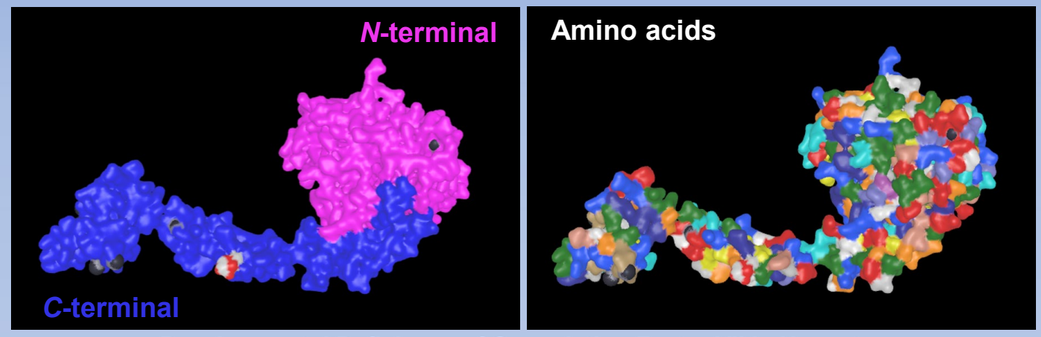
April–June 2026 Volume 5 Issue 2 newborn Official Journal of the Global Newborn Society eISSN: 2769–514X

newborn

April-June 2026
Volume 5
Issue 2
eISSN 2769-514X

Official Journal of the Global Newborn Society and allied organizations
International Society for Marginalized Lives
Dr. Mozib Newborn Foundation
The Carlo GNS Center for Saving Lives at Birth
Vishwa Mahesh Parivaar
Autism Care Network Foundation

And
GNS Down Syndrome Foundation
Newborn Foundation of Azerbaijan
GNS Bangladesh Newborn Foundation
GNS Foundation of Germany
Global Newborn Society Foundation of Italy
Mongolian Association of Obstetrics Gynecology and Neonatology
Foundation for Human Milk Feeding in the Islamic World
The organization, Protecting Brains and Saving Futures, Brasil
Association of Neonatologists in the United Kingdom
Polish Nursing Association - Płock, Poland
Panlibyan Neonatal Association
Association for Indigenous Peoples in India
Association for Newborn Care in Pakistan
GNS Association for Perinatal Care
Association for Infant Nutrition in the Middle East
Sociedad Latinoamericana de Residentes de Neonatologia (SolaReNeo)
Uruguayan Neonatal Association
Paraguayan Society of Pediatrics Committee for Neonatology
Armenian Association of Neonatal Medicine
Association of Pediatricians of Uzbekistan
Iranian Forum for Infant Nutrition
Nepalese Association for Newborn Health
GNS Forum for Transgenerational Inheritance
PreemieWorld Foundation
GNS Forum for Data Analytics
GNS Forum for Nanomaterials
Neonatology Branch of the Chilean Pediatric Society
Dudeja GNS Center for Infectious Diarrheal Diseases
Anatolian Midwives Association
GNS Western Australia
Perinatal Society of Singapore
Pioneers - looking for sustainable ways to reduce infant mortality
Bhutan Neonatal Care Forum
Global Newborn Society Iran Chapter
National Federation of Neonatologists of Mexico
College of Neonatologists of the State of Jalisco, Mexico
The Skylar Project
International Society for Marginalized Lives
Friends Aid Africa, Bukedea, Uganda
Society of Bacteriophage Research and Therapy
GNS Center for Computational Scientific Methodology
GNS International Association of Neonatal POCUS
SABREE Enrichment Academy: Empowering Ability
The Caribbean Association for Hematology and Oncology
First Breath of Life
GNS Neonatal Radiology Forum
Global Newborn Society, Orthopedic Surgery Section

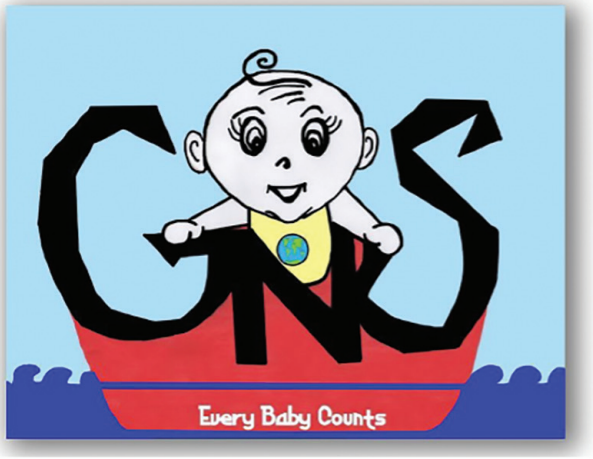


Developmental Deficiency of Coagulation Factor VII in Neonates

Other highlighted articles:
Duodenal Atresia in Down Syndrome
World Quantum Day 2026

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.

Issue Information

Volume 5, Issue 2; April–June 2026

eISSN: 2769-514X

Published: GNS, LLC; 6114 Lily Garden, Clarksville, MD, USA; Ph +1 708 910 8729

Printed: Jaypee Brothers Medical Publishers
4838/24, Ansari Road, Daryaganj, New Delhi 110 002, India
Phone: +91 11 4357 4357, Fax: +91 11 4357 4314

Contents

EDITORIAL 10.5005/newborn-5-2-iv

Connection Starts in the Cradle

Our fight for infants/children with special needs has to focus on loneliness and isolation.[1–3] As mentioned below, the World Down Syndrome Day in 2026 has emphasized the theme "Together Against Loneliness".[4] Parents, families, advocates, and organizations are advocating for inclusive communities, early social intervention, and caregiver support to support these children in their formative years.[5] Loneliness is a subjective and distressing feeling that arises when there is a gap between the social relationships a person desires and those they actually experience;[6] there is a sense of emotional, social, or relational disconnection, even when surrounded by others.[7] This interpretation of the word is, to some extent, focused on how older individuals express their distress, but infants can also be lonely.[8,9] They are dependent on caregivers for emotional comfort.[10–12] If/when their needs for responsive caregiving, affection, and social connection are not met, they may experience distressing social and emotional disconnection.[13] This has been viewed more as disrupted attachment, social deprivation, or lack of responsive relationships than as subjective loneliness – we just don't know because infants cannot talk or vote.[1,14–16] Early negative experiences such as neglect, separation from caregivers, limited social engagement can adversely affect emotional development and social functioning.[17,18]

Loneliness is a multidimensional experience[3,19,20] and can be categorized in several ways:

Emotional loneliness in babies may result from a lack of close, nurturing, and responsive relationships with primary caregivers.[21,22] Even though infants cannot express themselves verbally, they are biologically wired to seek comfort, protection, and emotional connection through attachment relationships.[23] Parental sensitivity to an infant's expression of distress cues has been described as nurturance, and that to non-distress cues as synchrony.[24] These likely represent distinct contexts in which parents can be differentially sensitive/insensitive in responding.[1,24] When consistent emotional support is absent/deficient due to caregiver separation, neglect, inconsistent caregiving, parental illness, or other disruptions, infants show signs of distress.[18,25] And this is problematic because early emotional connections are essential for attachment, emotional regulation, and healthy development, making supportive family relationships a critical protective factor for social-emotional development, stress responses, and the formation of healthy relationships later in life.[11,26–28]

Social loneliness in babies can be viewed as a lack of opportunities for meaningful social interaction and engagement with caregivers, family members, and the broader social environment.[12,18,25] Even though infants might not perceive loneliness in the same way as older children or adults, they rely on frequent social exchanges.[29] These may include eye contact, talking, play, touch, and responsive caregiving, and all possibly support healthy social, emotional, and cognitive development.[30] When these interactions are limited because of social isolation, neglect, prolonged hospitalization, institutional care, or restricted family and community engagement, infants may experience reduced social stimulation and difficulties in developing secure relationships and social skills.[31] In this sense, social loneliness in infancy reflects a deficit in social connectedness and participation rather than a conscious awareness of being lonely.[1,32,33]

Existential Loneliness is a deeper sense of separateness related to the human condition.[3,34,35] It may involve feelings that no one can fully understand the experiences, thoughts, or emotions of an individual.[35] This type can occur even in people with strong social relationships; in babies, it might be difficult to define as they do not communicate similar to older children and adults.[1,35] However, some developmental theorists suggest that infants could very well begin to experience existential separateness when they become aware that they are distinct individuals from their caregivers.[36,37] During this process, disruptions in consistent, responsive caregiving may contribute to feelings of insecurity, disconnection, or distress.[38,39] Lack/paucity of nurturing relationships characterized by sensitive caregiving, physical closeness, emotional attunement, and secure attachment can disrupt emotions of security, belonging, and connections that format the healthy emotional development throughout life.[40,41]

Situational loneliness may be seen when infants get isolated or disconnected from families for short periods, and resolves when the causative difficulties are resolved.[1,42] Some instances may be related to hospitalization, changes in caregiving arrangements, relocation, parental illness, or other disruptions to familiar routines and relationships.[43] Even though infants cannot express loneliness verbally, they may show signs of distress through crying, fussiness, withdrawal, sleep disturbances, feeding difficulties, or increased clinginess.[44] There is a need for comfort, security, and social connection.[19] Consistent presence of parents, family members, and other trusted caregivers usually helps restore a sense of safety and connectedness.[45,46] Although occasional episodes are a normal part of development, prolonged or repeated disruptions in nurturing relationships may affect emotional well-being and attachment formation, highlighting the importance of stable, supportive caregiving environments during early life.[28,47]

Chronic loneliness refers to a persistent and prolonged lack of meaningful social and emotional connection.[48] In infants, this can occur due to prolonged neglect, repeated caregiver absence, severe social deprivation, institutionalization with limited individual attention, or environments where their emotional and developmental needs are not consistently met.[1,48] Over time, chronic loneliness can affect cognitive development, stress regulation, emotional security, and social-emotional growth.[19,49] Research on attachment and early childhood development demonstrates that stable, responsive relationships are essential for healthy infant development, helping to build trust, resilience, and a sense of safety.[11,41] Preventing chronic loneliness in infancy requires supportive family environments, sensitive caregiving, early identification of at-risk families, and interventions that strengthen caregiver-infant relationships.[22] By ensuring that infants experience consistent emotional connection and responsive care, societies can promote healthier developmental outcomes and reduce the long-term consequences of social and emotional deprivation.[10,50]

Collective loneliness refers to a sense of disconnection from a broader community, group, or social network.[12,25] In adults, it involves feeling detached from society or lacking a sense of belonging to a larger collective.[19] In infants, the term collective loneliness could be

visualized to describe situations with limited opportunities to be embedded within supportive family, community, and social networks.[18,51] We know that infants thrive not only through relationships with primary caregivers but also through interactions with extended family members, peers, healthcare providers, and community support systems.[18,52,53] Strengthening these social connections can enhance caregiver well-being, promote responsive caregiving, and provide infants with a rich social environment that supports emotional, cognitive, and social development from the earliest stages of life **Fig 1**.[54,55]

In each issue of this journal, our editorial team highlights the achievements of one of our partnering members. Here, we present the Neonatal Intensive Care Units (NICUs) at the Emirates Hospital Jumeirah and Emirates Specialty Hospital, Dubai Healthcare City (DHCC).[56] This NICU provides comprehensive Level III neonatal care and is known for evidence-based clinical practice, advanced technology, and family-centered care. It is equipped with state-of-the-art technology, including conventional and high-frequency ventilation with volume guarantee, inhaled nitric oxide therapy, whole-body therapeutic hypothermia, continuous EEG monitoring, advanced hemodynamic monitoring, neonatal echocardiography, and comprehensive respiratory support systems. There is a highly skilled multidisciplinary team of neonatologists, neonatal nurses, respiratory therapists, lactation consultants, and allied healthcare professionals. A distinguishing feature of the unit is its strong commitment to family-centered care, beginning with antenatal counselling for high-risk pregnancies and extending throughout the infant's hospitalization and follow-up. Dr. Monika Kaushal,[57–59] a senior neonatologist with more than 25 years of experience in neonatal-perinatal medicine, has established and led this unit. She is known worldwide for her pioneering leadership in neonatal intensive care, and for her efforts in the Global Newborn Society **Fig 2**.

This journal aims to cover fetal/neonatal problems that begin during pregnancy, at the time of birth, or during the first 1,000 days after birth. As in our previous issues, we present 8 articles here (**Fig. 3**).

We were all inspired by the article written by Dr. Srijan Singh about the World Down Syndrome Day 2026[60] and hence dedicated the opening of this preface article to this theme. Down Syndrome (DS) continues to be a pressing yet often overlooked challenge with medical difficulties, loneliness, and social isolation. There has been many a discussion about these problems - loneliness is a subjective emotional experience with inadequate social relationships, whereas social isolation is an objective state characterized by limited interpersonal interactions.[61,62] Research suggests that people with intellectual disabilities experience loneliness at rates up to seven times higher than those seen in the general population, underscoring the urgent need for greater social inclusion and meaningful community participation.[63] Beyond its emotional and psychological effects, chronic loneliness may also have medical dimensions – these individuals often show elevated levels of stress hormones such as cortisol, increased inflammation, impaired immune function, and disrupted sleep patterns.[64,65] They may be at a higher risk of cardiovascular disease, hypertension, obesity, diabetes, and weak immune responses.[66–68]

Maheshwari and his colleagues[69] have reviewed the biological importance, structure, evolution, and the clinical relevance of coagulation factor VII (FVII). FVII is a vitamin K–dependent coagulation protein that plays a pivotal role in initiating the extrinsic pathway of blood clotting.[70] Following vascular injury, FVII binds tissue factor (TF), becomes activated to FVIIa, and triggers a cascade leading to thrombin generation, fibrin formation, and stable clot development.[71] The TF–FVIIa complex not only drives coagulation but also influences inflammatory signaling pathways, while tissue factor pathway inhibitor (TFPI) serves as a critical regulator that limits excessive coagulation. Evolutionary analyses suggest that FVII emerged in early jawed vertebrates and has remained highly conserved for over 400 million years, reflecting its fundamental importance in hemostasis.[72,73] The clinical importance of FVII is known in patients with hemophilia, particularly when they develop inhibitors to factors VIII or IX, and in many other inherited and acquired bleeding disorders.[74] In neonates, rFVIIa has been used as rescue therapy for severe, life-threatening hemorrhage that is unresponsive to conventional treatment.[75] However, randomized neonatal trials are lacking, and concerns remain regarding thromboembolic complications.[76]

Kaushal, Balla, and Ponnazhagan have written about the potential importance of quantum science in medicine.[77] World Quantum Day is an international, community-driven initiative dedicated to increasing public awareness and understanding of quantum science and technology.[78] First launched in 2021 by a global group of scientists, educators, historians, and science communicators, it is celebrated annually on April 14, a date chosen to reflect the first three digits of Planck's constant[79] (4.14×10^{-15} eV·s), a fundamental constant in quantum physics. Through lectures, workshops, exhibitions, and public outreach activities, the event brings together researchers, students, industry representatives, and the wider public to explore the scientific discoveries and technological advances enabled by

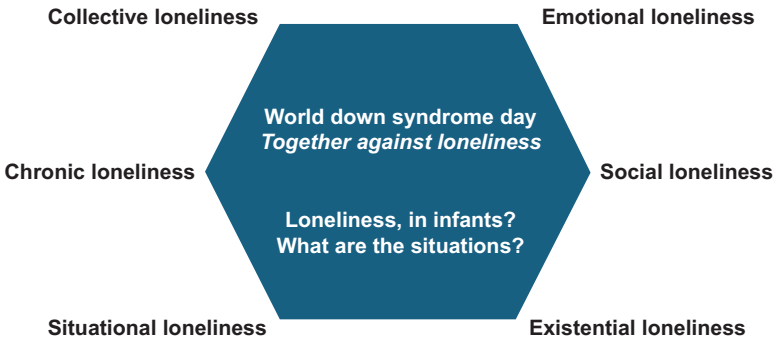
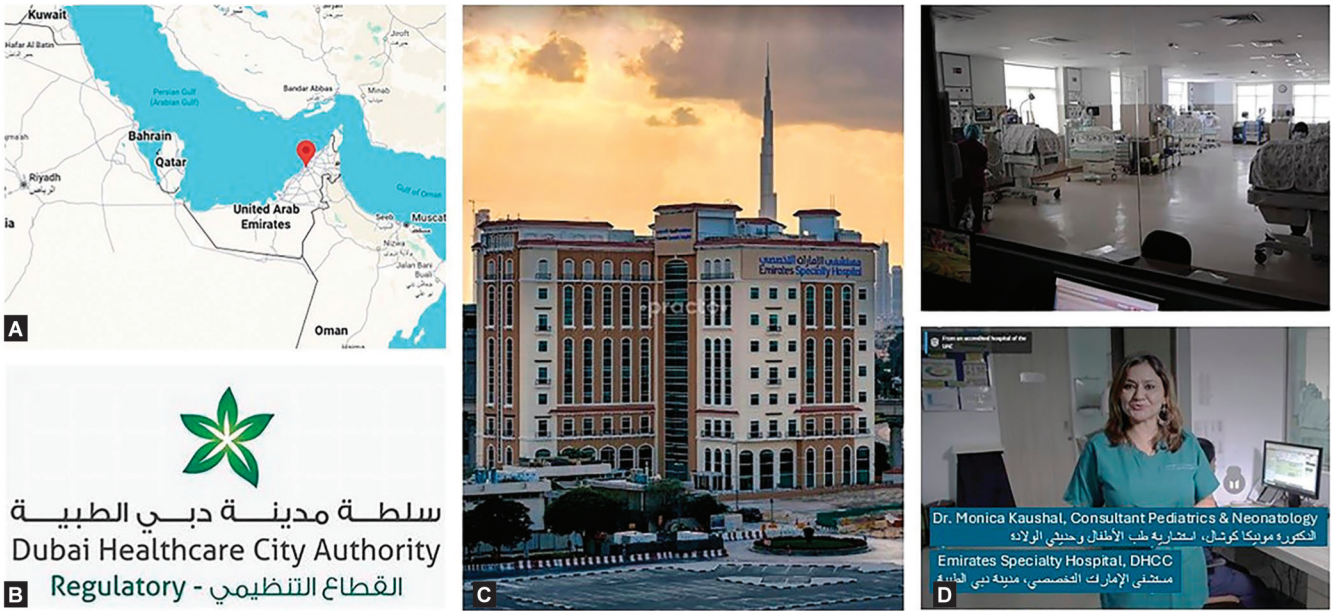


Fig. 1: Infants may experience several forms of loneliness through disrupted relationships and limited social connection. Emotional loneliness reflects a lack of close nurturing bonds; social loneliness is due to limited interaction; existential loneliness indicates early feelings of separateness; situational loneliness is temporary disconnection; chronic loneliness indicates persistent relational deprivation; and collective loneliness occurs due to reduced connection to supportive family and community networks



Figs 2A to D: (A) The Dubai Metropolitan Area and the (B) Dubai Healthcare City (DHCC), a free zone ecosystem dedicated to health and wellness, are known for its facilities for neonatal intensive care and specialized pediatric support; (C) The Emirates Hospital Jumeirah and Emirates Specialty Hospital DHCC provides (D) Level III neonatal care founded on evidence-based practice, advanced technology, and family-centered care. This unit has growth under the leadership of Dr. Monika Kaushal, a renowned neonatologist with extensive clinical and academic experience in neonatal-perinatal medicine

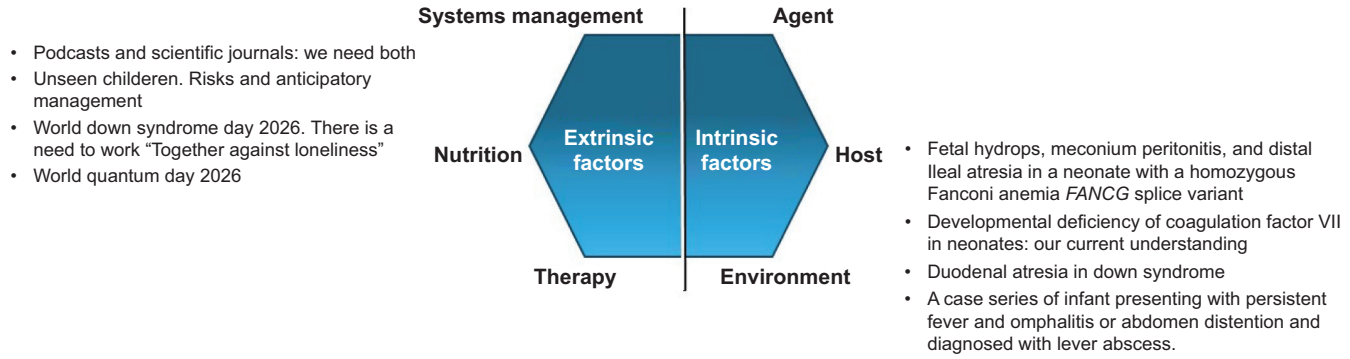


Fig. 3: Areas of focus in the *newborn*, Volume 5, Issue 2. We have expanded the traditional agent-host-environment trinodal disease model to a hexagonal system. The three additional foci represent extrinsic factors that can affect health - those originating in therapy, nutrition, and systems management are shown. This issue covers 2 nodes, with articles focused on host factors and systems management.

quantum mechanics. Unlike many international observances, World Quantum Day is not governed by a single organization but operates as a decentralized global collaboration involving universities, research institutes, scientific societies, museums, and volunteers.

Fanconi anemia is a rare inherited genetic disorder characterized by defective DNA repair, leading to progressive bone marrow failure, congenital abnormalities, and an increased risk of cancer.[80] The condition commonly presents with reduced production of red blood cells, white blood cells, and platelets, causing anemia, recurrent infections, and bleeding tendencies. Ravishankar and Rishika[81] report the clinical profile of a male infant born to consanguineous parents who was noted to have non-immune hydrops fetalis *in utero* and, then meconium peritonitis after birth. Surgical exploration revealed distal ileal atresia with necrosis. Whole exome sequencing showed a homozygous 5′ splice site variant in the *FANCG* gene[82] (c.307+1G>T). The findings in this patient suggest that defective DNA repair and endothelial fragility may cause vascular disruption sequences in the gastrointestinal tract. Timely genetic diagnosis in infants with atypical gastrointestinal atresias may help with appropriate peri-operative and long-term management of these patients.

Colin Michie has raised a very important point about "unseen children".[83] These infants and children miss scheduled healthcare or educational appointments and are often recorded as "Did Not Attend" (DNA) or "Was Not Brought" (WNB). The missed encounters can lead to delayed immunizations, inadequate growth and developmental surveillance, and unmet healthcare needs.[84,85] Non-attendance may also be an indicator of broader safeguarding concerns, including social disadvantage, family instability, neglect, abuse, displacement, or barriers to accessing care. Beyond the impact on individual children, missed appointments create substantial healthcare costs, reduce service efficiency, and delay the identification of children requiring medical attention, many of whom later present to emergency or acute

care services. Addressing this issue requires proactive, child-centered approaches, including community outreach, integrated health and social services, flexible appointment systems, culturally sensitive engagement, and strengthened safeguarding frameworks to ensure that vulnerable children remain visible and connected to essential services.

Bagga et al.[86] have described the genetic etiopathogenesis of duodenal atresia in patients with Down Syndrome (DS). About 20–30% of infants with duodenal atresia have DS.[87,88] The authors have reported a term male infant with DS who developed vomiting within 24 hours of life. Imaging demonstrated the classic "double bubble" sign, and surgical exploration confirmed duodenal atresia. The infant was successfully treated with duodenoduodenostomy.[89] Duodenal obstruction can be intrinsic, resulting from failure of normal fetal recanalization of the duodenal lumen, or extrinsic, rooted in conditions such as annular pancreas or intestinal malrotation. Current evidence suggests that overexpression of two chromosome 21 genes, which encode the dual specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) and regulator of calcineurin 1 (RCAN1) can be related to DS-related duodenal atresia. These molecular abnormalities may impair duodenal recanalization during embryogenesis. Understanding the pathogenesis of DS-associated duodenal obstruction can help in early diagnosis, timely management, and prognostication in these patients.

Nikhil Jain has described a series of 6 infants with persistent fever, omphalitis, and hepatomegaly, who had liver abscess(es).[90] Neonatal liver abscess is a rare but potentially life-threatening complication of neonatal sepsis. Although uncommon due to the liver's rich blood supply and extensive reticuloendothelial defenses, abscesses can develop secondary to sepsis, omphalitis, umbilical venous catheterization, central venous lines, necrotizing enterocolitis, surgery, prematurity, or immune dysfunction.[91] Clinical manifestations are often non-specific and include fever, lethargy, feeding intolerance, vomiting, abdominal distension, hepatomegaly, and elevated inflammatory markers. This case series was notable because none of the affected infants had received umbilical venous catheters, suggesting that alternative mechanisms such as community-acquired umbilical infection and portal vein thrombosis, may play important roles in pathogenesis. A high index of suspicion and early diagnosis are essential to improve outcomes.

Finally, Huseynova and colleagues discuss about the increasing importance of using both academic journals and alternative methods of scientific communication such as podcasts.[83] Academic journals remain the cornerstone of evidence-based practice by providing rigorous peer review, methodological scrutiny, and scientific credibility. However, the impact of journal publications can be limited by technical language, paywalls, and static presentation. The integration of journals and podcasts creates a powerful knowledge translation ecosystem. Journals provide scientific depth and authority, while podcasts enhance accessibility, context, and practical application. This collaboration can take many forms, including author interviews, article summaries, editorial discussions, conference coverage, and continuing medical education content. Podcasts also serve as valuable tools for public science communication, helping explain research findings and counter misinformation. In resource-limited settings, downloadable audio content can improve access to current medical knowledge and reduce educational disparities. The Global Newborn Society recognizes podcasts as an important tool for engaging healthcare professionals, families, and communities to improve awareness and advocacy for newborn health worldwide.

References

1. Kwan C, Gitimoghaddam M, Collet JP. Effects of Social Isolation and Loneliness in Children with Neurodevelopmental Disabilities: A Scoping Review. Brain Sci. 2020 Oct 28;10(11). PMID: 33126519. doi: 10.3390/brainsci10110786.
2. Frey LM, Wilhite K. Our Five Basic Needs: Application for Understanding the Function of Behavior. Intervention School Clin. 2005;40(3):156-160. doi: 10.1177/10534512050400030401.
3. Bolmsjo I, Tengland PA, Ramgard M. Existential loneliness: An attempt at an analysis of the concept and the phenomenon. Nurs Ethics. 2019 Aug;26(5):1310-1325. PMID: 29471724. doi: 10.1177/0969733017748480.
4. United-Nations. World Down Syndrome Day 21 March New York City, New York, United States: United Nations; 2026 [Available from: https://www.un.org/en/observances/down-syndrome-day.
5. Ceci B, Walsh MM, Colaianni S, Pinks ME, Onnivello S, Van Deusen K, et al. What Motivates Parents of Young Children With Down Syndrome to Participate in Research: A Focus Group Analysis. J Appl Res Intellect Disabil. 2026 Jan;39(1):e70178. PMID: 41525769. doi: 10.1111/jar.70178.
6. McCarthy JM, Erdogan B, Bauer TN, Kudret S, Campion E. All the Lonely People: An Integrated Review and Research Agenda on Work and Loneliness. J Manage. 2026 Jan;52(1):283-330. PMID: 41395233. doi: 10.1177/01492063241313320.
7. Ma de Sousa AQ, Schwyck ME, Furtado Fernandes L, Ford E, Babur BG, Lu C, et al. Loneliness is associated with unstable and distorted emotion transition predictions. Commun Psychol. 2025 Aug 28;3(1):132. PMID: 40877578. doi: 10.1038/s44271-025-00310-w.
8. Forster-Gibson CJ. Behaviour changes in an adult with Down syndrome. Can Fam Physician. 2019 Apr;65(Suppl 1):S25-S26. PMID: 31023775. doi: Not assigned.
9. Gomez-Zuniga B, Pousada M, Armayones M. Loneliness and disability: A systematic review of loneliness conceptualization and intervention strategies. Front Psychol. 2022;13:1040651. PMID: 36760915. doi: 10.3389/fpsyg.2022.1040651.
10. Jahromi LB, Gulsrud A, Kasari C. Emotional competence in children with Down syndrome: negativity and regulation. Am J Ment Retard. 2008 Jan;113(1):32-43. PMID: 18173298. doi: 10.1352/0895-8017(2008)113[32:ECICWD]2.0.CO;2.
11. Schworer EK, Fidler DJ, Daunhauer LA. Early Regulatory Skills and Social Communication Development in Infants with Down Syndrome. Brain Sci. 2021 Feb 9;11(2). PMID: 33572121. doi: 10.3390/brainsci11020208.
12. AlShatti A, AlKandari D, AlMutairi H, AlEbrahim D, AlMutairi A, AlAnsari D, et al. Caregivers' perceptions and experience of caring for persons with Down syndrome in Kuwait: a qualitative study. Int J Dev Disabil. 2021;67(5):381-390. PMID: 34570835. doi: 10.1080/20473869.2021.1910780.
13. Ganiban J, Barnett D, Cicchetti D. Negative reactivity and attachment: Down syndrome's contribution to the attachment-temperament debate. Dev Psychopathol. 2000 Winter;12(1):1-21. PMID: 10774593. doi: 10.1017/s0954579400001012.
14. Global-Newborn-Society. Global Newborn Society - Our Philosophy Clarksville, Maryland, USA: Global Newborn Society; 2021 [Available from: https://www.globalnewbornsociety.org/our-philosophy.

