of these patients can benefit from intracranial pressure monitoring.[95,96] In other infants with milder manifestations, the clinical features might be delayed for many years,[22] and may present with seizures, headaches, motor abnormalities, or speech abnormalities.[97,98] Finally, a subset of patients remains asymptomatic.[99]

Mowat-Wilson syndrome[100] may be noted with micro- or macrocephaly. There may be dysmorphic features, such as ocular hypertelorism, pre-auricular skin tags, a small nose with anteverted nostrils, abnormally shaped pinnae, laryngeal abnormalities, loose skin on the neck, short hands, and digital abnormalities such as camptodactyly. Congenital heart defects and symptoms of Pierre-Robin syndrome could be seen. Some patients may only have growth failure.

Aicardi syndrome, an X-linked dominant disorder, may show agenesis of the CC.[101] These infants may present with infantile spasms; eye abnormalities in the choroid and the retinae; seizures; and developmental delay.

Andermann syndrome is another multisystem genetic disorder that can include agenesis of CC. These infants often show developmental delay and progressive sensorimotor neuropathy.[102] Many patients with this condition originate from the Charlevois County and the Saguenay-Lac St. Jean area of Quebec, Canada. The causative gene has been identified as the SLC12A6.

XLAG (X-linked lissencephaly with ambiguous genitalia)[103] is a rare genetic disorder in which males have abnormal cerebral gyration (lissencephaly), abnormal genital development such as with microphallus, severe developmental delay, and intractable seizures. The causative gene has been identified as ARX. Females can present with only agenesis of the CC.

Other Etiologies of Altered Development of CC with PBs

Some environmental and infectious causes have been identified to be associated with altered development of CC and PBs. Gamma irradiation in mice and Zika virus infection in a human fetus have been associated with agenesis of CC with PB formation.[45,104] Gamma irradiation resulted in altered midline remodeling with the absence of midline glia. Zika viruses disrupted midline glia, local microvasculature, and cortical development. There were fewer proliferating cortical cells, intermediate progenitors, and $SATB2^+$ neurons.[105] Viral-mediated neurodevelopmental deficits may be caused by disruption of the CC but formation of PBs when structural disorganization is less extreme.

Agenesis of CC without PBs

To understand the physiological importance of PBs, one group of investigators reviewed a total of 39 reports of human subjects and 30 of murine models of agenesis of CC who did not show PBs.[8] Most of these cases involved major nervous system malformations such as meningomyelocele/Chiari II malformations or classic holoprosencephaly. Reported mechanisms included deficits in genes encoding growth factors, such as Insulin-like growth factor-1 (Ifg1), and tubulins and proteins associated with cellular metabolism such as pyruvate dehydrogenase (PDH). These findings suggested that deficiencies in growth, and axonal outgrowth and metabolism could contribute to cerebral disorganization without the CC and PBs. However, there are 3 case reports where neurodevelopmental malformations that lacked CC but showed PBs, including syntelencephaly, myelomeningocele, and Chiari II malformations,

suggesting that PBs could form in these conditions. We clearly need additional studies to better understand the significance of the PBs.[8]

Probst bundles are seen in nearly all cases of agenesis of CC where the structure of the cerebral cortex is not significantly altered.[8] However, some murine models lacking the CC show contrary evidence; axons do not form PBs but appear halted in the hemispheres. Genotypes lacking slit guidance ligand 2 (Slit2), roundabout guidance receptor 1 (Robo1), or special AT-rich sequence binding protein 2 (Satb2) are notable, although the impact on axon growth is uncertain.[88] There is also a possibility that the axons could have been re-routed through a separate, non-callosal interhemispheric tract.[8,32] More studies are needed to understand the mechanisms involved in the formation of ectopic bundles or re-routing through existing commissures and tracts.

Clinical Significance of Altered Development of Commissures and PBs

The function of PBs is still unclear. One possibility could be related to less axonal elimination during development but these could also contain more functional connections.[8] Features such as the myelination patterns resemble those in mature brain structures. The functionality of PB fibers can be identified in glucose uptake, EEG coherence, fetal connectome, and electrophysiology. Probst bundles function could well be compensatory, neutral, or maladaptive to cognitive outcome.[8] These could promote neurodevelopmental outcomes and performance, but these findings are difficult to confirm as these structural findings are often associated with other gross malformations.

Compared with infants with complete absence of CC, those with partial absence have fewer anatomical changes in the brain and might have better behavioral outcomes.[106] However, existing data suggest that the contrary might be the case. In one connectome study, the functional connectivity patterns in patients with complete absence of the CC resembled those in controls. In contrast, those with callosal hypoplasia showed abnormal structural and functional connectivity patterns; disorganized cortical neurons projected inconsistently into the ectopic PB.[8] This high variability in connectivity could have explained the variability in behavioral and cognitive performance. Another explanation could be rooted in a higher frequency of minor brain abnormalities in these patients. More studies are required to confirm these findings.

Probst bundles might help maintain interhemispheric communication, and consequently, promote certain behavioral phenotypes.[8,92] Individuals with absence of CC may still show preserved interhemispheric connectivity on behavioral and resting-state functional MRI studies.[107] Virtual lesions also suggest that PBs may contribute to interhemispheric communication. Individuals born with absence of CC frequently do not display the disconnection syndrome, the PBs could well contribute to interhemispheric communication such as through the hippocampal commissure or subcortical routes.[8] Augmented ipsilateral connectivity with cortical hubs may enhance polysynaptic communication via other pre-existing interhemispheric circuits.[8]

The functional importance of PBs may well extend beyond interhemispheric communication.[8] These commissures have been associated with "syndromic" diagnoses such as the autism spectrum that also have altered structural and functional connectivity of different parts of the brain and reduced callosal volume.[34] The developmental plasticity of brain connections might help in understanding altered neurodevelopment and regulation of compensatory plasticity.[108]

Corpus callosum helps maintain communication between the left and right sides of the body.[109] Despite existing information that patients with agenesis of the CC may not always display a disconnection syndrome,[110] the morphological substrates facilitating intact interhemispheric communication in those infants remain unclear. Probst bundles seem to contain tangled and dysfunctional axons.[8] However, some anatomical consistency has been maintained in these topographic patterns through evolution, indicating that there could be some functional roles.[111] There might be some cognitive compensation that has maintained interhemispheric communication in the absence of CC.[112] Focused studies on developmental abnormalities in axon tracts may be helpful in understanding axon plasticity and connectivity disorders.

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