15. UNICEF. Convention on the Rights of the Child New York City, New York, USA: United Nations Children's Fund; 1989 [cited 2026. Available from: https://www.unicef.org/child-rights-convention/convention-text.
16. Stone L. The Minimum Voting Age Should be Zero New York City, New York, USA: The New York Times; 2021 [Available from: https://www.nytimes.com/2021/09/01/opinion/politics/kids-right-to-vote.html.
17. Herrero-Roldan S, Martin-Rodriguez A. Neglect and Neurodevelopment: A Narrative Review Understanding the Link Between Child Neglect and Executive Function Deficits. Biomedicines. 2025 Jun 26;13(7). PMID: 40722641. doi: 10.3390/biomedicines13071565.
18. Miller EJ, Cohen AB, Nagao S, Griffith D, Maunder RJ, Martin TR, et al. Elevated levels of NAP-1/interleukin-8 are present in the airspaces of patients with the adult respiratory distress syndrome and are associated with increased mortality. Am Rev Respir Dis. 1992 Aug;146(2):427-32. PMID: 1489135. doi: 10.1164/ajrccm/146.2.427.
19. Hawkley LC, Cacioppo JT. Loneliness matters: a theoretical and empirical review of consequences and mechanisms. Ann Behav Med. 2010 Oct;40(2):218-27. PMID: 20652462. doi: 10.1007/s12160-010-9210-8.
20. Yanguas J, Pinazo-Henandis S, Tarazona-Santabalbina FJ. The complexity of loneliness. Acta Biomed. 2018 Jun 7;89(2):302-314. PMID: 29957768. doi: 10.23750/abm.v89i2.7404.
21. Ahmad MH, Ali M, Hassan M, Ahmad RN, Yasin MU, Fatima H, et al. The Emotional and Psychological Impact on Families Raising Children With Special Needs: A Primary Care Perspective. Health Sci Rep. 2026 Mar;9(3):e71928. PMID: 41804501. doi: 10.1002/hsr2.71928.
22. Zhang XN, Zhang S, Liu CY, Ni ZH, Lv HT. Caregivers' experience of having a child with Down syndrome: a meta-synthesis. BMC Nurs. 2025 Jan 20;24(1):66. PMID: 39833779. doi: 10.1186/s12912-024-02652-y.
23. Perry RE, Blair C, Sullivan RM. Neurobiology of infant attachment: attachment despite adversity and parental programming of emotionality. Curr Opin Psychol. 2017 Oct;17:1-6. PMID: 28950954. doi: 10.1016/j.copsyc.2017.04.022.
24. Bernard K, Meade EB, Dozier M. Parental synchrony and nurturance as targets in an attachment based intervention: building upon Mary Ainsworth's insights about mother-infant interaction. Attach Hum Dev. 2013;15(5-6):507-23. PMID: 24299132. doi: 10.1080/14616734.2013.820920.
25. Band R, Rogers A. Understanding the Meaning of Loneliness and Social Engagement for the Workings of a Social Network Intervention Connecting People to Resources and Valued Activities. Health Expect. 2024 Dec;27(6):e70111. PMID: 39575523. doi: 10.1111/hex.70111.
26. Mengoni SE, Smith B, Wythe H, Rogers SL. Experiences of feeding young children with Down syndrome: parents' and health professionals' perspectives. Int J Dev Disabil. 2025;71(4):545-553. PMID: 40529193. doi: 10.1080/20473869.2023.2269321.
27. Hutton R, Allen LR. Opportunity Gaps in the Social-Emotional Development, Wellbeing, and Mental Health Experienced by Young Children. 2023. In: Opportunity Gaps in the Social-Emotional Development, Wellbeing, and Mental Health Experienced by Young Children [Internet]. Washington DC, USA . : National Academies Press [1]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK596376/.
28. Vaughn BE, Goldberg S, Atkinson L, Marcovitch S, MacGregor D, Seifer R. Quality of toddler-mother attachment in children with Down syndrome: limits to interpretation of strange situation behavior. Child Dev. 1994 Feb;65(1):95-108. PMID: 8131657. doi: 10.1111/j.1467-8624.1994.tb00737.x.
29. Hahn LJ, Loveall SJ, Savoy MT, Neumann AM, Ikuta T. Joint attention in Down syndrome: A meta-analysis. Res Dev Disabil. 2018 Jul;78:89-102. PMID: 29793102. doi: 10.1016/j.ridd.2018.03.013.
30. Lobo E, Mahapatra S, Babu GR, van Schayck OC, Srinivas PN, Mukherjee D. Practices and outcomes of responsive caregiving on child neurodevelopment and mental health across diverse global populations: a scoping review protocol. BMJ Open. 2024 Apr 3;14(4):e078712. PMID: 38569711. doi: 10.1136/bmjopen-2023-078712.
31. Guralnick MJ, Connor RT, Johnson LC. Peer-related social competence of young children with Down syndrome. Am J Intellect Dev Disabil. 2011 Jan;116(1):48-64. PMID: 21291310. doi: 10.1352/1944-7558-116.1.48.
32. Wickramaratne PJ, Yangchen T, Lepow L, Patra BG, Glicksburg B, Talati A, et al. Social connectedness as a determinant of mental health: A scoping review. PLoS One. 2022;17(10):e0275004. PMID: 36228007. doi: 10.1371/journal.pone.0275004.
33. Tsou Y-T, Nasri M, Li B, Blijd-Hoogewys EMA, Baratchi A, Koutamanis A, et al. Social connectedness and loneliness in school for autistic and allistic children. Autism. 2025;29(1):87-101. doi: 10.1177/13623613241259932.
34. van Tilburg TG. Social, Emotional, and Existential Loneliness: A Test of the Multidimensional Concept. Gerontologist. 2021 Sep 13;61(7):e335-e344. PMID: 32604416. doi: 10.1093/geront/gnaa082.
35. Garnow T, Einberg E-L, Garmy P, Edberg A-K. Trapped and lost in transition - existential loneliness during adolescence described in retrospect by Swedish university students. Int J Adol Youth 2024;29(1). doi: 10.1080/02673843.2024.2353205.
36. Raby KL, Cicchetti D, Carlson EA, Cutuli JJ, Englund MM, Egeland B. Genetic and caregiving-based contributions to infant attachment: unique associations with distress reactivity and attachment security. Psychol Sci. 2012 Sep 1;23(9):1016-23. PMID: 22829464. doi: 10.1177/0956797612438265.
37. Berry P, Gunn P, Andrews R. Behavior of Down syndrome infants in a strange situation. Am J Ment Defic. 1980 Nov;85(3):213-8. PMID: 6449871. doi: Not assigned.
38. Hawk BN, McCall RB, Groark CJ, Muhamedrahimov RJ, Palmov OI, Nikiforova NV. Caregiver Sensitivity and Consistency and Children's Prior Family Experience as Contexts for Early Development within Institutions. Infant Ment Health J. 2018 Jul;39(4):432-448. PMID: 29953627. doi: 10.1002/imhj.21721.
39. Bodde AE, Brooks JV, Forseth B, Wolfe T, Williams K, Ptomey LT. Caregiving for Adults With Down Syndrome: Caregiver Experiences and Support Needs. J Appl Res Intellect Disabil. 2025 Sep;38(5):e70118. PMID: 40922411. doi: 10.1111/jar.70118.
40. Humphreys KL, Garon-Bissonnette J, Hill KE, Bailes LG, Barnett W, Hare MM. Caregiving relationships are a cornerstone of developmental psychopathology. Dev Psychopathol. 2024 Dec;36(5):2218-2231. PMID: 38389283. doi: 10.1017/S0954579424000300.
41. Vanwalleghem S, Miljkovitch R. A systematic review on attachment and down syndrome. J Intellect Dev Disabil. 2023 Dec;48(4):409-420. PMID: 39815888. doi: 10.3109/13668250.2023.2208744.
42. Black AE, Hossain M, Rutherford HJV, Nelson-Coffey SK. Perceived connectedness during the perinatal period: Implications for parent and child well-being. J Fam Psychol. 2025 Dec 11. PMID: 41379707. doi: 10.1037/fam0001437.
43. Qian Y. Caregiving Considerations in Understanding Loneliness and Isolation. Clin Geriatr Med. 2025 Aug;41(3):419-433. PMID: 40653344. doi: 10.1016/j.cger.2025.04.002.
44. Eastwood J, Jalaludin B, Kemp L, Phung H, Barnett B, Tobin J. Social exclusion, infant behavior, social isolation, and maternal expectations independently predict maternal depressive symptoms. Brain Behav. 2013 Jan;3(1):14-23. PMID: 23408743. doi: 10.1002/brb3.107.

45. An J, Zhu X, Shi Z, An J. A serial mediating effect of perceived family support on psychological well-being. BMC Public Health. 2024 Apr 2;24(1):940. PMID: 38566105. doi: 10.1186/s12889-024-18476-z.
46. Noroozi F, Farrar Z, Gharibi T, Gashmard R. Family Self-Support in Managing Down Syndrome Children: A Qualitative Study. ScientificWorldJournal. 2024;2024:9992595. PMID: 38818108. doi: 10.1155/2024/9992595.
47. Doyle C, Cicchetti D. From the Cradle to the Grave: The Effect of Adverse Caregiving Environments on Attachment and Relationships Throughout the Lifespan. Clin Psychol (New York). 2017 Jun;24(2):203-217. PMID: 28924334. doi: 10.1111/cpsp.12192.
48. Ahmed M, Cerda I, Maloof M. Breaking the vicious cycle: The interplay between loneliness, metabolic illness, and mental health. Front Psychiatry. 2023;14:1134865. PMID: 36970267. doi: 10.3389/fpsyt.2023.1134865.
49. Finley AJ, Schaefer SM. Affective Neuroscience of Loneliness: Potential Mechanisms underlying the Association between Perceived Social Isolation, Health, and Well-Being. J Psychiatr Brain Sci. 2022;7(6). PMID: 36778655. doi: 10.20900/jpbs.20220011.
50. Hendrix JA, Amon A, Abbeduto L, Agiovlasitis S, Alsaied T, Anderson HA, et al. Opportunities, barriers, and recommendations in down syndrome research. Transl Sci Rare Dis. 2021;5(3-4):99-129. PMID: 34268067. doi: 10.3233/trd-200090.
51. Holt-Lunstad J, Robles TF, Sbarra DA. Advancing social connection as a public health priority in the United States. Am Psychol. 2017 Sep;72(6):517-530. PMID: 28880099. doi: 10.1037/amp0000103.
52. Buka SL, Beers LS, Biel MG, Counts NZ, Hudziak J, Parade SH, et al. The Family is the Patient: Promoting Early Childhood Mental Health in Pediatric Care. Pediatrics. 2022 May 1;149(Suppl 5). PMID: 35503309. doi: 10.1542/peds.2021-053509L.
53. Reynolds K, Urbanowicz A, Mayston M, Foley S. Kids+ Parent Infant Program (PIP): a community model for supporting partnerships in early developmental follow-up and support. Front Pediatr. 2024;12:1354971. PMID: 38756970. doi: 10.3389/fped.2024.1354971.
54. Holt-Lunstad J. Social connection as a critical factor for mental and physical health: evidence, trends, challenges, and future implications. World Psychiatry. 2024 Oct;23(3):312-332. PMID: 39279411. doi: 10.1002/wps.21224.
55. Palamaro Munsell E, Kilmer RP, Cook JR, Reeve CL. The effects of caregiver social connections on caregiver, child, and family well-being. Am J Orthopsychiatry. 2012 Jan;82(1):137-45. PMID: 22239404. doi: 10.1111/j.1939-0025.2011.01129.x.
56 .Kaushal M. Emirates Specialty Hospital - Dubai Healthcare City Dubai, United Arab Emirates: DHCC; 2026 [Available from: https://emirateshospitals.ae/locations/emirates-specialty-hospital-dhcc/.
57. Kaushal M, Balla KC. Clinical Imaging: Point-of-care Ultrasound for Endotracheal Tube Localization in Neonates: Why It Matters. Newborn (Clarksville, Md). 2026;5(1):58–60. doi: 10.5005/jp-journals-11002-0141.
58. Kaushal M, Balla KC. Clinical Procedures: Use of Peripherally Inserted Central Catheters in Neonates. 2025;4(4):178–180. doi: 10.5005/jp-journals-11002-0143.
59. Singh S, Kaushal M, Guaragni B, Aversa S, Alghnimei N, Hayat MR, et al. Systematized Systemic Sonographic Surveillance (S4). Newborn (Clarksville, Md). 2025;4(4):181–193. doi: 10.5005/jp-journals-11002-0142.
60. Singh S. World Down Syndrome Day 2026. There is a Need to Work "Together Against Loneliness". Newborn (Clarksville, Md). 2026;5(2):To be assigned. doi: 10.5005/jp-journals-11002-0160.
61. Skotko BG, Levine SP, Goldstein R. Self-perceptions from people with Down syndrome. Am J Med Genet A. 2011 Oct;155A(10):2360-9. PMID: 21910246. doi: 10.1002/ajmg.a.34235.
62. Brandt L, Liu S, Heim C, Heinz A. The effects of social isolation stress and discrimination on mental health. Transl Psychiatry. 2022 Sep 21;12(1):398. PMID: 36130935. doi: 10.1038/s41398-022-02178-4.
63. Stokes JE, Waldron DA, Stam EJ. Loneliness Among Adults Aging With Intellectual and Developmental Disabilities: The Importance of Living Situation. Gerontologist. 2025 Mar 25;65(4). PMID: 39878057. doi: 10.1093/geront/gnaf031.
64. Doane LD, Adam EK. Loneliness and cortisol: momentary, day-to-day, and trait associations. Psychoneuroendocrinology. 2010 Apr;35(3):430-41. PMID: 19744794. doi: 10.1016/j.psyneuen.2009.08.005.
65. Mavrych V, Mansour GK, Hajjar AW, Bolgova O. Hormonal and Behavioral Consequences of Social Isolation and Loneliness: Neuroendocrine Mechanisms and Clinical Implications. Int J Mol Sci. 2025 Dec 21;27(1). PMID: 41515962. doi: 10.3390/ijms27010084.
66. Pourriyahi H, Yazdanpanah N, Saghazadeh A, Rezaei N. Loneliness: An Immunometabolic Syndrome. Int J Environ Res Public Health. 2021 Nov 19;18(22). PMID: 34831917. doi: 10.3390/ijerph182212162.
67. Xia N, Li H. Loneliness, Social Isolation, and Cardiovascular Health. Antioxid Redox Signal. 2018 Mar 20;28(9):837-851. PMID: 28903579. doi: 10.1089/ars.2017.7312.
68. Petitte T, Mallow J, Barnes E, Petrone A, Barr T, Theeke L. A Systematic Review of Loneliness and Common Chronic Physical Conditions in Adults. Open Psychol J. 2015;8(Suppl 2):113-132. PMID: 26550060. doi: 10.2174/1874350101508010113.
69. Maheshwari A, El-Atawi K, Ayad AB, Lui K, Garcia JGN, Ponnazhagan S. Developmental Deficiency of Coagulation Factor VII in Neonates: Our Current Understanding. Newborn (Clarksville, Md). 2026;5(2):xx. doi: 10.5005/jp-journals-11002-0162.
70. Bernardi F, Mariani G. Biochemical, molecular and clinical aspects of coagulation factor VII and its role in hemostasis and thrombosis. Haematologica. 2021 Feb 1;106(2):351-362. PMID: 33406812. doi: 10.3324/haematol.2020.248542.
71. D'Alessandro E, Posma JJN, Spronk HMH, Ten Cate H. Tissue factor (:Factor VIIa) in the heart and vasculature: More than an envelope. Thromb Res. 2018 Aug;168:130-137. PMID: 30064684. doi: 10.1016/j.thromres.2018.06.020.
72. Davidson CJ, Tuddenham EG, McVey JH. 450 million years of hemostasis. J Thromb Haemost. 2003 Jul;1(7):1487-94. PMID: 12871284. doi: 10.1046/j.1538-7836.2003.00334.x.
73. Beeler DL, Aird WC, Grant MA. Evolutionary conservation of the allosteric activation of factor VIIa by tissue factor in lamprey. J Thromb Haemost. 2018 Apr;16(4):734-748. PMID: 29418058. doi: 10.1111/jth.13968.
74. Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. Blood. 2004 Dec 15;104(13):3858-64. PMID: 15328151. doi: 10.1182/blood-2004-06-2223.
75. Dang CN, Katakam LI, Smith PB, Cotten CM, Goldberg RN, Chandler N, et al. Recombinant activated factor VIIa treatment for refractory hemorrhage in infants. J Perinatol. 2011 Mar;31(3):188-92. PMID: 20671714. doi: 10.1038/jp.2010.85.
76. Alten JA, Benner K, Green K, Toole B, Tofil NM, Winkler MK. Pediatric off-label use of recombinant factor VIIa. Pediatrics. 2009 Mar;123(3):1066-72. PMID: 19255041. doi: 10.1542/peds.2008-1685.

77. Kaushal M, Balla KC, Ponnazhagan S. World Quantum Day 2026. Newborn (Clarksville, Md). 2026;5(2):xx. doi: 10.5005/jp-journals-11002-0157.
78. Gupta S, Modgil S, Bhatt PC, Jabbour CJC, Sachin Kamble S. Quantum computing led innovation for achieving a more sustainable Covid-19 healthcare industry. Technovation. 2022 (120). doi: 10.1016/j.technovation.2022.102544.
79. Huang J, Wu D, Cai Y, Xu Y, Li C, Gao Q, et al. High precision determination of the Planck constant by modern photoemission spectroscopy. Rev Sci Instrum. 2020 Apr 1;91(4):045116. PMID: 32357680. doi: 10.1063/1.5129140.
80. Mamrak NE, Shimamura A, Howlett NG. Recent discoveries in the molecular pathogenesis of the inherited bone marrow failure syndrome Fanconi anemia. Blood Rev. 2017 May;31(3):93-99. PMID: 27760710. doi: 10.1016/j.blre.2016.10.002.
81. Ravishankar K, Rishika K. Fetal Hydrops, Meconium Peritonitis, and Distal Ileal Atresia in a Neonate with a Homozygous Fanconi Anemia FANCG Splice Variant: A Case Report. Newborn (Clarksville, Md). 2026;5(5):xx. doi: 10.5005/jp-journals-11002-0159.
82. Jeong E, Lee SG, Kim HS, Yang J, Shin J, Kim Y, et al. Structural basis of the fanconi anemia-associated mutations within the FANCA and FANCG complex. Nucleic Acids Res. 2020 Apr 6;48(6):3328-3342. PMID: 32002546. doi: 10.1093/nar/gkaa062.
83. Michie C. Unseen Children: Risks and Anticipatory Management. Newborn (Clarksville, Md). 2026;5(2):xx. doi: 10.5005/jp-journals-11002-0158.
84. Wolf ER, O'Neil J, Pecsok J, Etz RS, Opel DJ, Wasserman R, et al. Caregiver and Clinician Perspectives on Missed Well-Child Visits. Ann Fam Med. 2020 Jan;18(1):30-34. PMID: 31937530. doi: 10.1370/afm.2466.
85. Teasdale CA, Borrell LN, Shen Y, Kimball S, Zimba R, Kulkarni S, et al. Missed routine pediatric care and vaccinations in US children during the first year of the COVID-19 pandemic. Prev Med. 2022 May;158:107025. PMID: 35318030. doi: 10.1016/j.ypmed.2022.107025.
86. Bagga N, Kaushal M, Bandiya P, Bhartiya S, Corona MQ. Radiological Case Report: Duodenal Atresia in Down Syndrome. Newborn (Clarksville, Md). 2026;5(2):xx. doi: 10.5005/jp-journals-11002-0156.
87. Al Shahwani N, Mandhan P, Elkadhi A, Ali MJ, Latif A. Congenital duodenal obstruction associated with Down's syndrome presenting with hematemesis. J Surg Case Rep. 2013 Dec 16;2013(12). PMID: 24968438. doi: 10.1093/jscr/rjt108.
88. de Groot-van der Mooren MD, Scheerman BC, Rammeloo LAJ, van Wieringen H, van Wermeskerken AM, van der Plas R, et al. Neonatal mortality and morbidity in Down syndrome in the time of prenatal aneuploidy testing: a retrospective cohort study. Eur J Pediatr. 2023 Jan;182(1):319-328. PMID: 36350406. doi: 10.1007/s00431-022-04686-3.
89. Zani A, Yeh JB, King SK, Chiu PP, Wales PW. Duodeno-duodenostomy or duodeno-jejunostomy for duodenal atresia: is one repair better than the other? Pediatr Surg Int. 2017 Feb;33(2):245-248. PMID: 27858187. doi: 10.1007/s00383-016-4016-9.
90. Jain N. Neonates with Persistent Fever, Omphalitis, and Hepatomegaly Need should be Evaluated for a Liver Abscess. Newborn (Clarksville, Md). 2026;5(2):xx. doi: 10.5005/jp-journals-11002-0155.
91. Simeunovic E, Arnold M, Sidler D, Moore SW. Liver abscess in neonates. Pediatr Surg Int. 2009 Feb;25(2):153-6. PMID: 19089433. doi: 10.1007/s00383-008-2307-5.
92. Phoenixmed-at-arizona.edu. Ling He Phoenix, Arizona, United States: University of Arizona; 2025 [Available from: https://phoenixmed.arizona.edu/directory/he-ling.
93. sabreeenrichmentacademy.org. Sonji-Fatima St. Louis, Missouri, United States: Sabree Enrichment Academy, St. Louis, United States; 2025 [Available from: https://www.drsonjifatima.com/.
94. Collegium Medicum P, Poland. Office of the Dean, Faculty of Health Sciences, Płock, Poland Płock, Poland: Collegium Medicum, Płock, Poland; 2025 [Available from: https://mazowiecka.edu.pl/en/collegium-medicum/.

EXPERT COMMENTARY

Podcasts and Scientific Journals: We Need Both

Roya Huseynova[1,2], Saida Khasanova[2,3], Moises Quiles-Corona[2,4–7], Sonali Korde[2,8], Adrianna Frydrysiak-Brzozowska,[2,9] Colin A Michie[2,10]

Received on: 30 April 2026; *Accepted on*: 29 May 2026; *Published on*: 22 June 2026

Abstract

Podcasts and academic journals are increasingly recognized and applied as complementary pillars of modern scholarly communication, together reshaping how scientific knowledge is produced, shared, and applied. Journals remain the foundation of academic rigor, ensuring that research is peer-reviewed, methodologically sound, and credible, thereby forming the basis of evidence-based practice across disciplines. However, the traditional journal format often limits accessibility due to technical language, paywalls, and static presentation. Podcasts address these limitations by translating complex research into accessible, narrative-driven, and conversational formats that can reach clinicians, trainees, policymakers, and the general public in a more engaging and timely manner. The integration of these media creates a powerful ecosystem for knowledge translation, where journals provide depth and authority, and podcasts can add clarity, context, and reach. This collaboration takes multiple forms, including journal-sponsored podcasts that feature author interviews and editorial commentary, audio abstracts that summarize key findings, panel discussions that explore interdisciplinary perspectives, and conference coverage that extends the impact of scientific meetings beyond physical attendance. These formats not only enhance understanding of research methodology and clinical implications but also promote lifelong learning through continuing medical education (CME) opportunities embedded within podcast content. Furthermore, podcasts are valued tools in public science communication, simplifying complex findings and helping counter misinformation, particularly in fields such as public health, environmental science, and emerging technologies. In global and resource-limited settings, downloadable podcast content improves equitable access to up-to-date medical knowledge, reducing disparities in education and clinical practice. Cross-promotion across digital platforms, including social media, journal websites, and newsletters, further amplifies engagement and drives readers between audio content and full-text articles. Multimedia integration, where podcasts are embedded within journal platforms alongside visual abstracts and video summaries, supports diverse learning preferences and enhances user interaction with research. Overall, the convergence of podcasts and journals represents a significant evolution in scholarly communication, fostering a more inclusive, dynamic, and participatory model that strengthens both the dissemination and application of scientific evidence in real-world contexts.

Keywords: Accessibility, Collaboration, Engagement, Evidence-based practice, Journals, Knowledge dissemination, Knowledge translation, Peer-review, Podcasts, Scholarly communication.

Newborn (2026): 10.5005/jp-journals-11002-0161

Key Points

- Podcasts and journals can be complementary tools that together improve knowledge dissemination and evidence-based practice. Journals provide peer-reviewed, credible scientific research rigorously, while podcasts translate this knowledge into accessible and engaging formats.
- Podcast formats are highly diverse, and can include interviews, storytelling, panel discussions, and educational lectures.
- Journal–podcast collaborations enhance and extend knowledge translation with colleagues through author interviews, audio abstracts, and expert commentary.
- The integration of communication through podcasts and journals can help expand the reach of research, improve public and professional engagement, accelerate the application of evidence into practice, and contribute to the education of parents in the healthcare of their children.

Introduction

Podcasts and academic journals may seem to be very different forms of communication, but they are increasingly complementary tools for knowledge dissemination.[1,2] Journals remain the backbone of scholarly communication, offering rigorously peer-reviewed, detailed research that establishes credibility and advances evidence-based practice.[3,4] Podcasts, on the other hand, translate this complex knowledge into accessible, narrative-driven

[1]Department of Neonatology, King Saud Medical City, Riyadh, Saudi Arabia

[2]Global Newborn Society, Laurel, Greater Washington Metropolitan Area, United States of America

[3]Department of Neonatology, Eurasia Multidisciplinary University, Tashkent, Uzbekistan

[4]Department of Neonatology/Pediatrics, University of Guadalajara School of Medicine, Jalisco, Mexico

[5]Department of Neonatology, Civil Hospital of Guadalajara, Jalisco, Mexico

[6]Mexican Federation of Neonatology, Mexico City, Mexico

[7]College of Neonatologists of Jalisco, Jalisco, Mexico

[8]Education Management, Compliance, and Management, Naupada, Thane, Maharashtra, India

[9]Wydział Nauk o Zdrowiu, Collegium Medicum, Akademia Mazowiecka w Płocku (Faculty of Health Sciences, Collegium Medicum, The Masovian University, Płock), Poland

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

Corresponding Author: Colin A Michie, Population, Policy, and Practice Research and Teaching Department, Institute of Child Health, University College, London, United Kingdom, Phone: +44 7590620293, e-mail: c.michie@ucl.ac.uk

How to cite this article: Huseynova R, Khasanova S, Quiles-Corona M, *et al*. Podcasts and Scientific Journals: We Need Both. Newborn 2026;5(2):65–71.

conversations that can reach clinicians, trainees, and even the public in a more engaging and timely way.[2,5] Collaboration between the two can bridge the longstanding gap between research production and real-world application—for example, journals can support podcast series that feature author interviews, article summaries, or clinical interpretations, while podcasts can drive readers back to full-text publications for deeper engagement.[6,7] This synergy not only expands the reach of scientific work but also accelerates the translation of evidence into practice, making both mediums stronger togeter than they are in isolation.[8,9]

Podcasts Can Enhance Scientific Communication

Many might think of podcasts as a single, uniform medium—essentially "talk shows on the internet"—but in reality, they represent a diverse ecosystem of formats, goals, and production styles.[10,11] Some podcasts are highly structured, research-driven productions akin to audio documentaries, while others are conversational interviews, panel discussions, or rapid commentary designed for immediacy and personality.[12] There are also educational podcasts that function almost like informal lectures, narrative storytelling podcasts that resemble serialized journalism, and clinical or academic podcasts that directly translate peer-reviewed evidence into practice-oriented discussion.[13] This diversity means podcasts cannot be treated as a monolithic category; rather, they are a flexible communication tool that adapts to different audiences, levels of complexity, and purposes—from entertainment to professional education and scholarly engagement.[14]

In the Global Newborn Society, all of us have felt the need for better ways to engage with medical/scientific experts, parents, and society on a wider scale. Each time we lose an infant, we lose a life and its great potential. Podcasts can be a powerful, important method of wider communication to promote understanding and engage with communities (Fig. 1).

The descriptions below show how the spectrum of podcasts is expanding rapidly. We need to learn about these avenues and techniques:

Journal-sponsored Podcasts

Many journals create their own official podcasts to discuss newly published articles, highlight important discoveries, and interview authors or editors.[1] This is an emerging hybrid model that blends the rigor of academic publishing with the accessibility and reach of digital audio media.[1,15] In this model, peer-reviewed journals extend the life and impact of published articles by curating podcast episodes that feature author interviews, expert commentary, and clinical interpretation of selected studies.[1] These podcasts help

Source of support: Nil
Conflict of interest: None

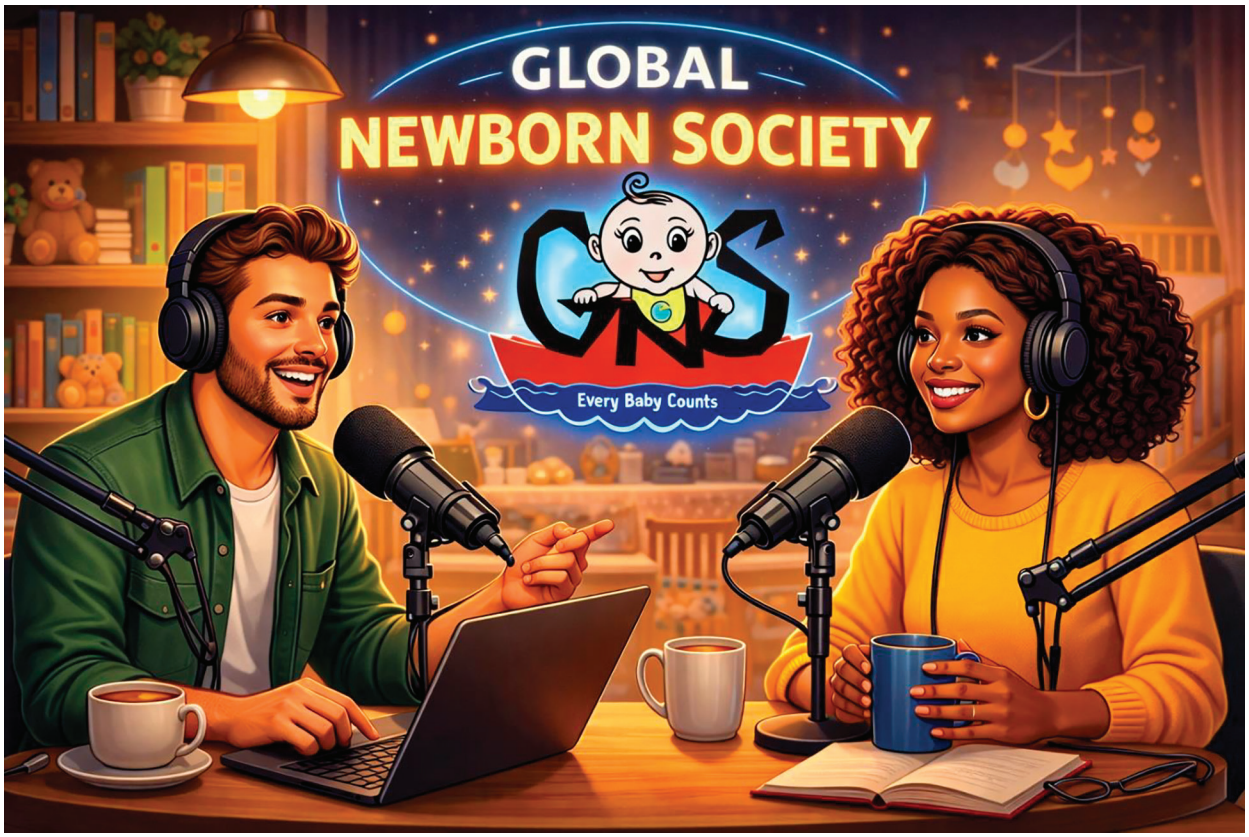


Fig. 1: In the Global Newborn Society, podcasts are increasingly being recognized as a need for mass communication

Source: The figure was created using artificial intelligence-assisted image generation (OpenAI 2026. ChatGPT version 5. https://chat.openai.com). A detailed figure legend describing the desired visual elements and conceptual framework was used as the initial prompt. Subsequent iterative modifications were performed through serial text-based refinements to adjust composition, symbolism, labeling, and visual emphasis until the final illustration met the intended design objectives.

contextualize research findings, highlighting methodological strengths, limitations, and real-world implications in a way that is often difficult to convey within the constraints of written articles alone.[2] By doing so, journal-sponsored podcasts enhance knowledge translation, broaden audience engagement beyond traditional readership, and support continuing education for clinicians and researchers.[1] Importantly, these also reinforce the credibility of podcast content by anchoring discussions in peer-reviewed literature, creating a structured bridge between formal scholarship and more dynamic, accessible scientific communication.[16] Good examples to consider include podcasts associated with journals published by organizations such as *The New England Journal of Medicine* (*NEJM*) and *The Lancet*.[17,18]

Article Summaries and Audio Abstracts

Journals can collaborate with podcast producers to create short audio/video summaries or "audio abstracts" of recently published articles.[19] Such spoken summaries distill key findings, methods, and implications into a short, accessible audio format, which allows busy professionals to stay informed while commuting or multitasking.[20,21] Audio abstracts improve accessibility for audiences who prefer auditory learning.[22] These tools can help readers quickly grasp the essence of a study and improve dissemination by making research more easily consumable across busy clinical and academic settings.[23]

Good examples of audio abstracts and related formats include the NEJM "Quick Take" audio summaries, which distill key clinical findings into a brief spoken overview, and the *Journal of the American Medical Association* (*JAMA*) podcast segments that often highlight major articles with author interviews and clinical context.[19,24,25] Similarly, *The Lancet* produces audio summaries and editor-led discussions that contextualize high-impact studies, while the *British Medical Journal* offers "visual abstracts" and podcast episodes that translate research into practical clinical insights for frontline practitioners.[26,27]

Author Interviews

Podcasts provide opportunities for researchers and authors to explain their studies in a conversational format.[28] Journal-podcast collaborations can feature interviews discussing study methodology, findings, limitations, and clinical implications.[29] This humanizes scientific communication and increases audience engagement; it also strengthens knowledge translation by helping listeners better understand how evidence can be applied in real-world clinical and research settings.[1,30]

Here are some concrete examples where journal articles were effectively extended into podcast-style discussions (or audio interviews).[2] The NEJM study on GLP-1 receptor agonists for obesity management (such as semaglutide trials) received attention; it was discussed in NEJM Quick Take and accompanying author interviews to unpack trial design, weight-loss outcomes, and clinical implications beyond the abstract.[31,32] Similarly, the JAMA Network podcast has featured discussions on landmark articles such as large cohort studies on cardiovascular risk factors and randomized trials in preventive medicine, where authors explain methodology choices and limitations in conversational form.[33] Another example is The Lancet's podcast coverage of major global health studies, including COVID-19 vaccine effectiveness and health systems research, where editors and authors contextualize findings for a broader clinical audience.[34] These each demonstrate that specific high-impact papers are translated into accessible dialogue that deepens understanding beyond the written article.

Continuing Medical and Professional Education

Medical and professional journals can partner with podcasts to develop educational episodes linked to continuing education credits or training modules.[28] These collaborations are especially useful in healthcare, where clinicians frequently use podcasts for ongoing learning and evidence-based practice updates.[5] Such initiatives can enhance participation and learning outcomes by integrating high-quality scholarly content into flexible, on-demand formats that fit into busy clinical workflows.[35]

Several established programs already use podcasts as part of accredited continuing medical education (CME).[28] For example, the American College of Cardiology (ACC) produces podcast-based updates such as *ACC Cardiology Hour* and *Cardiology Today*, some of which are linked to CME activities where listeners can complete post-tests for credit.[36] The American Medical Association (AMA) also integrates podcasts like *AMA Update* with educational content that supports lifelong learning and practice updates.[37] The American Academy of Pediatrics (AAP) offers podcasts such as the AAP *NeoReviews* to discuss major neonatal studies relevant to clinical practice.[38] The organization provides another set of podcasts, *Pediatrics On Call*, that covers pediatric and neonatal topics, current research, and clinical updates.[39]

In neurology, the American Academy of Neurology (AAN) podcast series often highlights guideline changes and clinical trials, with select episodes tied to CME opportunities.[40] Similarly, BMJ's "BMJ Best Practice" updates and podcast discussions are used by clinicians globally as structured learning tools that can be paired with formal continuing education requirements in institutional settings.[41]

Public Science Communication

Podcasts help journals communicate research findings to non-specialist audiences.[42] Through simplified explanations and storytelling approaches, podcasts can bridge the gap between academic research and public understanding.[43] This is particularly valuable in public health, environmental science, and emerging technologies.[5,44] By translating complex evidence into accessible narratives, podcasts can also help counter misinformation and improve trust in scientific communication.[44] In neonatology, there is the possibility that it could promote an understanding of complex antenatal care, empowering mothers in particular during their pregnancies and the births of their infants.

Several journals and publishers have developed podcast series specifically aimed at translating research for non-specialist audiences.[1] Nature podcasts regularly features short, narrative-driven episodes that summarize high-impact papers across science and explain their broader significance in accessible language.[7] The NEJM "Quick Take" and "Intubation" series similarly distill complex clinical studies into brief, plain-language summaries designed for clinicians outside the immediate specialty and informed lay listeners.[45] In environmental science, *Environmental Research Letters* podcasts translate climate and sustainability studies into implications that may be important for public health.[46]

Conference and Event Coverage

Podcasts are increasingly used to extend the reach of academic and professional conferences by providing real-time or post-event

coverage in an accessible audio format.[5,28] Recorded interviews, panel highlights, and expert commentary are useful for capturing key themes, debates, and emerging findings that might otherwise be limited to attendees.[28,47] This format allows journals, societies, and organizers to preserve the intellectual value of conferences beyond the event itself, enabling global audiences to engage with new research and discussions regardless of geographic or financial barriers.

There are good examples. The American Society of Clinical Oncology (ASCO) produces post-conference podcast coverage that summarizes key trial results and expert discussions from its annual meeting, helping clinicians quickly absorb major oncology updates.[48] The American Heart Association (AHA) also releases podcast episodes and audio interviews following its Scientific Sessions.[49] Similarly, the European Society of Cardiology (ESC) provides "ESC TV" and associated podcast-style audio summaries that distill major congress presentations into concise, clinically focused discussions.[50,51] In neurology, the AAN conference coverage includes podcast interviews and highlights that translate session content into accessible takeaways for practitioners who could not attend in person.[52,53]

Cross-promotion and Audience Expansion

As mentioned above, podcasts and journals can mutually promote each other's content through websites, social media, newsletters, and digital platforms. This reciprocal visibility strengthens engagement across platforms and helps build a sustained ecosystem where research dissemination and audience growth reinforce each other over time.[17,18,25–27,34,36,37,40,41,45,46,54–58]

There are well-documented examples in the *JAMA Network*, where podcast episodes such as *JAMA Clinical Reviews* and *JAMA Author Interviews* are released alongside selected journal articles and actively promoted through email alerts, Twitter/X threads, and article landing pages—often leading readers from the podcast directly to the full paper and related visual abstracts.[25] Other leading journals, including the *NEJM* and *The Lancet*, are using similar strategies.[17,18,25–27,41,45] The Nature Portfolio podcasts frequently feature author interviews tied to newly published papers, which are then cross-promoted across *Nature* journals, institutional newsletters, and digital platforms—driving measurable increases in article views and sustained engagement beyond the initial publication window.[57]

Multimedia and Digital Publishing

Modern publishing increasingly integrates text, audio, and video; as mentioned above, journals may embed podcast episodes within online articles, while podcasts may link directly to published studies. Such multimedia integration enhances user engagement and supports diverse learning styles.[2] Such integration can be seen in the *NEJM*, the *JAMA Network*, *The Lancet*, and the *BMJ* that are increasingly including podcast discussions within its online article ecosystems, enabling clinicians to benefit both from reading evidence to hearing expert interpretation within a unified digital platform.[17,18,25–27,41,45,46]

Expert Panel Discussions

Collaborative podcasts may feature panels of editors, researchers, clinicians, and policymakers discussing controversial or emerging topics.[9,59] These discussions encourage interdisciplinary communication and provide nuanced perspectives beyond traditional written articles.[55] Such panels allow for real-time exchange of ideas, where differing viewpoints can be explored in a dynamic and less constrained way.[60] They also help translate complex scientific and policy debates into more accessible discussions that highlight uncertainty, consensus, and practical implications.[7,61]

Dr Monica Lakhanpaul, a renowned Professor of Integrated Community Child Health at University College London, and I recently presented a discussion-style interview about Unseen Children in a podcast at the Excellence in Pediatrics Summit;[62] the participants in these meetings engaged in expert dialogues on topics such as child health, vaccination, and health equity. These conversations move beyond traditional lectures by emphasizing interdisciplinary perspectives, real-world implications, and policy relevance.[54] This collaborative approach can help translate complex research and public health evidence into more accessible and practice-oriented discussions for clinicians and broader audiences.[54,59]

Research Dissemination in Global Health

In global health and medical education, podcasts offer an effective way to disseminate knowledge in resource-limited settings where access to journals may be restricted.[2,63,64] Collaborative podcasting can therefore improve international access to scientific information and educational resources.[28,55] These can be downloaded and listened to offline, making them particularly useful in areas with limited or unstable internet connectivity.[55,65] This flexibility allows clinicians, students, and health workers in low-resource settings to access up-to-date medical knowledge without relying on costly journal subscriptions.[10,65] A useful example is the World Health Organization (WHO) podcast series, which provides freely accessible discussions on topics such as outbreak response, maternal and child health, and health system strengthening, designed specifically for global audiences including low- and middle-income countries.[58,66] Over time, these podcasts will likely help in reducing global disparities in access to continuing education and evidence-based practice.[58,67]

Student and Early Career Engagement

Journals may collaborate with student-led or trainee-focused podcasts to encourage academic participation among early-career researchers and healthcare professionals.[28,63,64] Such initiatives can improve mentorship, research literacy, and scholarly communication skills.[67,68] These collaborations also give trainees a platform to engage directly with established researchers, fostering a sense of inclusion within the academic community.[2] By contributing to or hosting podcast discussions, students can develop critical skills in science communication, critical appraisal, and interview-based learning.[56,69] Over time, this exposure can help build confidence and encourage sustained involvement in research and scholarly publishing.[56]

Social Media and Community Building

Podcast-journal collaborations often extend to platforms such as X, LinkedIn, and YouTube, creating online communities around scientific discussion and professional networking.[70] These interactions can increase readership, citation visibility, and audience participation.[71] These platforms allow rapid sharing of podcast episodes and related journal content, enabling discussions to unfold in real time among researchers, clinicians, and students.[2,72] Hashtags, comment threads, and video clips help extend the

reach of individual episodes and encourage ongoing engagement beyond the initial publication.[73,74] Over time, this creates a more connected scholarly community where research dissemination is interactive, visible, and continuously amplified across digital networks.[75,76]

Epilogue

Collaborations between journals and podcasts represent a meaningful evolution in scholarly communication, reflecting a broader shift toward multimodal, audience-centered dissemination of knowledge. By combining the rigor, peer review, and methodological depth of academic publishing with the accessibility and narrative flexibility of audio storytelling, these partnerships make research more visible, more interpretable, and more widely usable across diverse audiences. They help bridge the traditional gap between knowledge production and knowledge translation, ensuring that important findings do not remain confined to static text but instead reach clinicians, policymakers, students, and the public in timely and engaging ways. They extend the skills of authors as presenters and teachers, contributing to postgraduate development.[77,78]

Importantly, podcasts support inclusivity in scientific communication by lowering barriers to access and accommodating different learning preferences and resource constraints. The podcast is a valuable tool that encourages extended dialogues around research rather than one-time publication events, allowing evidence to be discussed, critiqued, and contextualized in real time across platforms. Their value is evident from early studies of their use in different areas of medicine. As academic institutions and publishers increasingly adopt integrated digital ecosystems, podcast collaborations will complement journal articles, reinforcing a novel and dynamic, transparent, and participatory culture of scientific communication.[77]

References

1. Greeves S, Ledbetter R, McGovern R, et al. Journal podcasting of health and medical science. Front Commun 2025;1(1):1. DOI: 10.3389/fcomm.2025.1589099.
2. Kakhki SK, Aghebati N, Moonaghi HK. Exploring the impact, challenges, and integration of podcasts in patient education: A systematic review. BMC Med Educ 2025;25(1):690. DOI: 10.1186/s12909-025-07217-4.
3. Aczel B, Barwich AS, Diekman AB, et al. The present and future of peer review: Ideas, interventions, and evidence. Proc Natl Acad Sci U S A 2025;122(5):e2401232121. DOI: 10.1073/pnas.2401232121.
4. Weaver ML, Sundland R, Adams AM, et al. The art of peer review: Guidelines to become a credible and constructive peer reviewer. Semin Vasc Surg 2022;35(4):470–478. DOI: 10.1053/j.semvascsurg.2022.10.002.
5. Barton MJ, Okada M, Todorovic M. Podcasts in health education—insights from a scoping review and survey. Anat Sci Educ 2025;18(12):1388–1405. DOI: 10.1002/ase.70037.
6. Akintola A, Newbury-Birch D, Kilinc S. Bridging the gap between research evidence and its implementation in public health practice: Case studies of embedded research model. BMC Public Health 2024;24(1):1299. DOI: 10.1186/s12889-024-18727-z.
7. Rehman N, Edkins V, Ogrinc N. Using podcasts to bridge the gap between science communication and specialized scientific fields: A case study of mass spectrometry. Front Commun 2024;9:1384389. DOI: 10.3389/fcomm.2024.1384389.
8. Fox MP, Carr K, D'Agostino McGowan L, et al. Will podcasting and social media replace journals and traditional science communication? No, but. Am J Epidemiol 2021;190(8):1625–1631. DOI: 10.1093/aje/kwab172.
9. Kiernan MA, Mitchell BG, Russo PL. The power of podcasts: Exploring the endless possibilities of audio education and information in medicine, healthcare epidemiology, and antimicrobial stewardship. Antimicrob Steward Healthc Epidemiol 2023;3(1):e98. DOI: 10.1017/ash.2023.178.
10. Okonski R, Toy S, Wolpaw J. Podcasting as a learning tool in medical education: Prior to and during the pandemic period. Balkan Med J 2022;39(5):334–339. DOI: 10.4274/balkanmedj.galenos.2022.2022-7-81.
11. Michie C, He L, Harold SF, et al. Podcasts and Journal Articles. Personal Communication (Electronic) at the Leadership Conference, Global Newborn Society. May 15, 2026.
12. Li W. Podcast listening, perceived social presence, perceived social support, and subjective well-being among chinese young adults: Sequential explanatory mixed methods study. Behav Sci (Basel) 2026;16(2):267. DOI: 10.3390/bs16020267.
13. Lomayesva NL, Martin AS, Dowley PA, et al. Five medical education podcasts you need to know. Yale J Biol Med 2020;93(3):461–466. PMID: 32874153.
14. Lohmann S, Zagheni E. Diversity of social media use: Self-selection explains associations between using many platforms and well-being. PLOS Digit Health 2023;2(7):e0000292. DOI: 10.1371/journal.pdig.0000292.
15. Johnson L, Grayden S. Podcasts—an emerging form of digital publishing. Int J Comput Dent 2006;9(3):205–218. PMID: 17194047.
16. Carson RA, Sobolewski B. Evidence-based guidelines for podcast production and use in competency-based health professions education. J Pediatr Health Care 2026;40(2):286–296. DOI: 10.1016/j.pedhc.2025.12.009.
17. NEJM. NEJM Group Podcasts. Waltham, MA, USA: Massachusetts Medical Society; 2026. Available from: https://store.nejm.org/signup/nejmgroup/podcasts.
18. Lancet. Lancet Multimedia – Podcasts. London, UK: Elsevier; 2026. Available from: https://www.thelancet.com/multimedia/podcasts.
19. Bonnevie T, Repel A, Gravier FE, et al. Video abstracts are associated with an increase in research reports citations, views and social attention: A cross-sectional study. Scientometrics 2023;128(5):3001–3015. DOI: 10.1007/s11192-023-04675-9.
20. Ostrovsky T, Ungermann P, Donkin C. Using machine learning to automate the collection, transcription, and analysis of verbal-report data. Behav Res Methods 2025;57(10):285. DOI: 10.3758/s13428-025-02800-5.
21. Supriyono, Wibawa AP, Suyono FK. A survey of text summarization: Techniques, evaluation and challenges. Nat Lang Process J 2024;7(1):100070. DOI: 10.1016/j.nlp.2024.100070.
22. Moore DR, Halliday LF, Amitay S. Use of auditory learning to manage listening problems in children. Philos Trans R Soc Lond B Biol Sci 2009;364(1515):409–420. DOI: 10.1098/rstb.2008.0187.
23. Augustin RC, Bonifacino E, Tilstra SA. Morning report for all: The use of podcasts to disseminate clinical reasoning tools. Med Educ 2019;53(11):1150. DOI: 10.1111/medu.13964.
24. Malecki SL, Quinn KL, Zilbert N, et al. Understanding the use and perceived impact of a medical podcast: Qualitative study. JMIR Med Educ 2019;5(2):e12901. DOI: 10.2196/12901.
25. JAMA. JAMA Network. Chicago, IL, USA: JAMA; 2026. Available from: https://jamanetwork.com/pages/multimedia.
26. Lancet. Lancet Podcasts Directory. London, UK: Lancet; 2026. Available from: https://podcasts.apple.com/gb/podcast/the-lancet-voice/id1499803146.
27. BMJ. BMJ Visual Abstracts. London, UK: BMJ; 2026. Available from: https://www.bmj.com/content/bmj-visual-abstracts.
28. Kelly JM, Perseghin A, Dow AW, et al. Learning through listening: A scoping review of podcast use in medical education. Acad Med 2022;97(7):1079–1085. DOI: 10.1097/ACM.0000000000004565.
29. López-Martín O, Zabala Baños MDC, Chaparro JD. Creating podcasts to develop communication and teamwork in nursing and

occupational therapy. Teach Learn Nurs 2025;20(4):e1113–e1118. DOI: 10.1016/j.teln.2025.05.027.
30. Eljiz K, Greenfield D, Hogden A, et al. Improving knowledge translation for increased engagement and impact in healthcare. BMJ Open Qual 2020;9(3). DOI: 10.1136/bmjoq-2020-000983.
31. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med 2023;389(24):2221–2232. DOI: 10.1056/NEJMoa2307563.
32. Reisdorf A. GLP-1 Hub: Support, Community, and Weight Loss. Cupertino, CA, USA: Apple, Inc.; 2026. Available from: https://podcasts.apple.com/us/podcast/glp-1-hub-support-community-and-weight-loss/id1798502905.
33. Nayak A, Vakili S, Nayak K, et al. Use of voice-based conversational artificial intelligence for basal insulin prescription management among patients with type 2 diabetes: A randomized clinical trial. JAMA Netw Open 2023;6(12):e2340232. DOI: 10.1001/jamanetworkopen.2023.40232.
34. Cleaver G. The Lancet Global Health in conversation with. London, UK: The Lancet Group; 2026. Available from: https://podcasts.apple.com/gb/podcast/the-lancet-global-health-in-conversation-with/id1532199876.
35. Persohn L, Branson S. Broadening legitimacy of scholarly podcasting as knowledge dissemination: Metrics, opportunities and considerations. Pub Res 2024;Q40(1):269–286. DOI: 10.1007/s12109-024-10005-5.
36. ACC. ACC Podcasts. Washington, DC, USA: American College of Cardiology; 2026. Available from: https://www.acc.org/latest-in-cardiology/features/podcasts.
37. AMA. AMA Podcasts. Chicago, IL, USA: American Medical Association; 2026. Available from: https://www.ama-assn.org/about/publications-newsletters/ama-podcasts.
38. Korioth T. Podcasts a convenient CME option. AAP News 2007;28(5):18–18. DOI: 10.1542/28.5.18a.
39. AAP. Pediatrics On Call Podcasts: Telehealth. Itasca, Illinois: American Academy of Health; 2026. Available from: https://www.aap.org/en/practice-management/care-delivery-approaches/telehealth/pediatrics-on-call-podcasts-telehealth.
40. AAN. AAN – Podcasts. Minneapolis, MN, USA: American Academy of Neurology; 2026. Available from: https://www.aan.com/education/podcasts.
41. BMJ. BMJ Best Practice – Podcasts. London, UK: British Medical Journal; 2026. Available from: https://www.bmj.com/podcasts.
42. Persohn L, Branson S. Scholarly podcasting for research dissemination: A scoping review. SAGE Open 2025;15(1):1–16. DOI: 10.1177/21582440241311694.
43. Westwood J, Davidson M-C, Worsley A, et al. 'We hear not just the words': An evaluation of storytelling using podcasts in social work education. Soc Work Edu 2025;1(1):1–18. DOI: 10.1080/02615479.2025.2581713.
44. Ringle VM, Jensen-Doss A. A critical health literacy podcast to counter health misinformation at scale: Randomized controlled trial. JMIR Public Health Surveill 2026;12:e78003. DOI: 10.2196/78003.
45. NEJM. NEJM "Quick Takes". Waltham, MA, USA: New England Journal of Medicine; 2026. Available from: https://www.youtube.com/nejmvideo.
46. IOP. Environmental Research Letters. London, UK: IOP Publishing, Institute of Physics; 2026. Available from: https://ioppublishing.org/publications/environmental-research-series/.
47. Tripp JS, Duvall SL, Cowan DL, et al. Academic podcasting: Quality media delivery. AMIA Annu Symp Proc 2006;2006:1125. PMID: 17238744.
48. ASCO. ASCO Podcasts. Alexandria, VA, USA: American Society of Clinical Oncology; 2026. Available from: https://www.asco.org/news-initiatives/podcasts.
49. AHA_Ed-Hub. Cardiovascular Highlights From AHA Scientific Sessions 2025. Dallas, TX, USA: American Heart Association; 2025. Available from: https://edhub.ama-assn.org/jn-learning/audio-player/19023165.
50. ESC. ESC TV Today. Brussels, Belgium: European Society of Cardiology; 2026. Available from: https://www.escardio.org/news/news-room/esc-tv-today/.
51. ESC. Podcasts. Brussels, Belgium: European Society of Cardiology; 2026. Available from: https://esc365.escardio.org/collections/podcasts/podcasts/.
52. AAN. Podcasts. Minneapolis, MN, USA: American Academy of Neurology; 2026. Available from: https://www.aan.com/education/podcasts.
53. AAN. Conferences On Demand. Minneapolis, MN, USA: American Academy of Neurology; 2026. Available from: https://www.aan.com/education/conferences-on-demand.
54. EIP. Excellence in Pediatrics Institute. London, UK: EIP Institute; 2026. Available from: https://www.ineip.org/.
55. Fantini E. Podcasting for interdisciplinary education: Active listening, negotiation, reflexivity, and communication skills. Humanit Soc Sci Commun 2024;11(1):1583. DOI: 10.1057/s41599-024-04119-6.
56. Kaur AW. Podcasting Neuroscience: A Science Communication Assignment. J Undergrad Neurosci Educ 2022;20(2):A120–A145. DOI: 10.59390/FKXM3006.
57. Nature.com. Portfolio: Nature Podcasts. London, UK: Nature.com; 2026. Available from: https://www.youtube.com/@nature.
58. WHO. WHO Podcasts Geneva. Switzerland: World Health Organization; 2026. Available from: https://www.who.int/podcasts.
59. Palm ME, Phares S, Hirsch G. Enhancing translational research impact through collaborative process innovation. J Clin Transl Sci 2025;9(1):e276. DOI: 10.1017/cts.2025.10186.
60. Agnello DM, Anand-Kumar V, An Q, et al. Co-creation methods for public health research-characteristics, benefits, and challenges: A Health CASCADE scoping review. BMC Med Res Methodol 2025;25(1):60. DOI: 10.1186/s12874-025-02514-4.
61. Koechlin H, Schuler S, Heuss SC. "Turning science into video" Scientific communication for and with vocational students—a pilot study. Res Involv Engagem 2025;11(1):128. DOI: 10.1186/s40900-025-00790-4.
62. Michie C. Interview: Monica Lakhanpaul. The Invisible Children. Excellence in Pediatrics Institute. London, UK: Excellence in Pediatrics Institute; 2025. Available from: https://www.ineip.org/announcements/interview-monica-lakhanpaul-unseen-children.
63. Ahmed AAE, Biswas A, Bempong-Ahun N, et al. Barriers and enablers to the production of open access medical education platforms: Scoping review. JMIR Med Educ 2025;11:e65306. DOI: 10.2196/65306.
64. Kamal Z, Khan RA, Ali S, et al. A comparative analysis of descriptive podcasts vs. interview-based podcasts in enhancing clinical reasoning skills of undergraduate medical students. Pak J Med Sci 2026;42(1):130–135. DOI: 10.12669/pjms.42.1.12332.
65. Newman J, Liew A, Bowles J, et al. Podcasts for the delivery of medical education and remote learning. J Med Internet Res 2021;23(8):e29168. DOI: 10.2196/29168.
66. Eneh SC, Tuwleh L, Onukansi FO, et al. Strengthening health systems in lower-middle-income countries (LMICs) in Africa through the WHO Hub for emergency preparedness and outbreak response. One Health Outlook 2026;8(1):12. DOI: 10.1186/s42522-026-00197-5.
67. Zou Y, Sharpe A, Demant D. The effectiveness of podcasts in promoting health among young people: A scoping review. Health Promot Int 2025;40(4). DOI: 10.1093/heapro/daaf102.
68. McCarthy J, Porada K, Treat R. Educational podcast impact on student study habits and exam performance. Fam Med 2023;55(1):34–37. DOI: 10.22454/FamMed.55.183124.
69. Kelp NC, Paredes GC, Ea L, et al. Students as science communicators: Using podcast creation and reflection via collaborative autoethnography to develop students' science communication skills. J Microbiol Biol Educ 2026;27(1):e0022225. DOI: 10.1128/jmbe.00222-25.
70. Russo I, Patrucco AS, Klumpp M, et al. Leveraging social media to bridge academia and industry in supply chain management research: A framework for integrated strategies. Int J Phys Distrib Log Manag 2025;55(11):144–162. DOI: 10.1108/IJPDLM-10-2024-0387.

71. Abou-Ismail MY, van der Wal DE, Cheong MA, et al. Can scientific journals benefit from a social media presence? An analysis of online traffic data and author perspectives. Res Pract Thromb Haemost 2024;8(3):102387. DOI: 10.1016/j.rpth.2024.102387.
72. Whittaker L, Espinosa-Cabrera E, Haar H, et al. Podcasts as a platform for sharing and disseminating experiences and expertise between young adults with cancer and radiotherapy researchers. Res Involv Engagem 2025;11(1):64. DOI: 10.1186/s40900-025-00718-y.
73. Chakrabarti P, Malvi E, Bansal S, et al. Hashtag recommendation for enhancing the popularity of social media posts. Soc Netw Anal Min 2023;13(1):21. DOI: 10.1007/s13278-023-01024-9.
74. Cinelli M, Peruzzi A, Schmidt AL, et al. Promoting engagement with quality communication in social media. PLoS One 2022;17(10):e0275534. DOI: 10.1371/journal.pone.0275534.
75. Ross-Hellauer T, Tennant JP, Banelyte V, et al. Ten simple rules for innovative dissemination of research. PLoS Comput Biol 2020;16(4):e1007704. DOI: 10.1371/journal.pcbi.1007704.
76. Gazi AI, Rahaman A, Rabbi F, et al. The role of social media in enhancing communication among individuals: Prospects and problems. Env Soc Psychol 2024;9(11):1. DOI: 10.59429/esp.v9i11.2979.
77. Saville RL, Agius SJ. A sound education: A qualitative study of the role of podcasts in postgraduate medical education. Med Sci Educ 2026;36(2):765–776. DOI: 10.1007/s40670-025-02553-y.
78. Shen L, Shi Q, Panda D, et al. Digital technology diffusion through supply chain orchestration. Technol Forecasting Soc Change 2026;225:124554. DOI: 10.1016/j.techfore.2026.124554.

REVIEW ARTICLE

World Quantum Day 2026

Monika Kaushal[1,2], Kalyan C Balla[2,3], Selvarangan Ponnazhagan[2,4]

Received on: 12 April 2026; *Accepted on:* 13 May 2026; *Published on:* 22 June 2026

Abstract

World Quantum Day is an international initiative dedicated to promoting public understanding of quantum science and technology. Celebrated annually on April 14, the date reflects the first three digits of Planck's constant (expressed as 4.14×10^{-15} electronvolt-seconds). The word quantum refers to the smallest discrete unit of a physical quantity that can be exchanged or measured. Quantum science developed during the early 20th century. Pioneers such as Max Planck, Albert Einstein, Niels Bohr, and Erwin Schrödinger developed theories explaining how energy and matter behave at atomic and subatomic scales. Medical applications of quantum mechanics include imaging such as ultrasound, magnetic resonance, and positron emission tomography; tissue imaging in microscopy, radiation therapy, and nuclear medicine; drug discovery; quantum communication and cybersecurity; education and public outreach, decision-making, and the development of new computational systems. In this review, we present an updated overview of quantum computing based on an extensive literature review using the databases PubMed, EMBASE, and Scopus.

Keywords: Cybersecurity, Eigenvalues, Entanglement, Fluorescence microscopy, Fluorine-18, Grover's algorithm, Intensity-modulated radiation therapy, Laser-based imaging systems, Optical coherence tomography, Particle-like entity, Planck's constant, Positron-emitting radioactive isotope, Positron emission tomography, Proton beam therapy, Public-key encryption systems, Quantum key distribution, Quantum cognition, Quantum mechanics, Quantum optics, Quantum probability, Quantum science, Quantum tunneling, Quantum workforce, Qubits, Radioactive isotopes, RSA, Scanning electron microscopy, Search optimization, Single-photon emission computed tomography, Speculative neuroscience, State space, Superposition, Transmission electron microscopy, Waves and particles.

Newborn (2026): 10.5005/jp-journals-11002-0157

Key Points

- World Quantum Day is an international initiative dedicated to promoting public understanding of quantum science and technology.
- Celebrated annually on April 14, the date reflects the first three digits of Planck's constant (expressed as 4.14×10^{-15} electronvolt-seconds).
- Quantum science developed during the early twentieth century. Pioneers such as Max Planck, Albert Einstein, Niels Bohr, and Erwin Schrödinger developed theories explaining how energy and matter behave at atomic and subatomic scales.
- The word quantum refers to the smallest discrete unit of a physical quantity that can be exchanged or measured.
- Medical applications of quantum mechanics include imaging, such as in ultrasound, magnetic resonance, and positron emission tomography; tissue imaging in microscopy, radiation therapy, and nuclear medicine; drug discovery; quantum communication and cybersecurity; education and public outreach; decision-making; and development of new computational systems.

Introduction

World Quantum Day is an international initiative dedicated to promoting public understanding of quantum science and technology (Fig. 1).[1] The idea was proposed by an international group of scientists, educators, historians, and science communicators to create a global initiative to promote public understanding of quantum science and technology. The event was officially launched in 2021 and quickly gained support from universities, research institutes, scientific organizations, and educational communities across many countries.[2]

Celebrated annually on April 14, the date reflects the first three digits of Planck's constant (expressed as 4.14×10^{-15} electronvolt-seconds or 6.626×10^{-34} Joule-seconds; Fig. 2), one of the foundational constants in quantum physics.[2,3] The day brings together scientists, educators, students, industry representatives, and the general public to explore how quantum mechanics has transformed our understanding of the universe and enabled revolutionary technologies. Through lectures, workshops, exhibitions, and outreach activities, World Quantum Day seeks to make quantum science accessible and inspiring globally. The day is important in medicine because it highlights the growing role of quantum science in transforming healthcare, diagnostics, imaging, and therapeutic technologies.

World Quantum Day is not governed by a single organization or formal authority. Instead, it is a decentralized, community-driven initiative coordinated by an international network of scientists, educators, students, and science communicators.[1,2] The event was

[1]Department of Neonatology, Emirates Specialty Hospital, Dubai Healthcare City, Dubai, United Arab Emirates

[2]Global Newborn Society, Laurel, Maryland, United States of America

[3]Department of Neonatology, Emirates Hospital, Jumeirah, Dubai, United Arab Emirates

[4]Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama, United States of America

Corresponding Author: Monika Kaushal, Department of Neonatology, Emirates Specialty Hospital, Dubai Healthcare City, Dubai, United Arab Emirates, Phone: +971 503761828, e-mail: monikakaushal022@gmail.com

How to cite this article: Kaushal M, Balla KC, Ponnazhagan S. World Quantum Day 2026. Newborn 2026;5(2):72–80.

Source of support: Nil

Conflict of interest: None

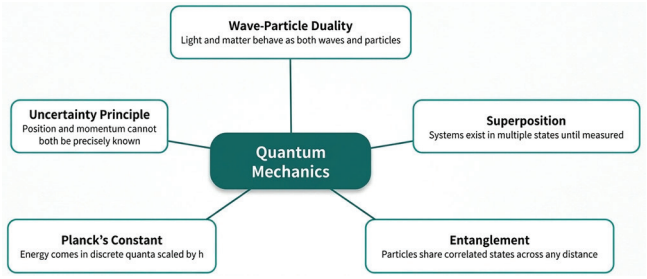


Fig. 1: There are five core principles of quantum mechanics

Fig. 2: Planck's constant. In 1900, Max Planck solved the black-body radiation problem by proposing that energy is emitted in discrete packets called quanta, not as a continuous stream. His constant, $h = 4.14 \times 10^{-15}$ electronvolt-seconds (or 6.626×10^{-34} joule-seconds) sets the scale of quantum effects. The photon energy is described by the equation at any given frequency: $E = hf$. Planck's constant threads through all quantum equations. It links photon energy to frequency, governs de Broglie's matter waves, and sets the limit in Heisenberg's uncertainty principle. Its tiny value explains why quantum effects are invisible in daily life. The black body radiation problem referred to the inability to explain the observed spectra of black-body radiation, which diverged significantly at higher frequencies from that predicted by existing theories. This illustration was generated by placing serial questions in artificial intelligence programs until a desired figure was obtained

created to promote public engagement with quantum science, and since its launch, it has remained intentionally open and collaborative rather than institutionalized. Activities and outreach efforts are organized independently by universities, research institutes, scientific societies, museums, and volunteers; this structure reflects the global and collaborative nature of quantum science itself, allowing participation from anyone interested in promoting awareness and understanding of quantum physics.

Although World Quantum Day is not directly a neonatal medicine, it may have meaningful relevance to neonatology.[4] Neonatology depends heavily on advanced diagnostic and monitoring technologies, many of which are rooted, directly or indirectly, in quantum physics.[5] As described below, education, neonatal imaging techniques, drug-discovery, optimization of treatment strategies, improved analysis of large neonatal intensive care datasets, and better decision-making could eventually support more personalized and precise neonatal medicine. In the following sections, we present a review of quantum computing based on extensive literature analysis using PubMed, EMBASE, and Scopus.

History

Quantum science developed during the early 20th century, when physicists began questioning the limitations of classical mechanics.[6] Pioneers such as Max Planck, Albert Einstein, Niels Bohr, and Erwin Schrödinger developed theories explaining how energy and matter behave at atomic and subatomic scales.[7] They showed that particles can behave both as waves and particles, that energy exists in discrete packets called quanta, and that uncertainty is an intrinsic property of nature.[8]

The Concept of Quanta

The word quantum (plural: quanta) refers to the smallest discrete unit of a physical quantity that can be exchanged or measured.[8] The idea of "structure of quanta" does not mean quanta have internal parts like classical objects; rather, it refers to how these discrete units are described within physical theory.[8]

The quantum theory proposes that certain physical properties are not continuous, but come in fixed packets.[9] When an atom changes state, it does so by absorbing or emitting a quantum of energy, such as a photon.[10] This discreteness is the "structure" of quanta, where nature is organized into allowed states rather than continuous ranges. A key example is the photon, the quantum of light. A photon has no internal substructure in the classical sense; instead, it is defined by a set of properties—energy, frequency, momentum, polarization, and spin, which arise from the underlying quantum field. In modern physics, quanta are understood as excitations of fields, meaning each particle-like entity corresponds to a localized excitation of a fundamental field that permeates space.

In atoms, electrons occupy quantized energy levels due to the wave nature of matter and boundary conditions imposed by the atomic potential.[11] These energy levels form a structured ladder, and transitions between them involve absorption or emission of discrete quanta. This explains phenomena such as spectral lines in hydrogen and other elements.

More broadly, quantum theory organizes physical reality into:[12]

- States (represent mathematical descriptions of systems).
- Operators (represent measurable quantities).
- Eigenvalues (represent discrete outcomes that correspond to quanta; Fig. 3).

Thus, the "structure of quanta" is not a physical architecture but a mathematical/physical framework of discreteness, where measurable properties emerge in quantized steps rather than continuous values. In summary, quanta are not composed of smaller parts; instead, they represent the fundamental discrete units of physical interaction arising from the deeper structure of quantum fields (Fig. 4).

In attempts to understand the quantum theory, four key principles have emerged—wave-particle duality, superposition, entanglement, and the uncertainty principle (Fig. 5).[13] These concepts have fundamentally changed physics and laid the groundwork for modern quantum technologies. Unlike classical computers that process information using bits represented as zeros or ones, quantum computers use quantum bits, or qubits, which can exist in multiple states simultaneously through a phenomenon called superposition. Quantum computers also exploit entanglement, a unique quantum property where particles become interconnected regardless of distance.

Several physical systems can function as qubits. These include superconducting circuits, trapped ions, photons, and quantum dots.[14] The mathematical representation of a qubit is often shown as:

$$|\psi\rangle = \alpha|0\rangle + \beta|1\rangle$$

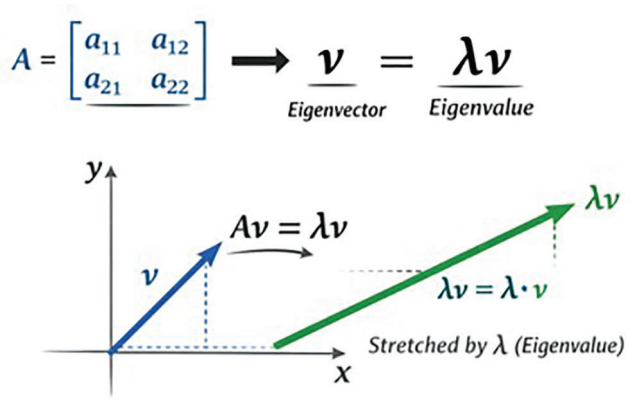
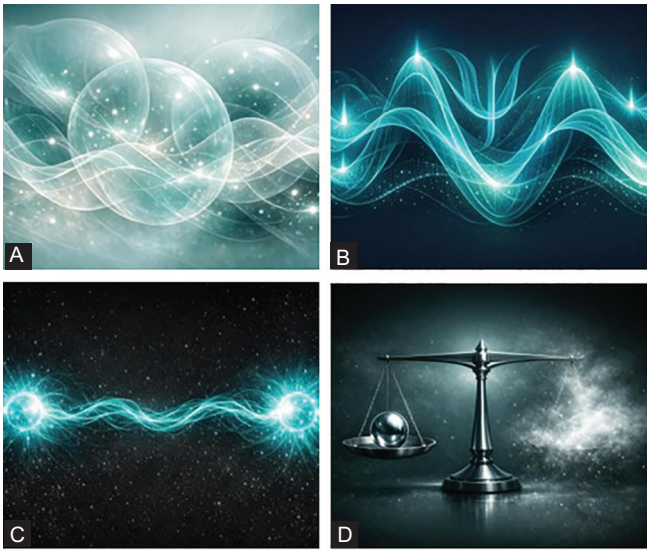


Fig. 3: In the Eigenvalue diagram, the capital *A* is the matrix (usually a square matrix such as 2 × 2 or 3 × 3), a linear transformation that acts on vectors. The equation $Av = \lambda v$, shows that the matrix *A* transforms the vector *v*. The lowercase "*a*" entries are the elements of the matrix *A*. For instance, $A = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}$, each a_{ij} is just a number inside the matrix. Here, a_{11} indicates row 1, column 1; a_{12} indicates row 1, column 2, and so on

Fig. 4: As we currently understand, quanta are not composed of smaller parts. These represent the fundamental discrete units of physical interaction arising from the deeper structure of quantum fields and the mathematical wave-particle rules of quantum theory. This illustration was generated by placing serial questions in artificial intelligence programs until a desired figure was obtained

The symbols α and β represent probability amplitudes that determine the likelihood of measuring the qubit as 0 or 1. However, this equation also illustrates how a qubit can exist in a superposed quantum state rather than a single definite value. Qubits are the foundation of quantum computing, a major shift from traditional computing methods. By harnessing the unique properties of



Figs 5A to D: Key concepts in quantum mechanics. These measurements are not a limitation of our instruments but are a fundamental feature of reality. The universe is genuinely indeterminate at the quantum scale. These illustrations were generated by placing serial questions in artificial intelligence programs until a desired figure was obtained. (A) Wave-particle duality: A fundamental concept in quantum mechanics. Every particle or quantum entity (such as electrons or photons) exhibits both wave- and particle-like characteristics depending on the methods of measurement. Light acts as a wave in diffraction experiments, yet as a particle (photon) in photoelectric effects. Similarly, electrons show wave-like interference. A quantum object exists in a superposition of states, both a wave and a particle, until a measurement forces it to "choose." The Copenhagen interpretation says the wave function describes probabilities, not physical waves. Measurement causes collapse into a definite state; (B) Superposition: Quantum mechanics says the atom exists in a superposition of decayed and not-decayed states. Wave function covers the mathematical framework with the $\psi = \alpha|0\rangle + \beta|1\rangle$ equation and probability interpretation. In 1935, Erwin Schrödinger proposed a thought experiment: A cat sealed in a box with a radioactive atom, a Geiger counter, and a vial of poison. If the atom decays, the poison is released. By entanglement, the cat is simultaneously alive and dead, until someone opens the box; (C) Entanglement: When two particles interact and become entangled, their quantum states become linked. These effects are not related to the distance separating the particles; measuring one particle instantly determines the state of the other. This correlation is stronger than anything classical physics allows. If one entangled electron is measured as spin-up, its partner is guaranteed to be spin-down even when separated by galactic distances. Today, entanglement powers quantum cryptography, teleportation, and underpins quantum computing; (D) Uncertainty principle: The same tradeoff applies to energy and time: $\Delta E \cdot \Delta t \geq h/2$ (position uncertainty × momentum uncertainty ≥ reduced Planck's constant/2). This allows "virtual particles" to briefly pop in and out of existence—borrowed energy over tiny timescales. Uncertainty powers quantum tunneling—particles passing through barriers they classically cannot cross. This effect drives nuclear fusion in stars and makes modern transistors possible. Far from a limitation, uncertainty prevents atoms from collapsing and keeps the universe stable. In 1927, Werner Heisenberg had shown that certain properties, such as position and momentum, cannot both be measured with perfect precision at the same time

quantum mechanics, qubits enable new forms of computation that could solve scientific and technological challenges beyond

the capabilities of today's most powerful classical computers. Major technology companies and research institutions are currently competing to build stable and scalable quantum computers using these approaches. However, qubits are highly sensitive to environmental disturbances such as heat and electromagnetic noise, making quantum systems difficult to maintain and operate reliably.[15]

Medical Applications of Quantum Mechanics

Quantum mechanics can explain the behavior of atoms, electrons, photons, and molecules.[13] Many technologies used in daily life depend on quantum principles; devices such as lasers, semiconductors, magnetic resonance imaging (MRI), and transistors all emerged from advances in quantum physics.

Imaging

- Magnetic resonance imaging has evolved using quantum mechanical properties of atomic nuclei and magnetic fields to generate detailed images of internal organs and tissues.[16] It works because many atomic nuclei, especially hydrogen nuclei (protons) in water molecules, possess an intrinsic quantum property called spin.[16,17] In quantum mechanics, spin behaves like a tiny magnetic moment, meaning that each proton acts like a miniature magnet.[18] In an MRI scanner, these proton spins align either parallel or antiparallel to the external magnetic field.[16] Quantum mechanics predicts that only specific discrete energy states are allowed; a slightly larger number of protons occupies the lower-energy aligned state, creating a net magnetization in the body.[19] This difference between energy states is fundamental to the MRI signal. Magnetic resonance imaging machines apply radiofrequency pulses at a precise resonance frequency known as the Larmor frequency.[20,21] These pulses provide energy that causes some protons to transition between quantum energy states and change their orientation.[16,20] After the pulse is turned off, the protons gradually relax back to their original alignment. During this relaxation process, they emit radiofrequency signals that are detected by receiver coils.[16,20]

  Different tissues relax at different rates because their molecular environments influence proton behavior.[16,20,22] These differences in relaxation times, called T1 and T2 relaxation, allow MRI to distinguish between structures such as brain tissue, muscle, fat, tumors, and fluid.[16,20,23] Quantum interactions between spins and their surroundings therefore, contribute directly to image contrast and diagnostic detail.

  Quantum mechanics also explains more advanced MRI techniques. In functional MRI, subtle changes in blood oxygenation alter local magnetic properties and help map brain activity.[24] Diffusion MRI measures the movement of water molecules through tissues, revealing neural pathways and microscopic structural abnormalities.[25] Magnetic resonance spectroscopy can even analyze biochemical compounds within tissues based on their unique quantum resonance patterns.[26] Magnetic resonance imaging is not simply a medical imaging tool but also a practical clinical application of quantum physics. The principles of spin, quantized energy levels, resonance, and magnetic interactions allow physicians to obtain detailed images of internal organs and tissues without using ionizing radiation.
- Positron emission tomography (PET) scanning also relies on quantum processes involving radioactive decay, antimatter interactions, and photon detection to visualize metabolic and physiological activity inside the body.[27] In PET imaging, a patient receives a biologically active molecule labeled with a positron-emitting radioactive isotope, such as fluorine-18.[28] As the isotope undergoes radioactive decay, it emits a positron, which is the antimatter counterpart of the electron.[28,29] Quantum mechanics governs this decay process and determines the probability and energy of particle emission.

  After traveling a short distance within tissue, the positron encounters an electron.[28,29] The two particles annihilate each other, converting their mass into energy according to Einstein's relation. This annihilation produces two gamma-ray photons that travel in nearly opposite directions.[29,30] Conservation laws derived from quantum physics ensure the characteristic energies and trajectories of these photons.

  Positron emission tomography scanners contain rings of detectors that simultaneously detect these paired photons.[28,29,31] By analyzing the timing and direction of photon detection, computers reconstruct three-dimensional images showing where the radioactive tracer accumulated in the body.[27,29] Because many diseases alter cellular metabolism, PET imaging can identify abnormal biological activity even before structural changes become visible on conventional imaging. Rapidly multiplying cells often consume glucose at higher rates than normal tissues, allowing PET tracers such as fluorodeoxyglucose to highlight these regions.[29,32]

  Modern hybrid systems such as PET/computed tomography (CT) and PET/MRI combine quantum-based functional imaging with detailed anatomical imaging, improving diagnostic accuracy.[33] Thus, PET represents another major medical application of quantum principles, demonstrating how subatomic particle interactions can be harnessed to study complex biological processes in living patients.
- Ultrasound imaging has benefited from understanding the role of quantum mechanics in determining the physical properties of biological tissues at the atomic and molecular level.[34,35] While ultrasound itself is based on classical sound wave propagation, the way those waves travel through the body depends on how molecules interact, bond, and respond to mechanical forces, which are ultimately governed by quantum physics.[36,37]

  Even though ultrasound does not directly involve quantum effects such as superposition or nuclear spin, every vibration of a sound wave involves the collective motion of atoms whose interactions are quantum mechanical in origin.[38] This means that the clarity and contrast of ultrasound images are ultimately rooted in quantum-level behavior, even if the imaging technique itself operates at a macroscopic scale.[39,40] High-frequency sound waves are transmitted into the body and reflect back from tissue interfaces with different densities and elastic properties. These differences arise from molecular structures, such as proteins, lipids, and water content, which differ in stiffness/compressibility.[40] Quantum mechanics explains the nature of chemical bonding and intermolecular forces that give tissues their unique acoustic characteristics.[36,40] In medical practice, this connection enables safe and effective imaging for applications such as fetal monitoring, cardiac assessment, and real-time guidance of procedures. Thus, quantum mechanics provides an explanation for the material properties that make ultrasound imaging possible, even though this imaging is governed by classical wave physics.[40,41]

Microscopy

Microscopy has benefited from the use of quantum methods.[42] Quantum mechanics supports many forms of advanced microscopy that allow scientists to study structures at cellular, molecular, and even atomic scales:[42,43]

- Electron microscopy: In techniques such as transmission electron microscopy and scanning electron microscopy, beams of electrons are used instead of visible light.[44,45] According to quantum mechanics, electrons behave both as particles and as waves, a property known as wave-particle duality.[44,46] Because electron wavelengths are much shorter than visible light wavelengths, electron microscopes can resolve extremely small structures, including viruses, organelles, proteins, and individual atoms.[46]

  Quantum tunneling is another principle used in scanning tunneling microscopy.[47,48] In this method, electrons can "tunnel" through an energy barrier between a sharp conductive probe and a sample surface even when classical physics would predict that crossing is impossible. Tiny changes in tunneling current allow scientists to map atomic-scale surfaces with extraordinary precision.[48] This technique has enabled direct visualization and manipulation of individual atoms.

  Fluorescence microscopy also depends heavily on quantum phenomena.[49] Molecules absorb photons and transition to higher quantum energy states, and emit light at characteristic wavelengths when they return to the baseline.[50] Advanced methods such as confocal microscopy, super-resolution microscopy, and fluorescence resonance energy transfer exploit these quantum transitions to visualize cellular processes in living tissues with remarkable sensitivity and specificity. Laser-based imaging systems can also help physicians to diagnose diseases earlier and assess the severity.[51]
- Quantum optics has further improved imaging performance through techniques involving entangled photons and squeezed light.[52] Photon-based imaging such as in optical coherence tomography and super-resolution microscopy are advancing rapidly.[53] Emerging quantum microscopy methods can minimize noise and enhance resolution; these may eventually permit ultra-sensitive detection of molecular interactions, neural activity, and nanoscale biological changes that are difficult to observe with conventional instruments.[54]
- In confocal laser scanning microscopy, focused laser beams illuminate specific layers within a specimen while rejecting out-of-focus light, allowing high-resolution three-dimensional imaging of cells and tissues.[55] Quantum interactions between photons and fluorescent molecules enable precise visualization of biological structures and molecular activity.[56] Multiphoton excitation microscopy further demonstrates the role of quantum principles.[57] In this technique, two or more lower-energy photons are absorbed simultaneously to excite a fluorescent molecule. Because simultaneous absorption is a quantum probability phenomenon, it occurs only at the focal point of intense laser light, reducing tissue damage and allowing deeper imaging in living organisms. Raman spectroscopy also uses quantum vibrational energy transitions in molecules to identify tissue composition, while laser fluorescence imaging can detect abnormal cellular activity.[58]

Radiation Therapy and Nuclear Medicine

Quantum mechanics has advanced radiation therapy and nuclear medicine as these fields depend on the behavior of subatomic particles, radioactive decay, and energy interactions within biological tissues.[59] Quantum physics explains how unstable atomic nuclei emit radiation and how this radiation interacts with cells, allowing physicians to diagnose and treat disease with remarkable precision.[60]

In radiation therapy, high-energy photons, electrons, protons, or other particles are directed toward tumors to damage the DNA of cancer cells and prevent their growth.[61] The interaction of radiation with matter occurs through quantum processes such as photoelectric absorption, Compton scattering, and pair production.[62] These interactions determine how energy is deposited within tissues and allow clinicians to calculate radiation doses accurately while minimizing injury to surrounding healthy organs.

Modern techniques such as intensity-modulated radiation therapy and proton beam therapy rely on detailed quantum-based models of particle behavior.[63] Proton therapy is especially important because protons deposit most of their energy at a specific depth known as the Bragg peak, enabling highly targeted treatment of tumors near sensitive structures such as the brain, spinal cord, or eyes.[64] Quantum physics helps predict and optimize these energy distributions.

In nuclear medicine, radioactive isotopes are introduced into the body to study organ function or treat disease.[65] These isotopes undergo radioactive decay according to quantum mechanical principles, emitting gamma rays, positrons, or other particles that can be detected externally. Quantum principles are also important in targeted radio nuclide therapy, where radioactive compounds deliver localized radiation.[66] Examples include radioiodine treatment for thyroid disease and newer radiopharmaceutical therapies used in neuroendocrine tumors. These approaches combine molecular biology with quantum nuclear processes to improve treatment precision.

Drug Discovery

Quantum computing has the potential to transform drug discovery by solving molecular and chemical problems that are extremely difficult for conventional computers.[67] Drug development depends on understanding how molecules interact with proteins, DNA, and other biological targets at the atomic level.[68] Because these interactions follow the laws of quantum mechanics, accurately simulating them often requires enormous computational resources.[69] Quantum computers can be useful as they are designed to process information using quantum bits, or qubits, which can represent multiple states simultaneously and may eventually perform certain calculations much faster than classical systems.

One major application of quantum computing is molecular simulation.[70] Quantum algorithms can help model the structure, energy states, and behavior of complex molecules with greater precision.[67,70] This could improve understanding of how potential drugs bind to disease targets. More accurate simulations may reduce dependence on trial-and-error laboratory testing and lower the cost of pharmaceutical research. Quantum computing may enable better virtual screening, for faster and more accurate evaluation of candidate molecules that are most likely to become effective drugs.[71]

Quantum Communication and Cybersecurity

Quantum communication can have important implications for healthcare systems. Hospitals and medical institutions increasingly rely on digital records, telemedicine, and cloud-based health data storage.[72] Quantum communication offers the possibility of highly secure communication systems that protect confidential patient information from cyber threats.[72,73] The need for secure quantum communication is increasing as healthcare becomes more digitally interconnected, to safeguard medical data and maintain patient privacy.[74] As mentioned above, a rapidly emerging idea is the use of photons, or particles of light, to transmit data in quantum bits (qubits).[8] Because quantum states are extremely sensitive to observation, any attempt to intercept or measure the transmitted information changes the state of the photons.[75] This property allows communicating parties to immediately detect eavesdropping attempts, making quantum communication potentially far more secure than classical systems. Networks with experimental quantum satellites and fiber-optic quantum communication systems can potentially secure long-distance transmission of information and are being tested. We are all aware that hospitals, research institutions, and telemedicine systems handle enormous amounts of sensitive patient data.[76] Quantum-secure communication can help by increasing the security levels in digital technologies.

The quantum key distribution (QKD) is one way for two parties to generate and share encryption keys securely.[77] If a third party tries to intercept the key during transmission, the disturbance caused by measurement alerts the users that the communication has been compromised. The BB84 protocol, developed in the 1980s, demonstrated how quantum mechanics could be applied directly to secure communication systems.[78] However, quantum cybersecurity is becoming increasingly important because future quantum computers may be capable of breaking many current encryption methods, such as the RSA and other public-key cryptographic systems.[79] The RSA cryptosystem, as we know, is one of the more widely used public-key encryption systems in cybersecurity (as known, it was developed in 1977 by Ron Rivest, Adi Shamir, and Leonard Adleman—the name "RSA" comes from the initials of their surnames).[80] These classical encryption systems depend on the difficulty of solving certain mathematical problems, such as factoring large numbers. Powerful quantum algorithms could potentially solve these problems much faster than conventional computers, creating risks for banking systems, government networks, healthcare databases, and global communications infrastructure. To address some of these concerns, post-QC encryption methods may help resist attacks from both classical and quantum computers.[79] Governments and technology companies are investing heavily in quantum-safe communication networks.[81] These efforts aim to ensure the security of sensitive personal information.[82]

Education and Public Outreach

World Quantum Day places strong emphasis on education and public outreach because quantum science can seem abstract and difficult for the general public to understand.[1] The goal is to provide accessible learning opportunities to students, educators, policymakers, and communities about how quantum physics shapes modern technology and scientific discovery. Public lectures, school activities, demonstrations, exhibitions, and online campaigns are organized worldwide to make complex quantum concepts easier to understand and more engaging. By introducing students to quantum concepts early, educators hope to inspire future generations of physicists, engineers, mathematicians, and innovators who will contribute to the rapidly evolving quantum workforce. In medicine, quantum mechanics can promote interdisciplinary education and research.

Decision Making

Quantum mechanics has inspired several modern frameworks for understanding decision-making.[83] The idea is not that the mind literally operates using quantum physics, but that some aspects of human decision making, such as uncertainty, ambiguity, and context dependence, could be modeled effectively using mathematical structures borrowed from quantum theory.[84]

In classical decision theory, choices are usually assumed to follow fixed probabilities: People evaluate options, assign likelihoods, and then select the highest expected utility.[85] However, real human behavior often violates these assumptions. For example, people's preferences can change depending on the order in which information is presented, or they may make inconsistent choices under uncertainty. These patterns are difficult to explain using classical probability alone.

Quantum probability models offer an alternative framework. Instead of treating uncertainty as purely random, they represent mental states as vectors in a mathematical "state space," similar to how quantum states are represented in physics.[86,87] In this view, decision outcomes can interfere with one another, similar to wave interference, leading to context-dependent choices.[88] This can help explain paradoxes such as preference reversals, framing effects, and violations of classical rationality in psychology.[89]

In cognitive science and behavioral economics, quantum-like models have been used to describe how humans evaluate risk and ambiguity.[90] These models can capture situations where a person's decision depends not only on the available information but also on how that information is presented or mentally structured. This is sometimes referred to as "quantum cognition," though it is a mathematical analogy rather than a claim about physical brain processes.[84] Algorithms based on quantum probability can improve how systems handle uncertain or incomplete data, potentially enhancing recommendation systems, search ranking, and predictive modeling.[91]

Development of New Computational Systems

Quantum Mechanics can help develop new computational systems as it defines how information can be encoded, processed, and transmitted at the smallest physical scales.[8] Unlike classical physics, where bits are either 0 or 1, quantum mechanics allows for new approaches to processing information.[92] Newer systems could factor larger numbers, simulate molecules, or solve more complex optimization tasks.[93]

Quantum algorithms such as Shor's algorithm (for factoring) and Grover's algorithm (for search optimization) show theoretical speed advantages over classical methods.[94] Although large-scale, fault-tolerant quantum computers are still under development, early prototypes are already being used to test quantum circuits and hybrid classical–quantum systems.[95] Quantum-inspired algorithms, which mimic quantum behavior without requiring actual quantum hardware, are being used to improve optimization, machine learning, and data analysis.[96] These approaches may be useful in logistics, finance, drug discovery, and materials science, where complex problem spaces will be needed for efficient navigation and secure communication systems.[97] Quantum key distribution

uses quantum states of photons to detect eavesdropping, since any measurement of a quantum system inevitably disturbs it.[98] This is anticipated to help develop new levels of security for data transmission in future quantum networks or "quantum internet."

Development of New Ideas: "Thinking"

Quantum mechanics is sometimes discussed in relation to thinking and cognition.[99] It has inspired several theoretical and interdisciplinary frameworks that try to extend or reinterpret models of cognition:

- Quantum cognition (mathematical modeling): In fields like psychology and behavioral economics, researchers often use "quantum-like" probability models for decision making.[100,101] These models borrow mathematical tools from quantum theory, such as superposition-like states and interference patterns, to explain why people sometimes violate classical logic in framing effects or order-dependent choices.[86]
- Speculative neuroscience: Some theories have proposed that quantum effects might play a role in cognitive processes.[102] Quantum states could contribute to aspects of awareness or thought.[103] However, these programs are still in development; quantum physics still underpins thinking about molecular interactions in neurotransmitters and receptors, protein folding/cellular chemistry, and medical imaging tools.[104]

Summary

World Quantum Day represents more than a scientific celebration; it is important in medicine as it emphasizes how fundamental scientific discoveries can directly improve human health and quality of life.[60] Quantum science challenges conventional intuition and reveals a universe far more complex and interconnected than previously imagined.[105] National quantum initiatives worldwide can strengthen scientific leadership and economic competitiveness by promoting awareness, collaboration, and education. As quantum technologies continue to advance, the observance serves as a reminder that discoveries made in fundamental physics can profoundly influence medicine, communication, computing, and even the future of civilization.[106,107] Governments, private companies, and academic institutions are collaborating to accelerate breakthroughs in quantum computing, sensing, materials science, and artificial intelligence. The applications of quantum science in diagnostics, treatment, data security, and biomedical research is likely to reshape modern healthcare profoundly and open new possibilities for preventing and curing disease. The celebration raises awareness about the medical potential of quantum technologies while inspiring continued investment in research and innovation.[108]

References

1. World Quantum Day Coordination Team. World Quantum Day April 14 Decentralized Organization: WQD Coordination Team; 2026. Available from: https://worldquantumday.org/.
2. World Quantum Day Coordination Team. Why April 14 Decentralized Organization: WQD Coordination Team; 2026. Available from: https://worldquantumday.org/why-april-14.
3. NIST. Kilogram: Mass and Planck's Constant Gaithersburg. Maryland, USA: National Institute of Standards and Technology, US Department of Commerce; 2026. Available from: https://www.nist.gov/si-redefinition/kilogram-mass-and-plancks-constant.
4. Gorsky KG, Butala S, House M, et al. Uncertainty and the NICU experience: A qualitative evaluation of family and provider perspectives. Children (Basel) 2023;10(11):1745. DOI: 10.3390/children10111745.
5. Henriquet P. Quantum, the indispensable ally of modern medicine Paris, France: Polytechnique-insights, Institut Polytechniq de Paris; 2023. Available from: https://www.polytechnique-insights.com/en/columns/science/quantum-the-indispensable-ally-of-modern-medicine/.
6. Hegan M. Quantum Physics Ipswich. Massachusetts, USA: EBSCO; 2023. Available from: https://www.ebsco.com/research-starters/physics/quantum-physics.
7. Ball P. The Tumultuous Birth of Quantum Mechanics. College Park, MD, USA: American Physical Society; 2025. Available from: https://physics.aps.org/articles/v18/24.
8. Science Oo. DOE Explains...Quantum Mechanics. Washington, DC, USA: US Department of Energy; 2026.
9. Blog KW-SB. Max Planck's Quantum Theory: How Energy Quanta Changed Physics Forever. Barcelona, Spain: Kronecker Wallis; 2026. Available from: https://www.kroneckerwallis.com/max-plancks-quantum-theory-how-energy-quanta-changed-physics-forever/.
10. Zhang Y. Examples of atoms absorbing photon via Schrodinger equation and vacuum fluctuations. Sci Rep 2024;14(1):983. DOI: 10.1038/s41598-024-51411-1.
11. Chen F, Tao NJ. Electron transport in single molecules: From benzene to graphene. Acc Chem Res 2009;42(3):429–438. DOI: 10.1021/ar800199a.
12. Kupczynski M. Mathematical modeling of physical reality: From numbers to fractals, quantum mechanics and the standard model. Entropy (Basel) 2024;26(11):991. DOI: 10.3390/e26110991.
13. Fortier T. 5 Concepts Can Help You Understand Quantum Mechanics and Technology—Without Math! Gaithersburg, MD, USA: National Institute of Standards and Technology, US Department of Commerce; 2025. Available from: https://www.nist.gov/blogs/taking-measure/5-concepts-can-help-you-understand-quantum-mechanics-and-technology-without.
14. Chae E, Choi J, Kim J. An elementary review on basic principles and developments of qubits for quantum computing. Nano Converg 2024;11(1):11. DOI: 10.1186/s40580-024-00418-5.
15. Yang H, Kim NY. Material-inherent noise sources in quantum information architecture. Materials (Basel) 2023;16(7):2561. DOI: 10.3390/ma16072561.
16. Grover VP, Tognarelli JM, Crossey MM, et al. Magnetic resonance imaging: Principles and techniques: Lessons for clinicians. J Clin Exp Hepatol 2015;5(3):246–255. DOI: 10.1016/j.jceh.2015.08.001.
17. Mouhat F, Peria M, Morresi T, et al. Thermal dependence of the hydrated proton and optimal proton transfer in the protonated water hexamer. Nat Commun 2023;14(1):6930. DOI: 10.1038/s41467-023-42366-4.
18. Pipe JG. Basic spin physics. Magn Reson Imaging Clin N Am 1999;7(4):607–627. PMID: 10631671.
19. Berger A. Magnetic resonance imaging. BMJ 2002;324(7328):35. DOI: 10.1136/bmj.324.7328.35.
20. Pai A, Shetty R, Hodis B, et al. Magnetic resonance imaging physics. 2023. In: StatPearls. Treasure Island, FL, USA: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564320/.
21. Soher BJ, Dale BM, Merkle EM. A review of MR physics: 3T versus 1.5T. Magn Reson Imaging Clin N Am 2007;15(3):277–290. DOI: 10.1016/j.mric.2007.06.002.
22. Gaeta M, Galletta K, Cavallaro M, et al. T1 relaxation: Chemo-physical fundamentals of magnetic resonance imaging and clinical applications. Insights Imaging 2024;15(1):200. DOI: 10.1186/s13244-024-01744-2.
23. Bojorquez JZ, Bricq S, Acquitter C, et al. What are normal relaxation times of tissues at 3 T? Magn Reson Imaging 2017;35:69–80. DOI: 10.1016/j.mri.2016.08.021.

24. Buxton RB. The physics of functional magnetic resonance imaging (fMRI). Rep Prog Phys 2013;76(9):096601. DOI: 10.1088/0034-4885/76/9/096601.
25. Le Bihan D, Iima M. Diffusion Magnetic resonance imaging: What water tells us about biological tissues. PLoS Biol 2015;13(7):e1002203. DOI: 10.1371/journal.pbio.1002203.
26. Tognarelli JM, Dawood M, Shariff MIF, et al. Magnetic resonance spectroscopy: Principles and techniques: Lessons for clinicians. J Clin Exp Hepatol 2015;5(4):320–328. DOI: 10.1016/j.jceh.2015.10.006.
27. Vaquero JJ, Kinahan P. Positron emission tomography: Current challenges and opportunities for technological advances in clinical and preclinical imaging systems. Annu Rev Biomed Eng 2015;17:385–414. DOI: 10.1146/annurev-bioeng-071114-040723.
28. Alauddin MM. Positron emission tomography (PET) imaging with (18) F-based radiotracers. Am J Nucl Med Mol Imaging 2012;2(1):55–76. PMID: 23133802.
29. Shukla AK, Kumar U. Positron emission tomography: An overview. J Med Phys 2006;31(1):13–21. DOI: 10.4103/0971-6203.25665.
30. Watts DP, Bordes J, Brown JR, et al. Photon quantum entanglement in the MeV regime and its application in PET imaging. Nat Commun 2021;12(1):2646. DOI: 10.1038/s41467-021-22907-5.
31. Jiang W, Chalich Y, Deen MJ. Sensors for positron emission tomography applications. Sensors (Basel) 2019;19(22):5019. DOI: 10.3390/s19225019.
32. Phelps ME. Positron emission tomography provides molecular imaging of biological processes. Proc Natl Acad Sci U S A 2000;97(16):9226–9233. DOI: 10.1073/pnas.97.16.9226.
33. Radder N, Sonar S, Nanivadekar A, et al. Synergy in neuroimaging: PET-CT and MRI fusion for enhanced characterization of brain pathology. Cureus 2024;16(11):e74353. DOI: 10.7759/cureus.74353.
34. Deng CX, Hong X, Stegemann JP. Ultrasound imaging techniques for spatiotemporal characterization of composition, microstructure, and mechanical properties in tissue engineering. Tissue Eng Part B Rev 2016;22(4):311–321. DOI: 10.1089/ten.TEB.2015.0453.
35. Cloutier G, Destrempes F, Yu F, et al. Quantitative ultrasound imaging of soft biological tissues: A primer for radiologists and medical physicists. Insights Imaging 2021;12(1):127. DOI: 10.1186/s13244-021-01071-w.
36. Athanassiadis AG, Ma Z, Moreno-Gomez N, et al. Ultrasound-responsive systems as components for smart materials. Chem Rev 2021;122(5):5165–5208. DOI: 10.1021/acs.chemrev.1c00622.
37. O'Brien WD Jr. Ultrasound-biophysics mechanisms. Prog Biophys Mol Biol 2007;93(1–3):212–255. DOI: 10.1016/j.pbiomolbio.2006.07.010.
38. Humphrey VF. Ultrasound and matter—physical interactions. Prog Biophys Mol Biol 2007;93(1–3):195–211. DOI: 10.1016/j.pbiomolbio.2006.07.024.
39. Streeter JE, Dayton PA. WE-C-218-01: Ultrasound contrast agents. Med Phys 2012;39(6Part27):3953. DOI: 10.1118/1.4736133.
40. Grogan SP, Mount CA. Ultrasound physics and instrumentation. 2023. In: StatPearls. Treasure Island, FL, USA: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK570593/.
41. Kossoff G. Basic physics and imaging characteristics of ultrasound. World J Surg 2000;24(2):134–142. DOI: 10.1007/s002689910026.
42. Lotfipour H, Sobhani H, Dejpasand MT, et al. Application of quantum imaging in biology. Biomed Opt Express 2025;16(8):3349–3377. DOI: 10.1364/BOE.566801.
43. Xu F, Zhang S, Ma L, et al. Quantum-enhanced diamond molecular tension microscopy for quantifying cellular forces. Sci Adv 2024;10(4):eadi5300. DOI: 10.1126/sciadv.adi5300.
44. Malatesta M. Transmission electron microscopy as a powerful tool to investigate the interaction of nanoparticles with subcellular structures. Int J Mol Sci 2021;22(23):12789. DOI: 10.3390/ijms222312789.
45. Pennycook SJ, Li C, Li M, et al. Material structure, properties, and dynamics through scanning transmission electron microscopy. J Anal Sci Technol 2018;9(1):11. DOI: 10.1186/s40543-018-0142-4.
46. Imaging NRCUCoRCtAC. Imaging techniques: State of the art and future potential. Visualizing Chemistry: The Progress and Promise of Advanced Chemical Imaging 3. Washington, DC, USA: National Academies Press (US); 2006. p. 100.
47. Rodriguez-Galvan A, Contreras-Torres FF. Scanning tunneling microscopy of biological structures: An elusive goal for many years. Nanomaterials (Basel) 2022;12(17):3013. DOI: 10.3390/nano12173013.
48. Trixler F. Quantum tunnelling to the origin and evolution of life. Curr Org Chem 2013;17(16):1758–1770. DOI: 10.2174/13852728113179990083.
49. Drummen GPC. Fluorescent probes and fluorescence (microscopy) techniques—illuminating biological and biomedical research. Molecules 2012;17(12):14067–14090. DOI: 10.3390/molecules171214067.
50. Berezin MY, Achilefu S. Fluorescence lifetime measurements and biological imaging. Chem Rev 2010;110(5):2641–2684. DOI: 10.1021/cr900343z.
51. Yun S, Kwok S. Light in diagnosis, therapy and surgery. Nat Biomed Eng 2017;1(1):0008. DOI: 10.1038/s41551-016-0008.
52. Samimi S, Ghasemi Z, Mohammadi H. Quantum-enhanced imaging and metrology with undetected photons via squeezed-light homodyne detection. Sci Rep 2025;15(1):42966. DOI: 10.1038/s41598-025-27056-z.
53. Yang L, Chen Y, Ling S, et al. Research progress on the application of optical coherence tomography in the field of oncology. Front Oncol 2022;12:953934. DOI: 10.3389/fonc.2022.953934.
54. Gurjar V, Rajan AK, Chaturvedi A, et al. Deep learning-enabled quantum imaging: Future-ready nanosensing technologies for preventive health interventions. Comput Struct Biotech Rep 2025;2(1):100053. DOI: 10.1016/j.csbr.2025.100053.
55. Elliott AD. Confocal microscopy: Principles and modern practices. Curr Protoc Cytom 2020;92(1):e68. DOI: 10.1002/cpcy.68.
56. Vukojevic V, Heidkamp M, Ming Y, et al. Quantitative single-molecule imaging by confocal laser scanning microscopy. Proc Natl Acad Sci U S A 2008;105(47):18176–18181. DOI: 10.1073/pnas.0809250105.
57. Diaspro A, Bianchini P, Vicidomini G, et al. Multi-photon excitation microscopy. Biomed Eng Online 2006;5:36. DOI: 10.1186/1475-925X-5-36.
58. Fung AA, Shi L. Mammalian cell and tissue imaging using raman and coherent raman microscopy. Wiley Interdiscip Rev Syst Biol Med 2020;12(6):e1501. DOI: 10.1002/wsbm.1501.
59. Bock M, Reichenbach JR. Quantum physics at a historic milestone: How has it shaped medical physics? Z Med Phys 2025;35(2):123–126. DOI: 10.1016/j.zemedi.2025.02.002.
60. Bisiani J, Anugu A, Pentyala S. It's time to go quantum in medicine. J Clin Med 2023;12(13):4506. DOI: 10.3390/jcm12134506.
61. Chong LM, Tng DJH, Tan LLY, et al. Recent advances in radiation therapy and photodynamic therapy. Appl Phys Rev 2021;8(1):041322. DOI: 10.1063/5.0060424.
62. Khalaf M, Kaminer I. Compton scattering driven by intense quantum light. Sci Adv 2023;9(1):eade0932. DOI: 10.1126/sciadv.ade0932.
63. Sholaiman M, Islam MR, Islam MR, et al. Advancing proton beam dosimetry in water: A particle and heavy ion transport code system monte carlo simulation of depth dose, range characteristics, and linear energy transfer distributions. J Med Phys 2026;51(1):49–58. DOI: 10.4103/jmp.jmp_258_25.
64. Liu H, Chang JY. Proton therapy in clinical practice. Chin J Cancer 2011;30(5):315–326. DOI: 10.5732/cjc.010.10529.
65. Tafti D, Banks KP. Nuclear Medicine Physics. 2023. Treasure Island, FL, USA: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK568731/.
66. Shaikh MS, Kurhade RR, Siddiqui AAM, et al. Advancements in targeted radiopharmaceuticals: Innovations in diagnosis and therapy for enhanced cancer management. Chembiochem 2026;27(1):e202500676. DOI: 10.1002/cbic.202500676.
67. Suvvari TK, Konakanchi VSBP, Muppavarapu RS, et al. The potential role of quantum computing in biomedicine and healthcare: The next frontier beyond artificial intelligence. Cureus 2025;17(4):e82759. DOI: 10.7759/cureus.82759.

68. Braga DM, Rawal BS. Harnessing AI and quantum computing for accelerated drug discovery: Regulatory frameworks for in silico to in vivo validation. J Pharm BioTech Ind 2025;2(3):11. DOI: 10.3390/jpbi2030011.
69. Niazi SK. Quantum mechanics in drug discovery: A comprehensive review of methods, applications, and future directions. Int J Mol Sci 2025;26(13). DOI: 10.3390/ijms26136325.
70. Kuanysheva T, Kendrick B, Cincio L, et al. Quantum simulation of molecular dynamics processes—A benchmark study using a classical simulator and present-day quantum hardware. J Phys Chem A 2025;129(28):6470–6481. DOI: 10.1021/acs.jpca.5c02029.
71. Gorgulla C, Jayaraj A, Fackeldey K, et al. Emerging frontiers in virtual drug discovery: From quantum mechanical methods to deep learning approaches. Curr Opin Chem Biol 2022;69:102156. DOI: 10.1016/j.cbpa.2022.102156.
72. Bose R, Mondal S, Sutradhar S, et al. Enhancing cloud-based healthcare security with quantum-secure healthchain: A quantum computing and blockchain integrated framework. Health Sci Rep 2026;9(5):e72367. DOI: 10.1002/hsr2.72367.
73. He Y, Fan J, Zhang Y. Controlled quantum authentication confidential communication protocol for smart healthcare. Sci Rep 2025;15(1):18094. DOI: 10.1038/s41598-025-02448-3.
74. Freyer O, Ostermann M, Minssen T, et al. Quantum cryptography and data protection for medical devices before and after they meet Q-Day. NPJ Digit Med 2025;8(1):620. DOI: 10.1038/s41746-025-02082-3.
75. Bai CM, Shu YX, Zhang S. Authenticable quantum secret sharing based on special entangled state. Sci Rep 2025;15(1):10819. DOI: 10.1038/s41598-025-95608-4.
76. Basil NN, Ambe S, Ekhator C, et al. Health records database and inherent security concerns: A review of the literature. Cureus 2022;14(10):e30168. DOI: 10.7759/cureus.30168.
77. Pereira M, Kato G, Mizutani A, et al. Quantum key distribution with correlated sources. Sci Adv 2020;6(37):eaaz4487. DOI: 10.1126/sciadv.aaz4487.
78. Mantry H, Maheshwari A. Quantum cryptography for securing personal health information in hospitals. Newborn (Clarksville, Md) 2022;1(4):333–339. DOI: 10.5005/jp-journals-11002-0043.
79. Li S, Chen Y, Chen L, et al. Post-quantum security: Opportunities and challenges. Sensors (Basel) 2023;23(21):8744. DOI: 10.3390/s23218744.
80. Wardlaw WP. The RSA public key cryptosystem. In: Joyner D, ed. Coding Theory and Cryptography. Berlin, Germany: Springer; 2000. pp. 100–121.
81. XChange Q. Post-Quantum Cryptography in 2026: What Infrastructure Leaders Need to Know Bethesda, MD, USA: quantumxc.com; 2025. Available from: https://quantumxc.com/blogs-podcasts/quantum-predictions-it-network-infrastructure/.
82. Zhang H, Zhu H, He R, et al. Towards global quantum key distribution. Nat Rev Electr Eng 2025;2(1):806–818. DOI: 10.1038/s44287-025-00238-7.
83. Hu Y, Loo CK. A generalized quantum-inspired decision making model for intelligent agent. ScientificWorldJournal 2014;2014:240983. DOI: 10.1155/2014/240983.
84. Widdows D, Rani J, Pothos EM. Quantum circuit components for cognitive decision-making. Entropy (Basel) 2023;25(4):548. DOI: 10.3390/e25040548.
85. Cerreia-Vioglio S, Maccheroni F, Marinacci M, et al. Classical subjective expected utility. Proc Natl Acad Sci U S A 2013;110(17):6754–6759. DOI: 10.1073/pnas.1207805110.
86. Khrennikov A. Quantum-like modeling of cognition. Växjö, Sweden: Department of Mathematics, Linnaeus University; 2015.
87. Khrennikov A, Basieva I, Pothos EM, et al. Quantum probability in decision making from quantum information representation of neuronal states. Sci Rep 2018;8(1):16225. DOI: 10.1038/s41598-018-34531-3.
88. Shan ZH. Brainwave phase stability: Predictive modeling of irrational decision. Front Psychol 2022;13:617051. DOI: 10.3389/fpsyg.2022.617051.
89. Li C, Liu Y, Liu R. Standard and non-standard framing effects: A unified rational interpretation based on the new definition of frame. Humanit Soc Sci Commun 2025;12(1):1247. DOI: 10.1057/s41599-025-05604-2.
90. Orrell D, Houshmand M. Quantum propensity in economics. Front Artif Intell 2021;4:772294. DOI: 10.3389/frai.2021.772294.
91. Moreira C, Wichert A. Quantum probabilistic models revisited: The case of disjunction effects in cognition. Front Phys 2016;4:28. DOI: 10.3389/fphy.2016.00026.
92. Popkin G. Quantum Computing Explained. Gaithersburg, MD, USA: National Institute of Standards and Technology, US Department of Commerce; 2025. Available from: https://www.nist.gov/quantum-information-science/quantum-computing-explained.
93. Chow JCL. Quantum computing in medicine. Med Sci (Basel) 2024;12(4):67. DOI: 10.3390/medsci12040067.
94. Montanaro A. Quantum algorithms: An overview. npj Quantum Information 2016;2:15023. DOI: 10.1038/npjqi.2015.23.
95. National Academies of Sciences, Engineering, and Medicine. Essential Software Components of a Scalable Quantum Computer. Washington, DC, USA: The National Academies Press; 2019. Available from: https://www.nationalacademies.org/read/25196/chapter/8.
96. Lovane G. Quantum-inspired algorithms and perspectives for optimization. Electronics 2025;14(14):2839. DOI: 10.3390/electronics14142839.
97. Hakemi S, Houshmand M, KheirKhah E, et al. A review of recent advances in quantum-inspired metaheuristics. Evol Intell 2022:1–16. DOI: 10.1007/s12065-022-00783-2.
98. Solaiman S. Enhancing Quantum Key Distribution security through hybrid protocol integration. Symmetry 2025;17(3):458. DOI: 10.3390/sym17030458.
99. Fuyama M, Khrennikov A, Ozawa M. Quantum-like cognition and decision-making in the light of quantum measurement theory. Philos Trans A Math Phys Eng Sci 2025;383(2309):20240372. DOI: 10.1098/rsta.2024.0372.
100. Huang J, Epping G, Trueblood JS, et al. An overview of the quantum cognition research program. Psychon Bull Rev 2025;32(6):2507–2556. DOI: 10.3758/s13423-025-02675-9.
101. Takahashi T. Toward a physical theory of quantum cognition. Top Cogn Sci 2014;6(1):104–107. DOI: 10.1111/tops.12079.
102. Ray P, Daw D, Tudu J. Quantum theory of Consciousness: A ripple in the existing constructs. Indian J Psychiatry 2022;24(64(Suppl 3)):S636. DOI: 10.4103/0019-5545.341861.
103. Escolà-Gascón Á. Evidence of quantum-entangled higher states of consciousness. Comput Struct Biotechnol J 2025;30:21–40. DOI: 10.1016/j.csbj.2025.03.001.
104. Sung JY, Cheong JH. Quantum medicine: A quantum-mechanical framework for redox biology, disease and precision medicine. Clin Transl Med 2026;16(1):e70598. DOI: 10.1002/ctm2.70598.
105. Idris Z, Zakaria Z, Yee AS, et al. Quantum and electromagnetic fields in our universe and brain: A new perspective to comprehend brain function. Brain Sci 2021;11(5):558. DOI: 10.3390/brainsci11050558.
106. Monroe C, Raymer MG, Taylor J. The U.S. national quantum initiative: From act to action Science 2019;364(6439):440–442. DOI: 10.1126/science.aax0578.
107. Mafu M, Senekane M. Quantum technology for development framework as a tool for science diplomacy. Front Res Metr Anal 2023;8:1279376. DOI: 10.3389/frma.2023.1279376.
108. Jeyaraman N, Jeyaraman M, Yadav S, et al. Revolutionizing healthcare: The emerging role of quantum computing in enhancing medical technology and treatment. Cureus 2024;16(8):e67486. DOI: 10.7759/cureus.67486.

REVIEW ARTICLE

World Down Syndrome Day 2026. There is a Need to Work "Together Against Loneliness"

Srijan Singh[1–3]

Received on: 24 April 2026; *Accepted on*: 26 May 2026; *Published on*: 22 June 2026

Abstract

World Down Syndrome Day 2026, observed on 21 March, adopts the theme "Together Against Loneliness," highlighting the urgent need to address social isolation among individuals with Down syndrome (Trisomy 21) and other intellectual and developmental disabilities (IDD). Individuals with Down syndrome experience loneliness at rates up to seven times higher than the general population, with prevalence reaching approximately 44.7% in some studies. This loneliness, comparable in health risk to smoking 15 cigarettes daily, stems primarily from social exclusion rather than the condition itself and contributes significantly to anxiety, depression, and diminished quality of life. This narrative review outlines the etiology and clinical features of Down syndrome, emphasizing proactive multidisciplinary medical management—including timely cardiac evaluation, respiratory and endocrine surveillance, and hematologic monitoring—to optimize health and facilitate social participation. It further examines lifespan care following American Academy of Pediatrics (AAP) guidelines, psychosocial support strategies, and the transformative role of inclusive education, social skills training, supported employment, and community programs. Global success stories of individuals with Down syndrome in arts, sports, education, and public life illustrate the potential unlocked through genuine inclusion. The article concludes with a call for collective action among families, clinicians, educators, employers, and policymakers to move beyond physical integration toward meaningful belonging, advocating systemic changes that uphold the human right to connection and dignity for every individual with Down syndrome.

Keywords: Anxiety, Chromosomal disorder, Depression, Down syndrome, Inclusive environment, Infant, Intellectual and developmental disabilities, Loneliness, Multidisciplinary care, Neonate, Newborn, Psychosocial support, Social exclusion, Social skills training, Trisomy 21.

Newborn (2026): 10.5005/jp-journals-11002-0160

Key Points

- The 2026 World Down Syndrome Day theme "Together Against Loneliness" underscores that social exclusion, not Trisomy 21 itself, drives high rates of loneliness (up to 44.7%) among individuals with Down syndrome, leading to serious mental and physical health consequences.
- Comprehensive neonatal and lifelong care—particularly early cardiac surgery, sleep apnea management, thyroid screening, and multidisciplinary interventions—is essential to reduce health burdens and enable fuller social participation.
- Diagnosis disclosure should be empathetic and solution-oriented, with immediate linkage to support networks. Real inclusion through meaningful relationships, rather than mere physical presence, is critical to combat isolation.
- Inspirational global success stories across continents demonstrate that with appropriate medical support, inclusive education, and opportunities, individuals with Down syndrome can achieve remarkable personal, professional, and societal accomplishments.
- Collective, multi-sectoral efforts in inclusive education [using Universal Design for Learning and Individualized Education Programs (IEPs)], vocational training, anti-stigma initiatives, and policy advocacy are required to create environments of genuine belonging and fulfill the right to connection for people with Down syndrome.

Introduction

On 21 March 2026, the global community observes World Down Syndrome Day under the theme "Together Against Loneliness."[1–5] This theme addresses a stark reality: Individuals with Down syndrome and intellectual disabilities experience loneliness up to seven times more frequently than the general population. Loneliness is a serious health risk—comparable to smoking 15 cigarettes a day—increasing anxiety, depression, and physical ill-health.[6,7] It often stems from social exclusion: Being physically present in schools, workplaces, or communities is not the same as feeling genuinely included, valued, and truly belonging.

We need to recognize that social withdrawal, isolation, and estrangement are not inherent features of Trisomy 21.[8] It is more a consequence of restricted social networks and limited opportunities for community engagement.[9–11] Research indicates that individuals with intellectual and developmental disabilities (IDD) experience loneliness at significantly higher rates than the neurotypical population; some studies suggest that the prevalence could be as high as 44.7%.[9–11] This "belonging gap" is further exacerbated during major life transitions, such as the shift from inclusive secondary education to adulthood, where

[1]Department of Pediatrics and Neonatology, Yashoda Medicity, Indirapuram, Uttar Pradesh, India

[2]Global Newborn Society, Laurel, Maryland, United States of America

[3]GNS Forum for Transgenerational Inheritance, Laurel, Maryland, United States of America

Corresponding Author: Srijan Singh, Department of Pediatrics and Neonatology, Yashoda Medicity, Indirapuram, Uttar Pradesh, India, Phone: +91 9811209371, e-mail: srijanstar89@gmail.com

How to cite this article: Singh S. World Down Syndrome Day 2026. There is a Need to Work "Together Against Loneliness". Newborn 2026;5(2):81–85.

Source of support: Nil

Conflict of interest: None

Fig. 1: On World Down Syndrome Day 2026, we celebrate the strength, joy, and individuality of people with Down syndrome across the world. This day is a reminder that inclusion, respect, access to healthcare, education, and meaningful opportunities allow every individual to thrive. By fostering understanding and embracing diversity, we build communities where everyone is valued, supported, and empowered to reach their full potential

Source: These images have been created with the AI tool ChatGPT

the loss of structured social environments can lead to profound withdrawal and secondary mental health challenges, including depression and anxiety. Addressing this disparity requires a shift from mere physical integration to "real inclusion," characterized by meaningful relationships and the dismantling of stigma. By fostering environments that prioritize social reciprocity and vocational belonging, we can transition from a model of passive presence to one of active, valued participation, ensuring that the human right to connection is upheld for all individuals with Down syndrome. We can find solutions by working together (Fig. 1).

"Together Against Loneliness" is a call to collective action. Families, clinicians, educators, employers, and communities must collaborate to create real inclusion in education, employment, relationships, and daily life—ensuring every person with Down syndrome feels seen, respected, and connected.

Down syndrome (Trisomy 21) is the most common chromosomal disorder, with a global prevalence of ~1 in 700–800 live births.[12] In India, estimates range from 1 in 850 to 1,100 live births, resulting in approximately 21,000 affected children born each year.[13,14] Although the risk rises with advanced maternal age (>35 years), most cases occur in younger mothers due to higher birth rates.[15]

Etiology and Clinical Features

Three mechanisms produce the phenotype:

1) Free Trisomy 21 (nondisjunction): ~95% of cases; recurrence risk ~1%.
2) Translocation: 3–4%; higher recurrence (10–15% if maternal carrier)—requires parental karyotyping.
3) Mosaicism: 1–2%; often milder.[16]

Newborns typically show hypotonia, a flat facial profile, up-slanting palpebral fissures, small dysplastic ears, clinodactyly, single transverse palmar crease, and joint hyperflexibility. Hall's criteria aid early suspicion; karyotyping confirms diagnosis.[17]

Key Medical Priorities

Proactive clinical surveillance is paramount to mitigating secondary complications that frequently exacerbate social isolation and diminish quality of life. Within this framework, cardiovascular health is a primary concern, as approximately 50% of infants are born with congenital heart disease—most notably atrioventricular septal defects (AVSD).[18] Consequently, a mandatory postnatal echocardiogram performed by a pediatric cardiologist is essential, with surgical repair ideally completed by 6 months of age to prevent irreversible pulmonary hypertension.[19] Furthermore, respiratory and endocrine monitoring are critical, given that obstructive sleep apnea affects 50–79% of this population, necessitating baseline polysomnography by age four, while thyroid dysfunction occurs in 24–50% of cases, requiring thyroid-stimulating hormone (TSH) and thyroxine (T4) screening at birth, at 6 and 12 months, and annually thereafter.[20] Hematologic surveillance is equally vital to manage transient abnormal myelopoiesis (TAM), which presents in approximately 10% of neonates, and to monitor the elevated long-term risk of leukemia. Finally, clinicians must remain vigilant for gastrointestinal pathologies, including duodenal atresia and celiac disease, the latter of which affects between 5 and 12% of individuals, ensuring that physiological stressors do not impede the broader goals of social and developmental integration.

Prenatal Screening and Lifespan Care

A stepwise approach includes first/second-trimester screening, high-accuracy cell-free DNA (cfDNA)/non-invasive prenatal screening (NIPS) (>99% detection), and confirmatory chorionic villus sampling (CVS)/amniocentesis.[21]

Lifespan Management Follows American Academy of Pediatrics (AAP) Guidelines

Adhering to the clinical guidelines established by the AAP, lifespan management for individuals with Down syndrome necessitates a rigorous, stage-specific longitudinal approach. During the neonatal period, immediate priorities include diagnostic confirmation via karyotype, echocardiography to assess for congenital heart defects, hearing and thyroid screenings, and comprehensive feeding support, all framed within a paradigm of hopeful, family-centered counseling.[22] As patients transition into early childhood, clinical surveillance shifts toward the utilization of population-specific growth charts, the initiation of intensive multidisciplinary therapies—including physical, occupational, and speech-language interventions—and vigilant monitoring for sensory impairments and sleep apnea. Given that autism spectrum disorder co-occurs in approximately 7–19% of this population, routine autism screenings are a critical component of this developmental phase. During the school-age and adolescent years, the focus expands to include the implementation of IEPs, social skills training, and ongoing surveillance for medical comorbidities. Finally, the transition into adulthood emphasizes the cultivation of autonomy through vocational training and the provision of robust supports for independent living, ensuring a holistic continuum of care that fosters long-term integration and well-being.

Psychosocial Support: From Survival to Belonging

Delivering the diagnosis demands empathy: Start with congratulations, provide balanced facts, and link families immediately to the Down Syndrome Federation of India (DSFI) and local NGOs. Early medical care preserves life; genuine inclusion combats loneliness and builds belonging.

Inspiring Success Stories Illustrate the Power of Inclusion

Inspiring success stories of individuals with Down syndrome underscore the transformative impact of inclusion, early intervention, medical support, and equitable opportunities. Across continents, these personalities have excelled in diverse fields, shifting societal perceptions from isolation to active contribution and connection.

In Asia, figures such as Sania Khimji[23–25] (mainstream model, artist, pageant winner); Gopi Krishnan Varma[26] (first lead actor with DS in Indian cinema, including Sitaare Zameen Par); Rishi Shahani[27] (Special Olympics swimmer, actor); Prithvi Raj Sengupta[28] (national powerlifter); Swasti Mehta[29] (entrepreneur, "Pudina Punch" founder); Riza Reji[30] (self-advocate, artist, actress); exemplify artistic and performative achievement.

In Europe, Pablo Pineda[31] (Spain), the first person with Down syndrome to earn a university degree on the continent and an accomplished actor and educator, along with Ellie Goldstein[32–34] (UK), a fashion model for Gucci and Adidas, and Tommy Jessop (UK), a noted actor, highlight advancements in education, media, and advocacy.

North America features prominent talents, including Zack Gottsagen[35–37] (USA), an actor and Oscar presenter, Sofía Jirau[38–41] (fashion model), Lauren Potter (USA) from the television series Glee, and Chris Nikic[42] (USA), the first individual with Down syndrome to complete an Ironman triathlon. In South America, Isabella Springmuhl Tejada[43,44] (Guatemala), a fashion designer who showcased at London Fashion Week, and Bryan Russell Mujica[45–47] (Peru), the first person with Down syndrome to run for public office and a university graduate in communications, demonstrate innovation in design and political engagement.

Oceania is represented by Madeline Stuart,[48–51] an international fashion model who has walked at major fashion weeks worldwide. In Africa, Shéri Brynard[52,53] (South Africa), the only person with Down syndrome in her country to obtain a tertiary teaching diploma without modifications and a dedicated educator and advocate, illustrates resilience in professional and educational spheres.

Collectively, these narratives reveal that, with appropriate support and inclusive environments, individuals with Down syndrome can achieve meaningful personal growth, professional success, and societal participation, challenging stereotypes and enriching communities globally.

Inclusive Education and Interventions against Loneliness

Inclusive education is a cornerstone intervention: Placing children in mainstream classrooms with supports (UDL, differentiated instruction, co-teaching, IEPs) rather than segregation.[54–58] Benefits include better language/academic gains, social skills, self-esteem, and friendships. Models like Special Olympics Unified Champion Schools foster whole-school inclusion through unified sports and youth leadership.[59,60]

Broader interventions include social skills training, supported employment, community recreation, family peer support, and policy advocacy for accessibility and anti-stigma efforts. Addressing medical issues (hearing/vision/sleep) further reduces barriers to participation.

Call to Action on 21 March 2026

To advance the ethos of "Together Against Loneliness," health and social systems must adopt a longitudinal, integrated framework that supports neurodivergent and disabled individuals from conception through adulthood. This begins with the provision of routine prenatal screenings coupled with compassionate, non-directive counseling to empower families with informed perspectives. Upon birth, the focus shifts to the delivery of multidisciplinary clinical care and the implementation of early therapeutic interventions designed to optimize developmental trajectories. Beyond the clinical setting, societal structures must prioritize inclusive educational environments and robust vocational opportunities that facilitate active community participation. Ultimately, it is essential to champion systemic policies that dismantle social isolation, ensuring that every individual—regardless of ability—is afforded a profound sense of value and belonging within the civic fabric.

Medical excellence preserves life. Together Against Loneliness, we give it dignity, connection, and joy.

Disclosures

Nothing to disclose.

References

1. About the 2026 theme - World Down Syndrome Day. Available from: https://www.worlddownsyndromeday.org/about-the-2026-theme/. [Last accessed on 3 April 2026].
2. Motta M, Singhal A, Hoyos AB, et al. Down syndrome: Let's work together to end the stereotypes behalf of the global newborn society Down syndrome foundation. Newborn 2024;3(2):65–69. DOI: 10.5005/jp-journals-11002-0096.

3. Singh S, Maheshwari A. Epigenetics of Down syndrome. Newborn 2024;3(4):263–280. DOI: 10.5005/jp-journals-11002-0112.
4. Badarch J, Kumar G, Enkhbayar B, et al. Down syndrome is the leading indication for late-stage termination of pregnancy in Mongolia. Newborn 2024;3(3):180–189. DOI: 10.5005/jp-journals-11002-0099.
5. Maheshwari A, Singh S, Sharma V, et al. Many term infants with persistent patency of the ductus arteriosus could be Trisomy 21 mosaics. Newborn 2024;3(1):61–64. DOI: 10.5005/jp-journals-11002-0090.
6. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: A meta-analytic review. PLoS Med 2010;7(7):e1000316. DOI: 10.1371/journal.pmed.1000316.
7. HHS, Oash. Our Epidemic of Loneliness and Isolation: The U.S. Surgeon General's Advisory on the Healing Effects of Social Connection and Community; 2023.
8. Kim S, Jang YS, Park EC. Associations between social isolation, withdrawal, and depressive symptoms in young adults: A cross-sectional study. BMC Psychiatry 2025;25(1):327. DOI: 10.1186/S12888-025-06792-6.
9. Alexandra P, Angela H, Ali A. Loneliness in people with intellectual and developmental disorders across the lifespan: A systematic review of prevalence and interventions. J Appl Res Intellect Disabil 2018;31(5):643–658. DOI: 10.1111/JAR.12432.
10. Together Against Loneliness in People with Down Syndrome – Daily27. Available from: https://daily27.info/2026/03/21/together-against-loneliness-in-people-with-down-syndrome/. [Last accessed on 6 April 2026].
11. Stokes JE, Waldron DA, Stam EJ. Loneliness among adults aging with intellectual and developmental disabilities: The importance of living situation. Gerontologist 2025;65(4):gnaf031. DOI: 10.1093/GERONT/GNAF031.
12. Nations U. World Down Syndrome Day | United Nations. Available from: https://www.un.org/en/observances/down-syndrome-day. [Last accessed on 4 April 2026].
13. Kava MP, Tullu MS, Muranjan MN, et al. Down syndrome: Clinical profile from India. Arch Med Res 2004;35(1):31–35. DOI: 10.1016/J.ARCMED.2003.06.005.
14. Verma IC. Burden of genetic disorders in India. Indian J Pediatr 2000;67(12):893–898. DOI: 10.1007/BF02723953.
15. Panigrahi I, Bhatt Y, Malik S, et al. Clinical profile of Indian children with Down syndrome. J Pediatr Genet 2021;12(1):53. DOI: 10.1055/S-0041-1732475.
16. Lechpammer M, Bigio del M, Folkerth R. Down Syndrome - Trisomy 21. The 5-Minute Pediatric Consult, 8th Edition, 2021:260–264. DOI: 10.1017/9781316671863.043.
17. New York State Department of Health. Clinical Practice Guideline Report of the Recommendations Down Syndrome Assessment and Intervention for Young Children (Age 0-3 Years) Sponsored by New York State Department of Health Division of Family Health Bureau of Early Intervention. Available from: www.hes.org. [Last accessed on 4 April 2026].
18. Delany DR, Gaydos SS, Romeo DA, et al. Down syndrome and congenital heart disease: Perioperative planning and management. J Congenit Cardiol 2021;5(1):7. DOI: 10.1186/S40949-021-00061-3.
19. Peterson JK, Clarke S, Gelb BD, et al. Trisomy 21 and congenital heart disease: Impact on health and functional outcomes from birth through adolescence: A scientific statement from the American Heart Association. J Am Heart Assoc 2024;13(19):e036214. DOI: 10.1161/JAHA.124.036214.
20. Sultanate of Oman. Guideline for Medical Management of Children and Young People with Down syndrome; 2015.
21. Rafi I, Hill M, Hayward J, et al. Non-invasive prenatal testing: Use of cell-free fetal DNA in Down syndrome screening. Br J Gen Pract 2017;67(660):298–299. DOI: 10.3399/BJGP17X691625.
22. Bull MJ, Trotter T, Santoro SL, et al. Health supervision for children and adolescents with Down syndrome. Pediatrics 2022;149(5). DOI: 10.1542/PEDS.2022-057010/186778.
23. Sania Khimji - India Inclusion Summit. Available from: https://indiainclusionsummit.com/member/sania-khimji/. [Last accessed on 4 April 2026].
24. Fashion Model & Artist with Down Syndrome - Sania Khimji. Available from: https://www.beyond6seconds.net/fashion-model-artist-with-down-syndrome-sania-khimji/. [Last accessed on 4 April 2026].
25. Inspiring down syndrome success story of Sania Khimji. Available from: https://www.1specialplace.com/post/inspiring-down-syndrome-success-story-of-sania-khimji. [Last accessed on 4 April 2026].
26. Gopi Krishna Varma — The Movie Database (TMDB). Available from: https://www.themoviedb.org/person/5417689-gopi-krishna-varma. [Last accessed on 4 April 2026].
27. An interesting and inspiring trivia about Rishi Shahani who plays the role of Sharmaji in Sitaare Zameen Par - He won a Gold and Silver Medal in Swimming at the age of 17 at the 1999 Special Olympics in North Carolina: r/bollywood. Available from: https://www.reddit.com/r/bollywood/comments/1lnyqxa/an_interesting_and_inspiring_trivia_about_rishi/. [Last accessed on 4 April 2026].
28. Prithvi Samrat Sengupta – SPECIAL OLYMPICS BHARAT. Available from: https://specialolympicsbharat.org/prithvi-samrat-sengupta/. [Last accessed on 4 April 2026].
29. Swasti Mehta's 'Pudina Punch' - Nayi Disha. Available from: https://nayi-disha.org/article/caregiver-journey/swasti-mehtas-pudina-punch/. [Last accessed on 4 April 2026].
30. Meet Riza Reji, the young model with down syndrome - The Hindu. Available from: https://www.thehindu.com/life-and-style/fashion/meet-riza-reji-the-young-model-with-down-syndrome/article65657172.ece. [Last accessed on 4 April 2026].
31. Pablo Pineda (Author of Niños con capacidades especiales). Available from: https://www.goodreads.com/author/show/14972595.Pablo_Pineda. [Last accessed on 4 April 2026].
32. Ellie Goldstein | New City College. Available from: https://www.ncclondon.ac.uk/student-story/ellie-goldstein-2/. [Last accessed on 4 April 2026].
33. Ellie Goldstein's Strictly Come Dancing Stint "made history." Available from: https://www.bbc.com/news/articles/cddr5n2vm3do. [Last accessed on 4 April 2026].
34. Ellie Goldstein | Zebedee Talent Model Management. Available from: https://www.zbdtalent.com/uk/mainboard/women/39-ellie-g/. [Last accessed on 4 April 2026].
35. Zack Gottsagen Didn't Let Down Syndrome Stop His Dream of Acting - Los Angeles Times. Available from: https://www.latimes.com/entertainment-arts/movies/story/2019-12-03/zack-gottsagen-shia-labeouf-peanut-butter-falcon-dakota-johnson. [Last accessed on 4 April 2026].
36. Q&A With Zack Gottsagen - Star Of "The Peanut Butter Falcon" - Downs Syndrome Association. Available from: https://www.downs-syndrome.org.uk/news/our-stories/zack-gottsagen-star-of-the-peanut-butter-falcon/. [Last accessed on 4 April 2026].
37. Zack Gottsagen – Conquering Hollywood – Ruderman Family Foundation. Available from: https://rudermanfoundation.org/podcasts/zack-gottsagen-conquering-hollywood/. [Last accessed on 4 April 2026].
38. NYFW: Model with down syndrome says "There Are No Limits." PEOPLE.com. Available from: https://people.com/human-interest/latina-model-with-down-syndrome-stuns-at-nyfw/. [Last accessed on 4 April 2026].
39. Latina Model with Down Syndrome Sofía Jirau Walks at New York Fashion Week; 2020. Available from: https://www.yahoo.com/lifestyle/latina-model-down-syndrome-sof-185637937.html. [Last accessed on 4 April 2026].
40. Meet Sofía Jirau, The Puerto Rican Model with Down Syndrome Who Is Shaking Up the Exclusive Fashion Scene. Remezcla; 2020. Available

from: https://remezcla.com/culture/sofia-jirau-puerto-rico-model-new-york-fashion-week/. [Last accessed on 4 April 2026].
41. Puerto Rican model with Down Syndrome, Sofía Jirau is conquering the fashion world. HOLA! USA; 2020. Available from: https://us.hola.com/fashion/20200219fkth8l2664/puerto-rican-model-down-syndrome-sofia-jirau. [Last accessed on 4 April 2026].
42. How Chris Nikic Made History. Available from: https://www.specialolympics.org/how-chris-nikic-made-history. [Last accessed on 4 April 2026].
43. Isabella Springmühl de Guatemala Rumbo al London Fashion Week 2016. National Down Syndrome Congress; 2016. Available from: http://www.ndsccenter.org/isabella-springmuhl-de-guatemala-rumbo-al-london-fashion-week-2016/. [Last accessed on 6 April 2026].
44. Cacciatore MR. Isabella Springmuhl Brings Inclusive Guatemalan Designs to the Fashion World. WIPO Magazine. Available from: https://www.wipo.int/wipo_magazine/en/2022/01/article_0005.html. [Last accessed on 6 April 2026].
45. 'El Candidato': A Documentary About Bryan Russell, the First Man with Down Syndrome to Run for Public Office. - ABILITY Magazine. Available from: https://abilitymagazine.com/el-candidato-a-documentary-about-bryan-russell-the-first-man-with-down-syndrome-to-run-for-public-office/. [Last accessed on 6 April 2026].
46. Bryan Russell Mujica - Be Beautiful Be Yourself Fashion Show. Available from: https://bebeautifulbeyourself.org/bryan-russell-mujica/. [Last accessed on 6 April 2026].
47. Bryan Russell Mujica Statement | Human Rights Watch. Available from: https://www.hrw.org/news/2022/05/17/bryan-russell-mujica-statement. [Last accessed on 6 April 2026].
48. Johnson J, Sharkey L. Madeline Stuart: Down Syndrome Model Lands Two Modelling Jobs in a Week. The Independent; 2015. Available from: https://www.independent.co.uk/life-style/fashion/features/madeline-stuart-the-downs-syndrome-model-lands-two-modelling-jobs-in-a-week-10375794.html. [Last accessed on 4 April 2026].
49. Saul H. Madeline Stuart: Model with Down's Syndrome will Walk at New York Fashion Week. The Independent; 2015. Available from: https://www.independent.co.uk/news/people/madeline-stuart-model-with-downs-syndrome-will-walk-at-new-york-fashion-week-10457950.html. [Last accessed on 4 April 2026].
50. Free C. This Australian Fashion Model is in High Demand. She also has Down Syndrome. Washington Post; 2019. Available from: https://www.washingtonpost.com/lifestyle/2019/02/11/this-australian-fashion-model-is-high-demand-she-also-has-down-syndrome/. [Last accessed on 4 April 2026].
51. Down's Syndrome Model Madeline Stuart Sparks an Emotional Reaction with a New Bridal Shoot. Daily Telegraph; 2016. Available from: https://www.telegraph.co.uk/fashion/people/madeline-stuart-downs-syndrome-model-bridal-shoot/. [Last accessed on 4 April 2026].
52. Sheri Brynard – Changing People's Perception About Down Syndrome. Available from: https://sheribrynard.co.za/. [Last accessed on 6 April 2026].
53. About Sheri – Sheri Brynard. Available from: https://sheribrynard.co.za/about-sheri/. [Last accessed on 6 April 2026].
54. Article 24 - Education | Division for Inclusive Social Development (DISD). Available from: https://social.desa.un.org/issues/disability/crpd/article-24-education. [Last accessed on 4 April 2026].
55. UNESCO, España Ministerio de Educación y Ciencia. World Conference on Special Needs Education: Access and Quality, Salamanca, Spain. The Salamanca Statement and Framework for Action on Special Needs Education; 1994. Available from: https://unesdoc.unesco.org/ark:/48223/pf0000098427. [Last accessed on 4 April 2026].
56. The Salamanca Statement and Framework for Action on Special Needs Education - UNESCO Digital Library. Available from: https://unesdoc.unesco.org/ark:/48223/pf0000098427. [Last accessed on 4 April 2026].
57. Tomlinson CA. How to Differentiate Instruction in Academically Diverse Classrooms; 2017. p. 184. Available from: https://www.ascd.org/books/how-to-differentiate-instruction-in-academically-diverse-classrooms-3rd-edition?variant=117032. [Last accessed on 4 April 2026].
58. CAST Universal Design for Learning Guidelines. Available from: https://udlguidelines.cast.org/. [Last accessed on 4 April 2026].
59. Special Olympics Unified Champion Schools®. Available from: https://www.specialolympics.org/what-we-do/youth-and-schools/unified-champion-schools. [Last accessed on 4 April 2026].
60. Office of Special Education and Rehabilitative Services (OSERS) | U.S. Department of Education. Available from: https://www.ed.gov/about/ed-offices/osers. [Last accessed on 4 April 2026].

REVIEW ARTICLE

Developmental Deficiency of Coagulation Factor VII in Neonates: Our Current Understanding

Akhil Maheshwari[1–19], Khaled El-Atawi[20–22], Aimen B Ayad[2,23], Kei Lui[2,17,24–26], Joe GN Garcia[2,27,28], Selvarangan Ponnazhagan[2,3,29]

Received on: 01 May 2026; *Accepted on:* 01 June 2026; *Published on:* 22 June 2026

Abstract

Factor VII (FVII) is a vitamin K-dependent glycoprotein that serves as the principal initiator of the extrinsic coagulation pathway through its interaction with tissue factor (TF). Following vascular injury, TF binds and activates circulating FVII, generating the TF–FVIIa complex that promotes thrombin generation and fibrin clot formation. Neonates have physiologically reduced concentrations of FVII, typically 20–50% of adult values, rendering them vulnerable to hemorrhagic complications, particularly in the presence of prematurity, vitamin K deficiency, sepsis, liver dysfunction, or severe illness. This review summarizes the molecular biology, structure, activation, evolutionary origins, and clinical significance of FVII, with a particular emphasis on neonatal hemostasis. Factor VII is synthesized in the liver and undergoes extensive post-translational modification, including vitamin K-dependent γ-carboxylation that is essential for calcium-mediated membrane binding and coagulation activity. The protein contains a γ-carboxyglutamate-rich domain, two epidermal growth factor (EGF)-like domains, and a catalytic serine protease domain that together mediate TF binding and activation of factors IX and X. Evolutionary analyses indicate that FVII emerged in early jawed vertebrates and has remained highly conserved for more than 400 million years, reflecting its critical role in hemostatic regulation. Recombinant activated FVII (rFVIIa; eptacog alfa) has become an important therapeutic agent for congenital FVII deficiency, hemophilia with inhibitors, and selected cases of severe hemorrhage. In neonates, rFVIIa is increasingly used off-label as rescue therapy for refractory bleeding associated with disseminated intravascular coagulation (DIC), cardiac surgery, pulmonary hemorrhage, necrotizing enterocolitis (NEC), thrombocytopenia, and intracranial hemorrhage (ICH). Available evidence suggests that rFVIIa can reduce bleeding and transfusion requirements, although randomized neonatal trials remain lacking. Potential thromboembolic complications necessitate careful patient selection and monitoring. More studies are needed to define optimal dosing, establish safety profiles, and clarify the role of rFVIIa in neonatal and pediatric hemostatic disorders.

Keywords: Coagulation factor VII, Eptacog alfa, Factor VIIa, Factor VIII and factor IX inhibitors, Fibrinogen, Hemophilia, Prothrombin, Thrombin, Universal hemostatic agent.

Newborn (2026): 10.5005/jp-journals-11002-0162

Key Points

- Neonates typically show lower levels of coagulation factors such as factor VII (FVII) than adults, which has been associated with a higher risk of bleeding.
- Factor VII is a vitamin K-dependent protein mediator in the extrinsic pathway of blood coagulation, circulating in plasma in an inactive form.
- Following vascular injury, circulating FVII binds to tissue factor (TF) expressed on extravascular cells (fibroblasts and smooth muscle cells), which activates FVII to FVIIa.
- In the coagulation pathway, FVIIa catalyzes the activation of FX and FIX, initiating thrombin generation and fibrin clot formation.
- The now available recombinant FVIIa (rFVIIa) is a "universal hemostatic agent" with efficacy in congenital FVII deficiencies, hemophilic patients who have developed inhibitors to FVIII or IX, quantitative and qualitative platelet disorders, hepatic failure, liver transplantation, major surgery and trauma.

Introduction

Factor VII is a key vitamin K-dependent protein mediator in the extrinsic pathway of blood coagulation, circulating in plasma mainly as an inactive zymogen, with only a small active fraction (FVIIa).[1–5] Vascular injury exposes subendothelial TF, which binds FVII along with components of the phospholipid membranes and activates it (Fig. 1).[6] The resulting complex activates factor X (and, to a lesser extent, FIX), leading to thrombin generation and fibrin clot formation.[7]

[1]Department of Pediatrics/Neonatology, Boston Children's Health Physicians Group at the Maria Fareri Children's Hospital, New York Medical College, Valhalla, New York, United States of America
[2]Global Newborn Society, Laurel, Maryland, United States of America
[3]GNS Forum for Transgenerational Inheritance, New York, United States of America
[4]Mongolian Association of Obstetrics, Gynecology, and Neonatology, Ulaanbaatar, Mongolia
[5]Department of Neonatology, Institute of Maternal and Child Health, Matuail, Dhaka, Bangladesh
[6]Bangladesh Neonatal Foundation, Dhaka, Bangladesh
[7]Dr. Mozib Newborn Foundation, Dhaka, Bangladesh
[8]Pioneers—Looking for Sustainable Ways to Reduce Infant Mortality, Oslo, Norway
[9]Banaras Hindu University Institute of Excellence, Varanasi, Uttar Pradesh, India
[10]S.A.B.R.E.E. Enrichment Academy, Saint Louis, Missouri, United States of America
[11]The Skylar Project, Daphne, Alabama, United States of America
[12]International Society for Marginalized Lives, Harrison, New York, United States of America
[13]PreemieWorld Foundation, Springfield, Virginia, United States of America
[14]Carlo GNS Center for Saving Lives at Birth, Birmingham, Alabama, United States of America
[15]Autism Care Network Foundation, Chandigarh, India

Neonates are developmentally deficient in FVII, with blood FVII levels approximately 20–50% of adult levels during the early neonatal period, which contributes to an increased risk of bleeding in premature infants or those with additional risk factors such as vitamin K deficiency, sepsis, liver dysfunction, or birth trauma. Term infants are at lower risk, but may also develop hemorrhages during stress or critical illness. In this article, we present the current understanding of the expression, evolution, and clinical importance of FVII (Fig. 2). We combine data from our own preliminary studies with an extensive literature review using Embase, PubMed, and Scopus.[8,9] To minimize bias in study selection, identification of studies, and keywords were predefined *a priori* using PubMed's Medical Subject Headings (MeSH) terms.[10]

FVII Synthesis and Activation

Factor VII is synthesized primarily in the liver; translation begins on cytosolic ribosomes with an *N*-terminal signal peptide that targets the ribosome–nascent chain complex to the rough endoplasmic reticulum (ER).[11,12] The growing polypeptide is co-translationally translocated into the ER lumen, where the signal peptide is cleaved.[1] Here, FVII also undergoes post-translational modifications such as vitamin K-dependent γ-carboxylation of glutamate residues in a specific γ-carboxyglutamate-rich (Gla) domain.[13] Further processing with glycosylation and folding occurs in the ER and Golgi apparatus.[14] The mature protein is then secreted via the classical secretory pathway into the bloodstream.[14,15] Factor VII binds TF in a Ca^{++} and phospholipid-dependent manner in regions with vascular injury, and is activated by proteolytic cleavage at a single Arg152–Ile153 amino acid bond.[5] There is a three-dimensional re-organization, but no amino acids are lost in this process.[16] Two amino acid chains are created (Fig. 3), which are held together by a single disulfide bond:[5,17–20]

- *N*-terminal light chain: This is an approximately 20 kDa, 152-residue part of the molecule. There is a gamma-carboxyglutamic acid (Gla) domain and two epidermal growth factor-like (EGF1 and EGF2) domains.
- *C*-terminal heavy chain: This is an approximately 30 kDa, 254-residue part containing the serine protease (catalytic) domain.

There is a fair degree of confidence in the predicted protein structure (Figs 4A and B) and stability with minimal movement in physiological conditions (Fig. 4C).[21,22] Even though the amino acid sequence is balanced with hydrophilic and hydrophobic amino acids, the surface is predicted to maintain good water-solubility (Fig. 4D; the average accessible surface of residues in most folded proteins is around 20% relative to an unfolded state; a value of 35% in FVII suggests that the protein's surface is well-hydrated).[23,24] The amino acid composition of the FVII molecule is shown in Figure 4E. Finally, the protein shows a good overall balance of positively and negatively charged amino acid residues, but the surface of the protein molecules shows more neutral/positively charged regions (Fig. 4F).[25,26]

Factor VII contains two EGF-like domains (Fig. 3), which play critical structural and functional roles in the initiation of the extrinsic coagulation pathway.[27] These are positioned between the *N*-terminal Gla and the *C*-terminal serine protease domains.[21] The EGF-like domains help stabilize the overall conformation of FVII, orienting the catalytic domain correctly upon binding to TF.[5] These are directly involved in high-affinity binding of FVII/FVIIa to TF and the assembly of the TF–FVIIa complex on phospholipid membranes.[28] In addition, these participate in allosteric regulation and conformational changes in TF–FVIIa binding, thereby enhancing its catalytic efficiency toward downstream substrates such as factor X.[29] Overall, the EGF-like domains act as molecular linkers that couple membrane localization to enzymatic activation in coagulation.[21,30]

Calcium ions (Ca^{++}) located inside the FVII molecules (Fig. 2) bind post-translationally modified Gla residues and stabilize the negatively charged electro-environment containing glutamic acid (Glu), aspartic acid (Asp), asparagine (Asn), and glycine (Gly) residues.[31,32] These conformational changes promote FVII–TF binding with the negatively charged phospholipid membranes at sites of vascular injury.[33] The Ca^{++}-phospholipid complexes also promote correct positioning of the enzyme relative to its substrates,

[16]Neonatology-Certified Foundation, Brooksville, Texas, United States of America
[17]GNS Infant Nutrition Education Program, Harrison, New York, United States of America
[18]International Prader-Willi Syndrome Organization, Cambridge, United Kingdom
[19]First Breath of Life, Shreveport, Louisiana, United States of America
[20]Department of Neonatology, Latifa Women and Children Hospital, Dubai, United Arab Emirates
[21]Department of Neonatology, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates
[22]Department of Pediatrics, De Montfort University Dubai, United Arab Emirates
[23]Department of Pediatrics/Neonatology, Danat Al Emarat Hospital, Abu Dhabi, United Arab Emirates
[24]Department of Paediatrics and Child Health, School of Clinical Medicine, University of New South Wales, Sydney, New South Wales, Australia
[25]Australian and New Zealand Neonatal Network, University of New South Wales, Sydney, New South Wales, Australia
[26]Department of Newborn Care Level 1, Royal Hospital for Women, Randwick, New South Wales, Australia
[27]Center for Inflammation Sciences and Systems Medicine at The Herbert Wertheim UF Scripps Institute for Biomedical Innovation & Technology, University of Florida at Gainesville, Gainesville, Florida, United States of America
[28]Department of Medicine, University of Florida at Gainesville, Gainesville, Florida, United States of America
[29]Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama, United States of America

Corresponding Author: Akhil Maheshwari, Department of Pediatrics/Neonatology, Boston Children's Health Physicians Group at the Maria Fareri Children's Hospital, New York Medical College, Valhalla, New York, United States of America, Phone: +1-708-910-8729, e-mail: akhil@globalnewbornsociety.org

How to cite this article: Maheshwari A, El-Atawi K, Ayad AB, *et al*. Developmental Deficiency of Coagulation Factor VII in Neonates: Our Current Understanding. Newborn 2026;5(2):86–103.

Source of support: Nil

Conflict of interest: Dr Kei Lui is associated as Executive Advisory Board Member of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of the International Editorial and Advisory Board Member and his research group.

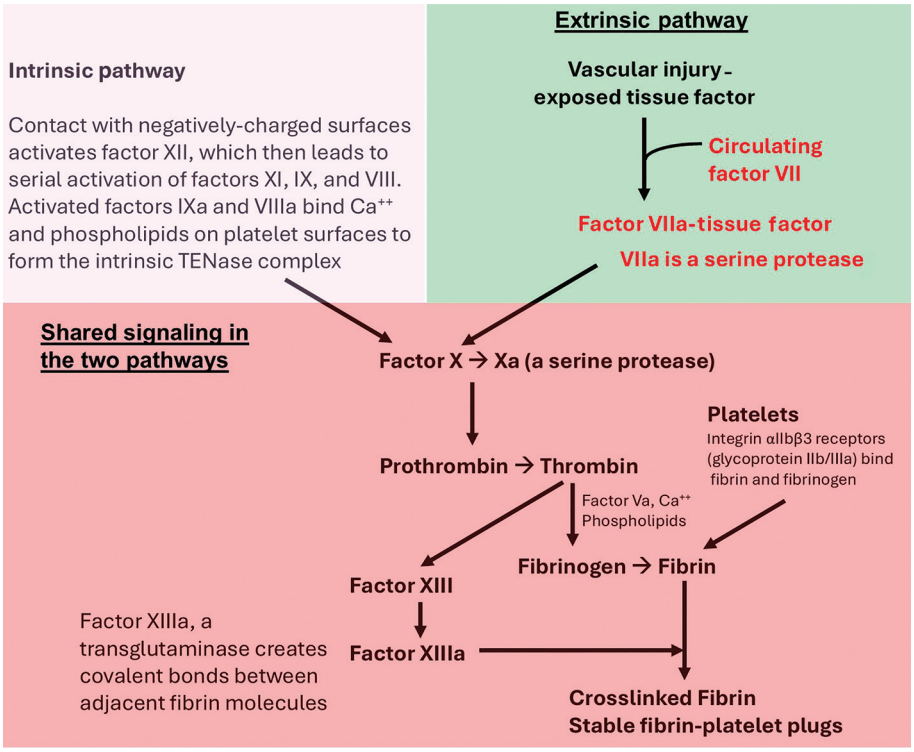


Fig. 1: Schematic diagram showing the role of FVII in the extrinsic pathway of coagulation

factors X and IX.[34] Additional Ca^{++}-binding sites in the EGF-like domains contribute to protein stability and domain orientation.[35,36]

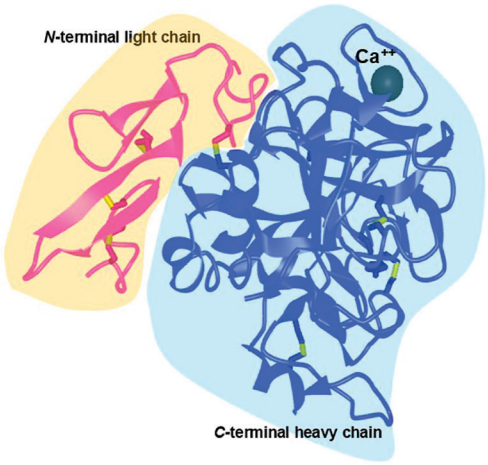
During tissue injury, the circulating FVII zymogen is exposed to TF that is constitutively expressed on subendothelial fibroblasts and smooth muscle cells.[6,37] Factor VII–TF binding induces a conformational change in FVII, and then it undergoes proteolytic activation upon exposure to small amounts of factor Xa (FXa) and thrombin.[38–40] The activated form of FVII, FVIIa, is a trypsin-like serine protease and catalyzes the activation of FX and FIX, promoting thrombin generation and fibrin clot formation.[2] A positive feedback loop is established with TF–FVIIa <—> FXa that amplifies coagulation.[41] By linking the extrinsic and intrinsic pathways, thrombin ensures rapid and localized clot formation while maintaining tight regulation of the coagulation cascade.[2] The regulated, localized activation of FVIIa limits its enzymatic activity to sites of vascular injury, preventing inappropriate systemic coagulation.[42]

Factor VII activation involves cleavage at Arg152–Ile153 to generate a new *N*-terminal on the heavy chain, which reorganizes the catalytic site.[19] This Ile153 residue is important for proper alignment of the catalytic site; it acts as a structural switch that locks the protease into its active conformation after zymogen cleavage.[21] The free α-amino group of Ile153 inserts into a conserved pocket within a serine protease domain and forms a stabilizing salt bridge with Asp194 (chymotrypsin numbering).[43] This interaction triggers conformational changes that position a catalytic triad (His57, Asp102, Ser195) and organize key substrate-binding loops that define the active site (Fig. 5).[43,44] In FVIIa, these structural changes are only partially stable on their own and have a low intrinsic activity.[5,45]

Tissue factor stabilizes the *N*-terminal insertion and allosteric conformational changes in surrounding loops in FVIIa, fully aligning the catalytic machinery for efficient proteolysis.[46] Thus, the *N*-terminus of the heavy chain is essential for converting FVII from an inactive precursor into a competent enzyme.[47] The FVIIa–TF complex can bind negatively charged phospholipid surfaces such as those on activated platelets or damaged cell membranes.[34] Factor VIIa is a rate-limiting catalytic enzyme in this process; it binds Ca^{++} ions, and FX and FIX on its Gla domain.[34,48] Gla is a product of a post-translational vitamin K-dependent carboxylation of glutamic acid residues in FVII; the modification adds an extra carboxyl group to the γ-carbon of glutamate and adds a strong negative charge (Fig. 6).[49] These residues are clustered in a specific domain and promote binding with negatively charged phospholipid membranes at sites of vascular injury.[49,50] Without γ-carboxylation, coagulation factors such as FVII are synthesized but remain functionally inactive; this is one reason for impaired blood clotting in vitamin K deficiency (Gla residues noted on positions 66, 67, 74, 76, 79, 80, 85, 86, 89, 95; Fig. 7).[13,51] These changes promote the formation of a fully competent protease complex capable of activating downstream coagulation factors.[5]

Role of TF (Factor III)

Tissue factor is a transmembrane glycoprotein that stabilizes and concentrates FVII at the site(s) of blood coagulation (Fig. 8).[37,42] It is normally expressed by extravascular fibroblasts and smooth muscle cells and is sequestered from the circulation.[52] It has a transmembrane glycoprotein with: (1) an extracellular, *N*-terminal 219 amino acid ectodomain that binds FVII/FVIIa; (2) an anchoring transmembrane part; and (3) a cytoplasmic domain involved in intracellular signaling unrelated to coagulation.[53] The extracellular domains contain a specific groove that binds and concentrates FVII.[54] The anchoring transmembrane region of TF contains specific



KEY STRUCTURAL ELEMENTS

Coagulation factor VII (FVII)

Synthesis: The major site of FVII synthesis is in hepatocytes. An *N*-terminal signal peptide directs it into the endoplasmic reticulum (ER). Here, it undergoes vitamin K–dependent γ-carboxylation of glutamate residues in its Gla domain, other post-translational modifications, is cleaved, and then secreted into the bloodstream. Similar to other coagulation factors, FVII functions extracellularly in plasma and on cell membranes.
Some minor non-classical FVII-like activity can be traced to leukocytes. These peptides are released passively in membrane-derived microvesicles or exosomes during cell activation, apoptosis, or necrosis. These vesicles may contribute to localized coagulation or inflammatory signaling.

Major Domains:
- **Signal:** residues 1–20; MVSQALRLLCLLLGLQGCLA
- **Propeptide:** residues 21–60; AGGVAKASGGETRDMPWKPGPHRVFVTQEEAHGVLHRRRR
- **Light chain:** residues 61–212; a γ-carboxyglutamate (Gla) domain followed by two epidermal growth factor (EGF)–like domains, which promote calcium-dependent membrane binding and interaction with tissue factor
  ANAFLEELRPGSLERECKEEQCSFEEAREIFKDAERTKLFWISYSDGDQCASSPCQNGGSCKDQLQSYICFCLPAFEGRNCETHKDDQLICVNENGGCEQYCSDHTGTKRSCRCHEGYSLL ADGVSCTPTVEYPCGKIPILEKRNASKPQGR;
- **Heavy chain:** residues 213–466; a serine protease catalytic domain, which contains the active site required for enzymatic activity.
  These two domains are linked by a disulfide bond after proteolytic activation of FVII to FVIIa, allowing coordinated regulation of membrane binding, cofactor interaction, and proteolytic function during coagulation.
  IVGGKVCPKGECPWQVLLLVNGAQLCGGTLINTIWVVSAAHCFDKIKNWRNLIAVLGEHDLSEHDGDEQSRRVAQVIIPSTYVPGTTNHDIALLRLHQPVVLTDHVVPLCLPERTFSERTLAFV RFSLVSGWGQLLDRGATALELMVLNVPRLMTQDCLQQSRKVGDSPNITEYMFCAGYSDGSKDSCKGDSGGPHATHYRGTWYLTGIVSWGQGCATVGHFGVYTRVSQYIEWLQKLMRSEP RPGVLLRAPFP

Conserved motifs:
- **γ-carboxyglutamate (Gla) motifs** are seen in the Gla domain. Coordinate Ca^{++} -binding and orientation/binding of factor VII to membrane phospholipids. Residues 66, 67, 74, 76, 79, 80, 85, 86, 89, 95;
- **Epidermal growth factor-like domains:** conserved cysteine residues form disulfide bonds that stabilize domain structure. These domains help in interactions with TF and in maintaining correct spacing between the membrane-binding and catalytic regions;
- **Serine protease domains:** contain strongly conserved motifs such as the catalytic triad (His, Asp, Ser) characteristic of trypsin-like proteases;
- **Activation cleavage site (Arg–Ile):** generates factor VIIa, as well as substrate-binding motifs that define specificity for factor X and factor IX.

Post-translational modifications:
- **Disulfide:** Residues 77↔82, 110↔121, 115↔130, 132↔141, 151↔162, 158↔172, 174↔187, 195↔322, 219↔224, 238↔254, 370↔389, 400↔428
- **Glycosylation:** Residues 112, 120, 205, 382
- **Modified (3R)-3-hydroxyaspartate:** Residue 123
- **Glycans:** 5 sites, 14 N-linked glycans (2 sites), 4 O-linked glycans (3 sites)

Function: FVII contains a trypsin-like serine protease domain that provides enzymatic activity in coagulation. This domain is in the heavy chain of activated FVII (FVIIa); there is a conserved fold characteristic of the trypsin family with a catalytic triad of histidine, aspartate, and serine. Proteolytic activation of FVII triggers conformational changes that align these residues, allowing efficient cleavage of downstream FX and FIX. Although the protease domain of factor VIIa has low intrinsic activity on its own, binding TF allosterically stabilizes the active-site, enhancing its catalytic efficiency in initiating the coagulation cascade.

- ***Calcium-binding residues:*** The Gla domain in FVII contains many Ca^{++}-binding residues; several γ-carboxyglutamic acid create a negatively-charged, Ca^{++}-bridged structure that enables FVII to bind the anionic phospholipid surfaces exposed at sites of vascular injury. Additional Ca^{++}-binding sites are present in the EGF-like domains that contribute to proper folding and stabilization of the protein. Together, these interactions help TF binding and active coagulation.
- ***Antimicrobial activity:*** FVII shows some indirect antimicrobial activity. Although FVII is not a classical antimicrobial peptide, the TF–FVIIa) complex can contribute to host defense by promoting localized thrombin generation and fibrin formation, which help trap and contain invading microorganisms at sites of infection or tissue injury. In addition, TF–FVIIa signaling through protease-activated receptors (particularly PAR-2) on immune and endothelial cells can modulate inflammatory and immune responses, enhancing barrier function and leukocyte recruitment.

Gene domains
- **Gla nucleotides:** nucleotides 61–105; Sequence: ANAFLEELRPGSLERECKEEQCSFEEAREIFKDAERTKLFWISYS
- **EGF-like 1, calcium-binding:** nucleotides 106–142; Sequence: DGDQCASSPCQNGGSCKDQLQSYICFCLPAFEGRNCE
- **EGF-like 2:** nucleotides 147–188; Sequence: DQLICVNENGGCEQYCSDHTGTKRSCRCHEGYSLLADGVSCT
- **Peptidase S1:** nucleotides 213–452; Sequence:
  IVGGKVCPKGECPWQVLLLVNGAQLCGGTLINTIWVVSAAHCFDKIKNWRNLIAVLGEHDLSEHDGDEQSRRVAQVIIPSTYVPGTTNHDIALLRLHQPVVLTDHVVPLCLPERTFSERTLAFVRFSLVSGWGQLLDRGATALELMVLNVPRLMTQDCLQQSRKVGDSPNITEYMFCAGYSDGSKDSCKGDSGGP HATHYRGTWYLTGIVSWGQGCATVGHFGVYTRVSQYIEWLQKLMR

Congenital FVII deficiency: These mutations are inherited as autosomal recessive bleeding disorders with variable clinical severity. More than 200 F7 mutations have been described, including missense mutations, nonsense mutations, splice-site defects, small insertions or deletions, and, rarely, large gene rearrangements. The most frequent genetic abnormalities involve missense mutations in the Gla domain, EGF-like domains, or the serine protease domain, impairing calcium binding, tissue factor interaction, protein folding, or catalytic activity. Splice-site mutations can result in reduced or abnormal FVII expression, while nonsense mutations typically cause severe deficiency due to truncated, nonfunctional protein. Clinically, these mutations lead to reduced plasma FVII activity, prolonged prothrombin time, and bleeding manifestations.

Genetic variants:
c.13L>P (dbSNP:rs387906507), c.59R>RR, c.64F>L, c.73L>Q (dbSNP:rs45572939), c.79E>Q, c.82C>F (dbSNP:rs1448296564), c.82C>R (dbSNP:rs745374448), c.84missing, c.85E>K (dbSNP:rs121964935), c. 88R>G (dbSNP:rs776354144), c.117N>D (rs121964932), c.120S>P, c.121C>F, c.125L>P, c.128Y>C, c.138G>D, c.139R>K, c.139R>Q (dbSNP:rs150525536), c.139R>W (dbSNP:rs776796178), c.151C>S, c.154E>K (dbSNP:rs146795869), c.156G>S (dbSNP:rs563972504), c.157G>S (dbSNP:rs763458490), c.157G>V (dbSNP:rs771335282), c.160Q>R (dbSNP:rs200016360), c.171S>F (dbSNP:rs143855920), c.177G>R, c.181L>P, c.183D>N (dbSNP:rs1258691292), c.186S>F (dbSNP:rs764971156), c.189P>S (dbSNP:rs1479693459), c.194P>L, c.194P>T (dbSNP:rs1234759020), c.195C>R (dbSNP:rs372577568), c.197K>E (dbSNP:rs1250204261), c.198I>T (dbSNP:rs762621913), c.212R>Q (dbSNP:rs868044209), c.213I>N, c.216G>D (dbSNP:rs1438503836), c.238C>F, c.238C>Y (dbSNP:rs121964928), c.240G>R (dbSNP:rs2036214367), c.241T>N (dbSNP:rs1160146175), c.250S>F, c.251A>P, c.251A>T (dbSNP:rs1269916662), c.252A>V, c.254C>R, c.254C>Y, c.264L>P (dbSNP:rs753266903), c.266A>T (dbSNP:rs764807079), c.272D>N (dbSNP:rs751028917), c.277D>N (dbSNP:rs550074221), c.283R>W (dbSNP:rs779589651), c.298T>I, c.301H>Q, c.302D>H, c.302D>N (dbSNP:rs770328850), c.304A>T (dbSNP:rs773627551), c.304A>V (dbSNP:rs121964931), c.307R>C (dbSNP:rs147680958), c.307R>H (dbSNP:rs121964929), c.312V>M (dbSNP:rs201991361), c.314L>V, c.321L>F (dbSNP:rs778138366), c.323L>R, c.325E>K (dbSNP:rs749760143), c.326R>Q (dbSNP:rs146698837), c.332T>M (dbSNP:rs200212201), c.336V>M (dbSNP:rs374305125), c.337R>C (dbSNP:rs139372641), c.341V>F, c.342S>G, c.343G>S (dbSNP:rs1250853566), c.344W>G, c.344W>R, c.345G>S (dbSNP:rs2036242082), c.350R>C (dbSNP:rs747876824), c.354A>V (dbSNP:rs36209567), c.358M>I (dbSNP:rs149283257), c.358M>V (dbSNP:rs928183869), c.360L>P, c.363P>H, c.363P>R (dbSNP:rs963430078), c.364R>Q (dbSNP:rs121964926), c.364R>W (dbSNP:rs750980786), c.370C>F (dbSNP:rs121964927), c.375R>W (dbSNP:rs137919286), c.384T>M (dbSNP:rs531225271), c.387M>T (dbSNP:rs1595080725), c.387M>V (dbSNP:rs121224419), c.388F>S (dbSNP:rs121964938), c.389C>G (dbSNP:rs121964934), c.391G>C, c.391G>S (dbSNP:rs190485816), c.398D>E, c.401K>E (dbSNP:rs748979195), c.402G>E, c.402G>R (dbSNP:rs2142234194), c.403D>H, c.404S>N, c.408H>Q (dbSNP:rs121964935), c.408H>R (dbSNP:rs1566910847), c.413R>G, c.414G>C (dbSNP:rs121964937), c.419T>M (dbSNP:rs121964930), c.420G>D, c.422V>F, c.425G>A, c.425G>C (dbSNP:rs2036249208), c.428A>T (dbSNP:rs755377592), c.432G>D (dbSNP:rs1450120320), c.432G>S (dbSNP:rs1317151633), c.435G>E (dbSNP:rs756956471), c.437Y>F (dbSNP:rs758213652)

Alternatively-spliced form: a FVII–activating protease–like protein, also known as the FVII alternative splice variant (FVII-ASV or FVIIa-like), has been characterized. This shorter isoform lacks the *C*-terminal serine protease domain but retains the signal peptide, Gla domain, and EGF-like domains. It does not show protease activity but can bind TF, potentially acting as a regulatory or decoy molecule that modulates TF–FVIIa activity and limits excessive coagulation. This alternatively spliced form shows low plasma concentrations; its precise physiological role is still under investigation, but it is thought to contribute to fine-tuning of coagulation and cell signaling.

Post-translational modifications:
- γ-carboxylation of specific glutamate residues in the N-terminal Gla domain (described above);
- N-linked glycosylation, primarily within the EGF-like domains and the serine protease domain; contribute to protein stability, plasma half-life, and proper secretion;
- signal peptide cleavage during translocation into the ER;
- disulfide bond formation between conserved cysteine residues that stabilize domain structure;
- proteolytic activation of FVII by cleavage at the Arg152–Ile153 bond

Fig. 2: Key structural elements of coagulation FVII

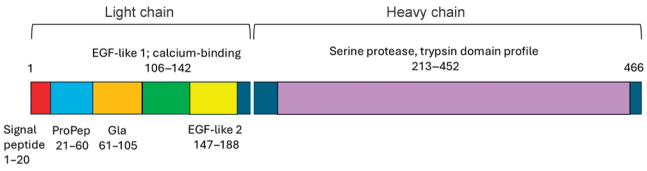
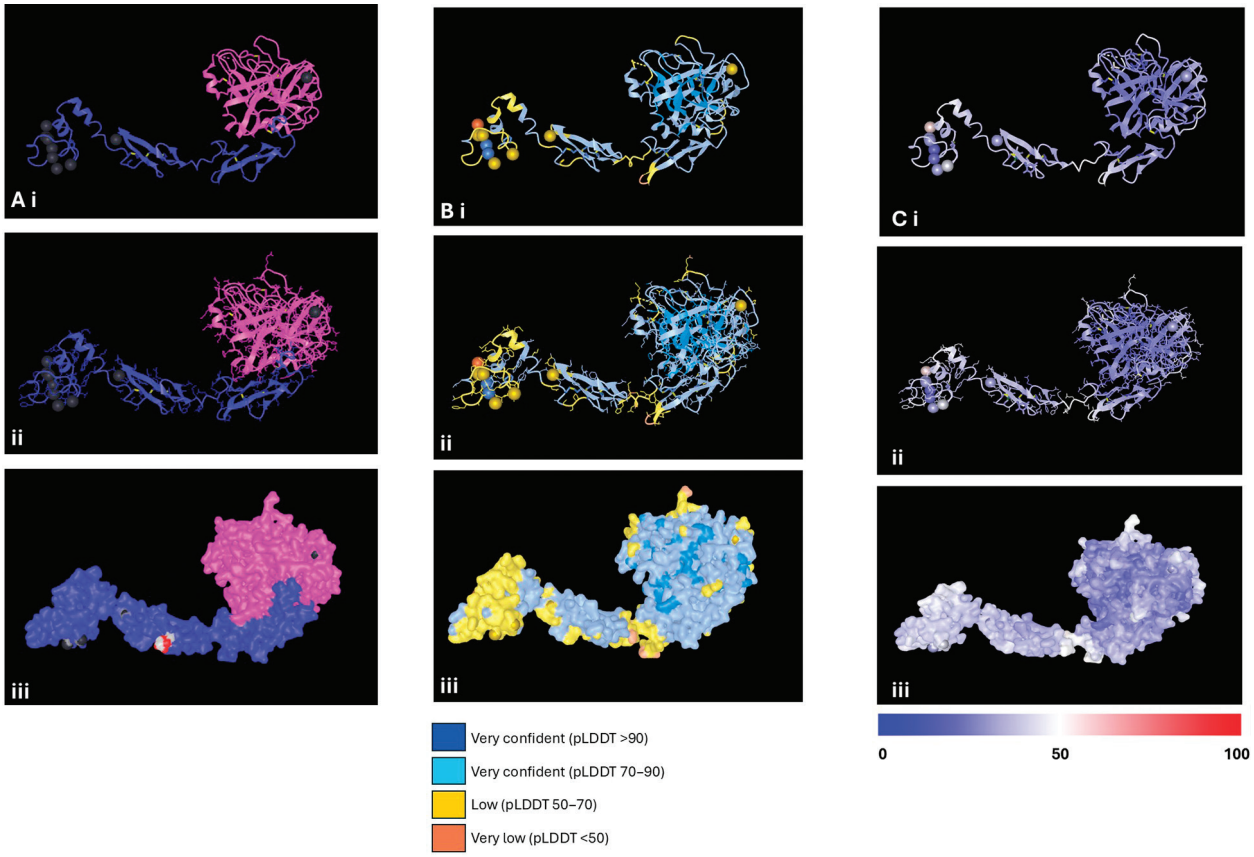
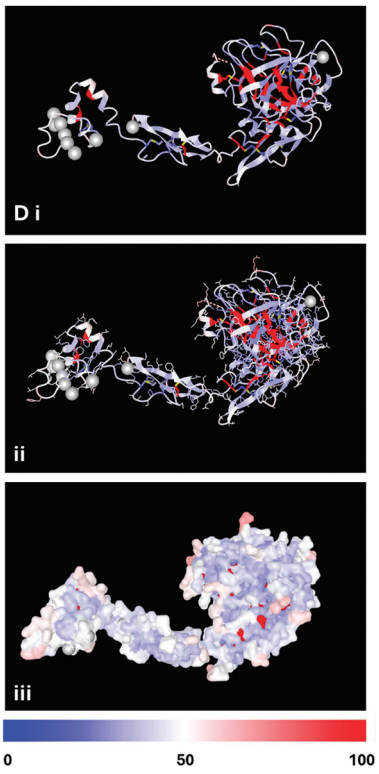


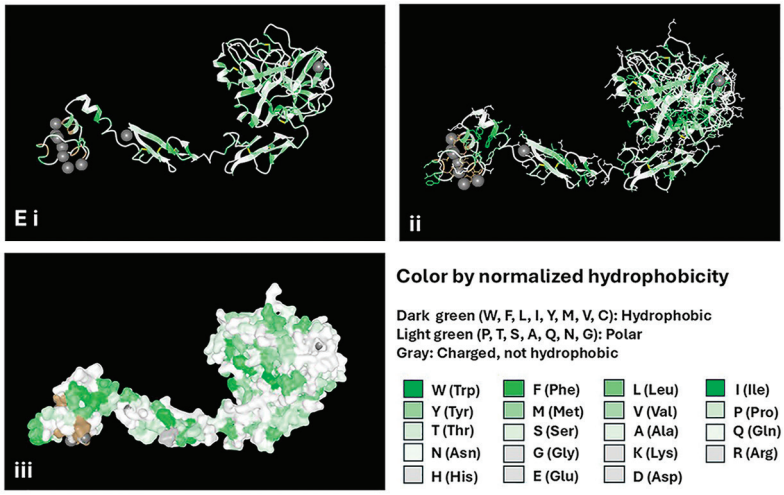
Fig. 3: Key structural elements and domains of coagulation FVII. Schematic diagram showing the light and heavy chains with known domains in the coagulation FVII. EGF, epidermal growth factor; Gla, *N*-terminal, vitamin K-dependent region containing 10 γ-carboxyglutamic acid residues that mediate membrane binding and complex formation with TF; ProPep, propeptide that undergoes vitamin K-dependent carboxylation prior to secretion into the blood

loops rich in Ca^{++} ions and phospholipids that interact with the Gla domain of FVII.[42,55] The protease domain of VIIa joins TF to form the active TF–VIIa complex.[56]

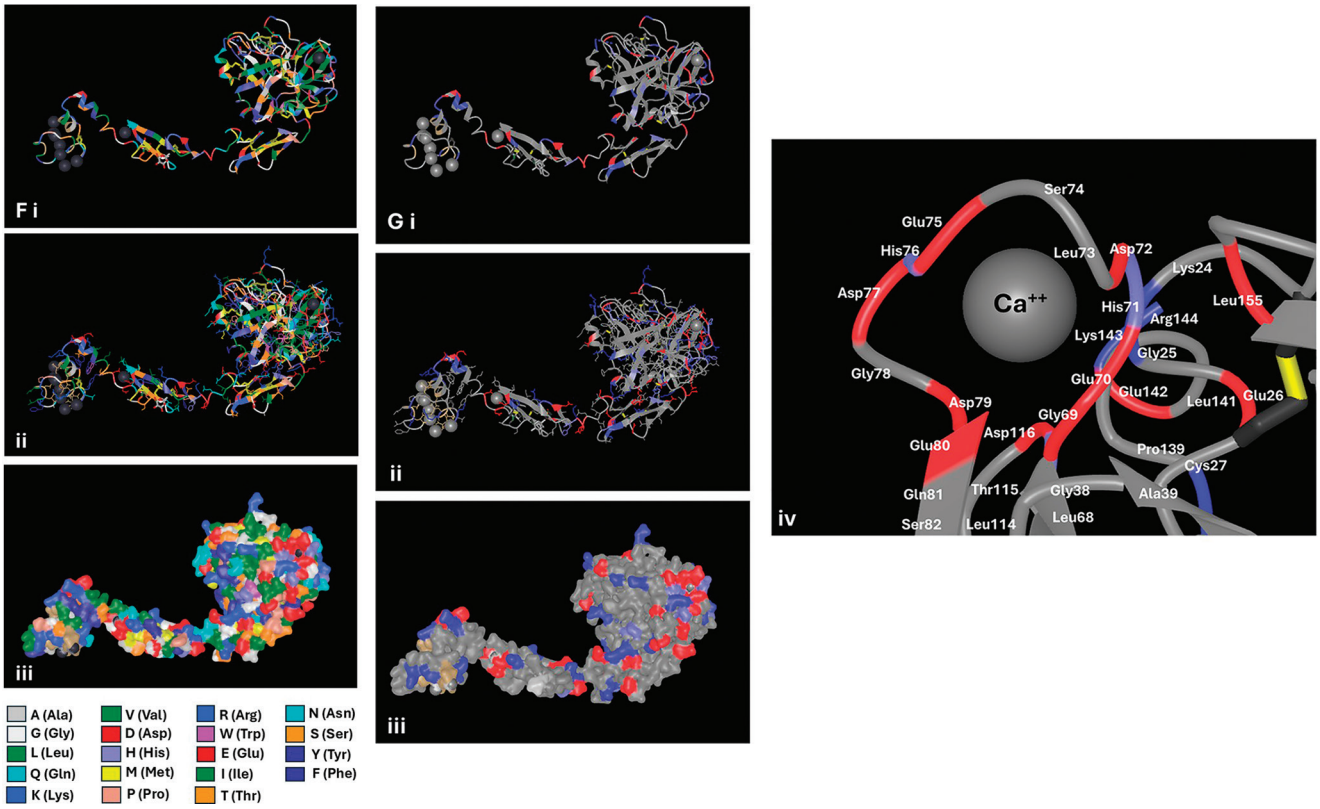
Endothelial damage due to tissue injury/inflammation can unblock the binding between the underlying TF and the circulating FVII. This binding activates FVII, and the TF–FVIIa complex then, in turn, activates FX and FIX, leading to thrombin generation and fibrin clot formation.[6,57] In addition, distinct from its role in coagulation, the TF–FVIIa complex can also stimulate inflammatory and stress-responsive signaling.[58] It activates protease-activated receptors (PAR-1 and PAR-2) on cell surfaces, inducing proinflammatory cytokines such as tumor necrosis factor (TNF); interleukin (IL)-6, IL-8, and IL-1β; adhesion molecules; oxidized lipids; and promoting leukocyte infiltration.[59–61] These mediators activate intracellular signaling cascades, including the NF-κB, mitogen-activated protein kinase pathways (ERK1/2, p38, and JNK), and AP-1.[62,63] These pathways, in turn, promote the expression of TF, resulting in feed-forward signaling loops.[64] Having reviewed the above information, it is also important to note that in some specific situations, FVIIa bound to the endothelial protein C receptor (EPCR) can trigger anti-inflammatory signaling in endothelial cells.[65]


A i
ii
iii
B i
ii
iii
C i
ii
iii
Very confident (pLDDT >90)
Very confident (pLDDT 70–90)
Low (pLDDT 50–70)
Very low (pLDDT <50)
0
50
100


D i
ii
iii
0
50
100


E i
ii
iii
Color by normalized hydrophobicity
Dark green (W, F, L, I, Y, M, V, C): Hydrophobic
Light green (P, T, S, A, Q, N, G): Polar
Gray: Charged, not hydrophobic
W (Trp)
F (Phe)
L (Leu)
I (Ile)
Y (Tyr)
M (Met)
V (Val)
P (Pro)
T (Thr)
S (Ser)
A (Ala)
Q (Gln)
N (Asn)
G (Gly)
K (Lys)
R (Arg)
H (His)
E (Glu)
D (Asp)

(Contd...)



Figs 4A to G: Factor VIIa. This figure shows three sequential illustrations of the FVIIa molecule. From top to bottom: (i) primary ribbon structures with the overall folds and organization of the protein backbone; alpha-helices are shown as coiled ribbons and beta-sheets as arrows; (ii) structure with side chains: The central alpha carbon of all amino acids carries unique aliphatic/aromatic side chains, the "R" groups, along with constituent amino, carboxyl, and hydrogen groups. These are not directly involved in the formation of peptide bonds between amino acids, but the size, shape, charge, and reactivity of R groups determine the polarity (hydrophilic/hydrophobic), acidity, basicity, and reactivity. Non-polar amino acids carry hydrophobic R groups that are primarily made of carbon and hydrogen. R groups in polar amino acids contain polar hydroxyls, thiols, or amides. Charged amino acids contain positively/negatively charged R groups; and (iii) molecular surface. These illustrations can be moved and manipulated within interactive 3D viewing programs such as iCn3D (details below).

(A) Factor VIIa is a heterodimer of an N-terminal light chain (pink; approximately 20 kDa, 152 amino acids) and a C-terminal heavy chain (blue; approximately 30 kDa, 254 residues). There is some uncertainty in the identity of the residue in the light chain that is depicted in white/red;

(B) Confidence in predicted protein structure. Predicted local distance difference test (pLDDT): It is a per-residue confidence metric used by AlphaFold2 and AlphaFold3 to estimate how well a computationally predicted 3D structure matches the actual protein structure. The color matrix below the figure shows the color coding for various levels of confidence in predictions;

(C) B-factor (or Debye-Waller factor, temperature factor, atomic displacement parameter) quantitates the uncertainty for each atom; a high B-factor reflects more vibration/disorder of atoms in proteins around their average positions. In this figure, color change from blue-to-white-to-red indicates increasing B factor of various amino acids;

(D) Solvent accessibility. Color change from blue-to-white-to-red indicates increasing solvent accessibility of various amino acids. The average accessible surface of residues in most folded proteins is around 20% relative to an unfolded state. A value of 35% suggests that the protein's surface is well-hydrated;

(E) Hydrophobicity. This figure adds to the evidence shown in panel (A). The predicted solvent-accessible surface area (SASA) is shown in a scale ranging from a deep green color at its low end to high white: (i–ii) primary ribbon structure and the structure with side-chains shows the green and white color residues as evenly distributed; (iii) solvent-accessible space-filling model predicts these surfaces as much whiter and hence, the hydrophobic residues green residues are buried away from the surface inside the core of the protein. We have used the SASA method to produce this illustration. Relative solvent accessible area (RSA)/SASA are standard measures to describe the degree of residue exposure in the protein surface. There are many methods for estimation of RSA/SASA that focus on the Cα atom-distance matrix and use deep learning methods; some of the existing RSA estimators are based on coordination numbers, half-sphere exposure, and SphereCon, one of the recognized RSA-estimation algorithms;

(F) Amino acid composition of the calprotectin heterodimer molecule. The amino acid color-coding is as shown below the figure; (G) Amino acid charge: (i and ii) showed a good overall balance of positively and negatively charged amino acid residues; (iii) the surface of the protein molecules showed more neutral/positively charged regions; (iv) a calcium ion (Ca^{2+}) was located inside the protein molecule close to negatively charged glutamic acid (Glu), aspartic acid (Asp), asparagine (Asn), and glycine (Gly) residues. Ca^{2+} may induce a significant conformational and charge alteration.

The base structures have been derived from the iCn3D (short for "I see in 3D") format, a web-based interactive tool for analysis of 3-dimensional macromolecular structures. This has been developed using the Web Graphics Library, a JavaScript Application Programming Interface to render 3D graphics in web browsers without requiring plugins. A JavaScript control and a shader code have been executed on the graphics processing unit for high-performance interactive graphics. These illustrations were prepared using data/tools provided on the web portals of the RCSB and NCBI PDBs, MMDB, GenBank, RefSeq, TPA, UniProtKB/Swiss-Prot database, PIR, PRF, and Microsoft PowerPoint, Microsoft Illustrator, and/or Adobe Photoshop.

Source: The structures in Panel A have been drawn from https://www.ncbi.nlm.nih.gov/Structure/icn3d/full.html?&mmdbid=107068&bu=1&showanno=1&source=full-feature. Panels 4B–G show features of the protein structure from https://www.ncbi.nlm.nih.gov/Structure/icn3d/full.html?&mmdbid=31344&bu=1&showanno=1&source=full-feature

A TF pathway inhibitor (TFPI) regulates the activity of this complex by forming a quaternary complex with the TF–FVIIa complex and FXa.[66,67] It regulates the extrinsic coagulation pathway through a precisely ordered molecular inhibition; TFPI is a multivalent Kunitz-type protease inhibitor composed of three Kunitz domains (K1–K3) and a highly basic *C*-terminal region.[68] The inhibitory process is initiated when the K2 domain binds and inhibits FXa, forming a TFPI–FXa complex.[67] This complex then engages the TF–FVIIa complex via the K1 domain, resulting in the formation of a quaternary TF–FVIIa–FXa–TFPI complex that effectively shuts down further factor X activation.[69] The K3 domain and *C*-terminal region mediate interactions with phospholipid surfaces, glycosaminoglycans, and lipoproteins, localizing TFPI to the endothelial surface and enhancing inhibitory efficiency.[70] Beyond anticoagulation, TFPI can influence cell signaling as TF–FVIIa–FXa complexes normally activate PAR-1 and PAR-2; TFPI disrupts this signaling axis, thereby linking molecular control of coagulation initiation with modulation of inflammatory and vascular responses.[67,71]

Quality of Blood Clots Induced by Recombinant Activated FVII (rFVIIa)

Studies have shown that rFVIIa-induced clots are physically and structurally different from a normal, physiological clot.[72,73] The higher, faster burst of thrombin can improve the strength of clots, which are localized and fibrin-rich with TF bound on damaged vascular subendothelium.[72,74] Histopathologically, these clots are relatively more dense, stable, and resistant to fibrinolysis.[72,75] These exhibit increased platelet contractile force, enhanced clot elastic modulus, and more dense fibrin networks, especially in FVIII/FIX deficiency.[72,73,76,77]

Evolution of FVII

Factor VII has been a highly conserved protein during evolution (Fig. 9). The evolutionary origins can be traced back to early jawed vertebrates, emerging approximately 485–419 million years ago during the Ordovician to Silurian periods.[78,79] During the Ordovician period, marine ecosystems diversified dramatically in an event known as the Great Ordovician Biodiversification Event (GOBE) with the expansion of invertebrates such as trilobites, brachiopods, and early echinoderms, alongside the emergence of the first jawed vertebrate ancestors.[80] This period ended with a mass extinction linked to global cooling and glaciation. The subsequent Silurian period saw a rapid biological recovery, highlighted by the radiation of jawed fishes, the establishment of complex reef systems, and the earliest evidence of terrestrial colonization by vascular plants and arthropods, laying foundational groundwork for modern ecosystems.[81] A vitamin K-dependent blood coagulation system first appeared during this period.[82] Gene duplication and specialization events in these early vertebrates gave rise to serine proteases like FVII, which later became conserved across mammals, including humans.[83] The basic structure and function of FVII have remained remarkably stable during this period of evolution.[29]

Factor VII shares a conserved modular architecture as in other coagulation proteases; there is an *N*-terminal Gla domain, two EGF-like domains, and a *C*-terminal region rich in positively charged residues.[84] The *C*-terminal regions mediate binding to endothelial surfaces, glycosaminoglycans, and lipoproteins, positioning TFPI at sites where TF-initiated coagulation occurs.[85] Comparative sequence analyses indicate strong conservation of residues required for Ca^{++}-dependent membrane binding, TF interaction, and catalytic activity, reflecting early functional constraint.[86] The evolution of a TF-responsive activation mechanism, including a circulating pool of partially active FVIIa, enabled rapid initiation of coagulation upon vascular injury.[29] Subtle lineage-specific variations in regulatory regions and activation loops fine-tuned FVII

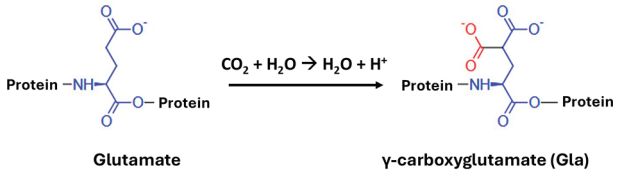


Fig. 6: γ-carboxyglutamate (Gla) is a product of a post-translational carboxylation of the γ-carbon of glutamate, giving the residue a strong negative charge

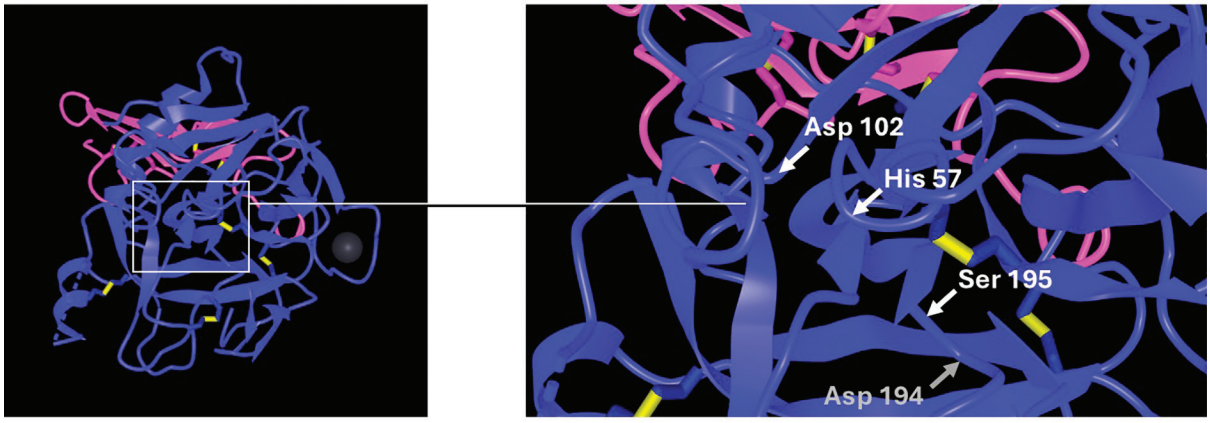


Fig. 5: Factor VIIa contains a serine protease catalytic site comprised of His57, Asp102, and Ser195 residues (white). Asp194 (gray) forms a stabilizing salt bridge. The *N*-terminal light chain are shown in pink, to contrast with the blue *C*-terminal heavy chain

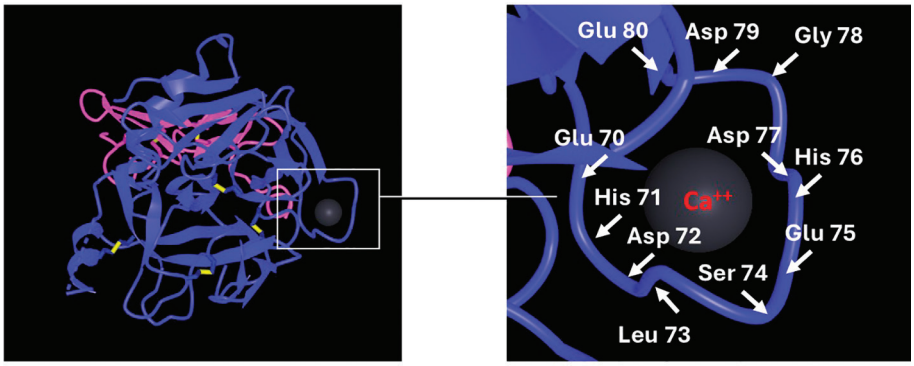
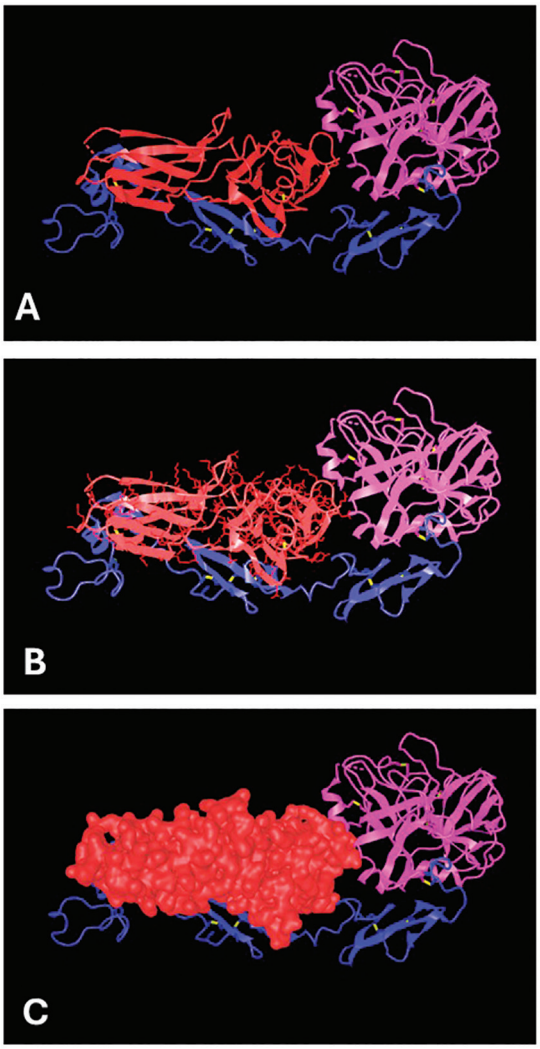
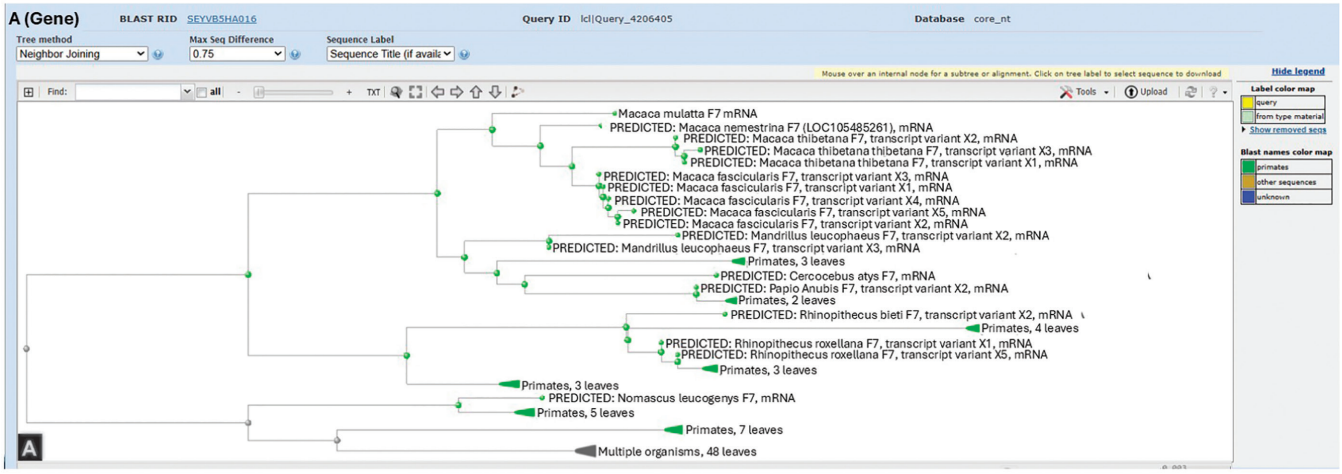
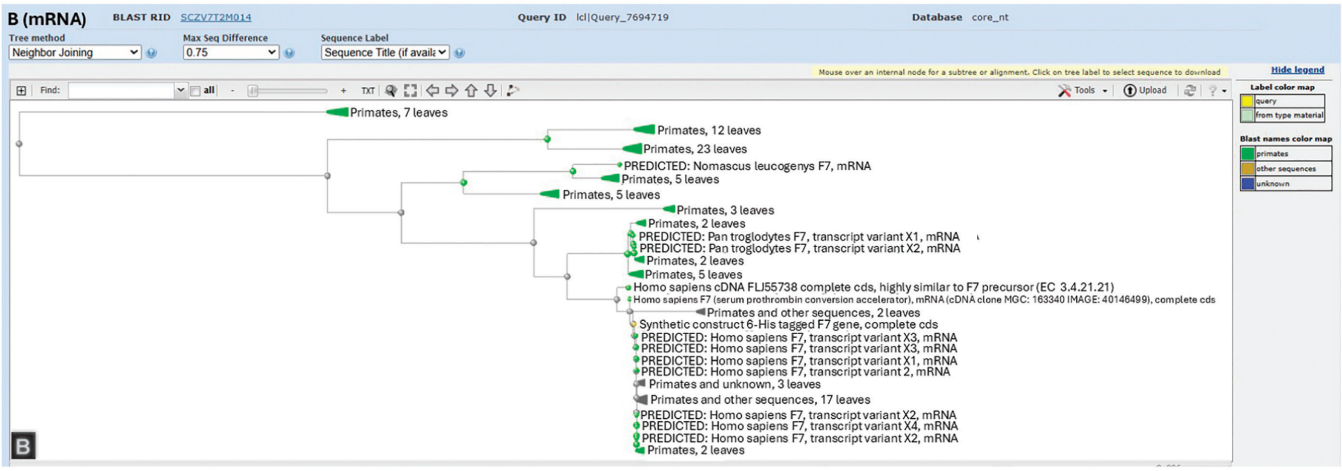


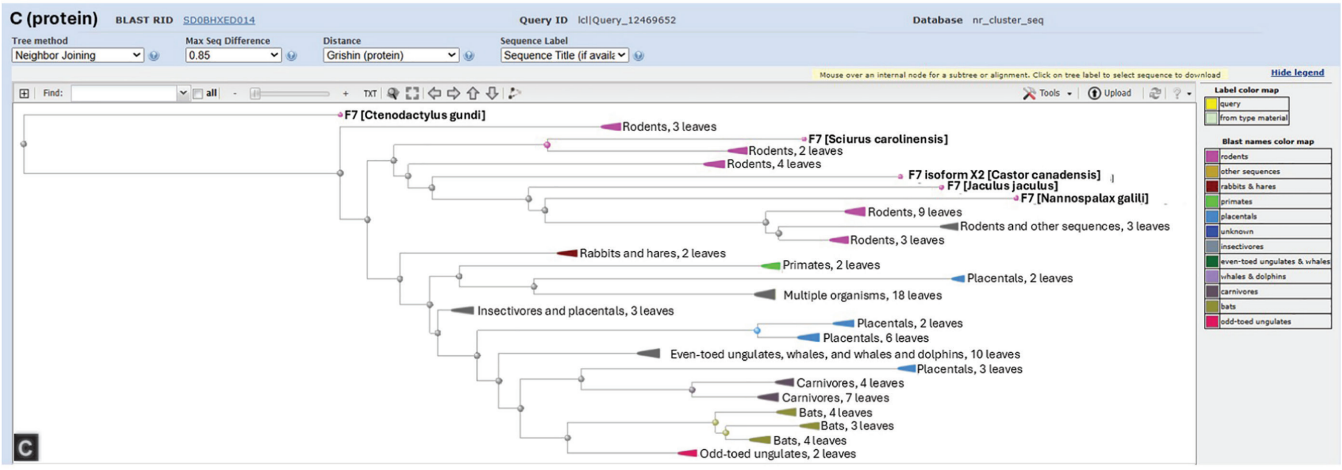
Fig. 7: The serine protease motif in FVIIa shows Ca^{++} ions located in its γ-carboxyglutamate (Gla) domain. Above illustration shows multiple Gla residues surrounding a Ca^{++} ion. The above illustration shows the *N*-terminal light chain in pink, whereas the *C*-terminal heavy chain is colored blue



Figs 8A to C: The relationship of FVIIa with the TF (red). All illustrations show the primary ribbon structures of FVIIa with alpha-helices as coiled ribbons and beta-sheets as bands. The *N*-terminal light chain of FVIIa is shown in pink and the *C*-terminal heavy chain in blue. (A–C) show the TF in increasing detail: (A) primary ribbon structures of TF with the overall organization of the protein backbones;
(B) TF structure with side chains; the central alpha carbon of all amino acids carries unique aliphatic/aromatic side chains, the "R" groups, along with constituent amino, carboxyl, and hydrogen groups. These are not directly involved in the formation of peptide bonds between amino acids, but the size, shape, charge, and reactivity of R groups determine the polarity (hydrophilic/hydrophobic), acidity, basicity, and reactivity. Non-polar amino acids carry hydrophobic R groups that are primarily made of carbon and hydrogen. R groups in polar amino acids contain polar hydroxyls, thiols, or amides; and
(C) the molecular surface of TF.
These illustrations can be moved and manipulated within interactive 3D viewing programs such as iCn3D. https://www.ncbi.nlm.nih.gov/Structure/icn3d/full.html?&mmdbid=107068&bu=1&showanno=1&source=full-feature

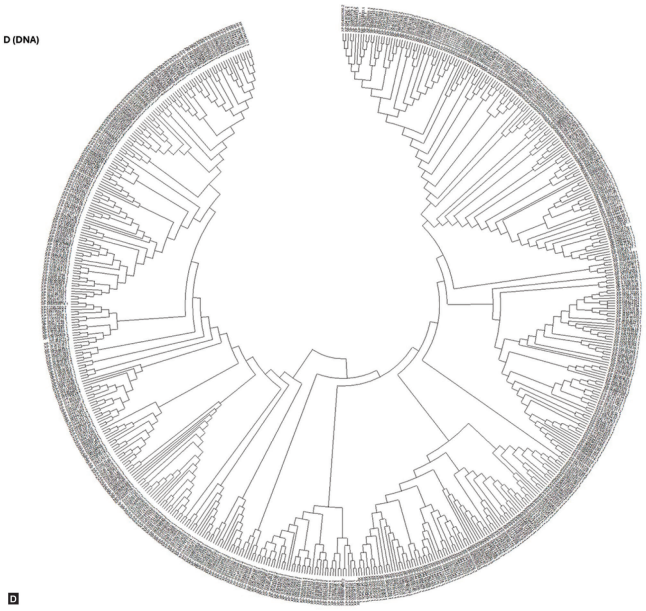

A (Gene)
BLAST RID SEYVB5HA016
Query ID lcl|Query_4206405
Database core_nt
Tree method
Neighbor Joining
Max Seq Difference
0.75
Sequence Label
Sequence Title (if availa
Mouse over an internal node for a subtree or alignment. Click on tree label to select sequence to download
Hide legend
Label color map
query
from type material
Show removed seqs
Blast names color map
primates
other sequences
unknown
Macaca mulatta F7 mRNA
PREDICTED: Macaca nemestrina F7 (LOC105485261), mRNA
PREDICTED: Macaca thibetana F7, transcript variant X2, mRNA
PREDICTED: Macaca thibetana thibetana F7, transcript variant X3, mRNA
PREDICTED: Macaca thibetana thibetana F7, transcript variant X1, mRNA
PREDICTED: Macaca fascicularis F7, transcript variant X3, mRNA
PREDICTED: Macaca fascicularis F7, transcript variant X1, mRNA
PREDICTED: Macaca fascicularis F7, transcript variant X4, mRNA
PREDICTED: Macaca fascicularis F7, transcript variant X5, mRNA
PREDICTED: Macaca fascicularis F7, transcript variant X2, mRNA
PREDICTED: Mandrillus leucophaeus F7, transcript variant X2, mRNA
PREDICTED: Mandrillus leucophaeus F7, transcript variant X3, mRNA
Primates, 3 leaves
PREDICTED: Cercocebus atys F7, mRNA
PREDICTED: Papio Anubis F7, transcript variant X2, mRNA
Primates, 2 leaves
PREDICTED: Rhinopithecus bieti F7, transcript variant X2, mRNA
Primates, 4 leaves
PREDICTED: Rhinopithecus roxellana F7, transcript variant X1, mRNA
PREDICTED: Rhinopithecus roxellana F7, transcript variant X5, mRNA
Primates, 3 leaves
Primates, 3 leaves
PREDICTED: Nomascus leucogenys F7, mRNA
Primates, 5 leaves
Primates, 7 leaves
Multiple organisms, 48 leaves
A


B (mRNA)
BLAST RID SCZV7T2M014
Query ID lcl|Query_7694719
Database core_nt
Tree method
Neighbor Joining
Max Seq Difference
0.75
Sequence Label
Sequence Title (if availa
Mouse over an internal node for a subtree or alignment. Click on tree label to select sequence to download
Hide legend
Label color map
query
from type material
Blast names color map
primates
other sequences
unknown
Primates, 7 leaves
Primates, 12 leaves
Primates, 23 leaves
PREDICTED: Nomascus leucogenys F7, mRNA
Primates, 5 leaves
Primates, 5 leaves
Primates, 3 leaves
Primates, 2 leaves
PREDICTED: Pan troglodytes F7, transcript variant X1, mRNA
PREDICTED: Pan troglodytes F7, transcript variant X2, mRNA
Primates, 2 leaves
Primates, 5 leaves
Homo sapiens cDNA FLJ55738 complete cds, highly similar to F7 precursor (EC 3.4.21.21)
Homo sapiens F7 (serum prothrombin conversion accelerator), mRNA (cDNA clone MGC: 163340 IMAGE: 40146499), complete cds
Primates and other sequences, 2 leaves
Synthetic construct 6-His tagged F7 gene, complete cds
PREDICTED: Homo sapiens F7, transcript variant X3, mRNA
PREDICTED: Homo sapiens F7, transcript variant X3, mRNA
PREDICTED: Homo sapiens F7, transcript variant X1, mRNA
PREDICTED: Homo sapiens F7, transcript variant 2, mRNA
Primates and unknown, 3 leaves
Primates and other sequences, 17 leaves
PREDICTED: Homo sapiens F7, transcript variant X2, mRNA
PREDICTED: Homo sapiens F7, transcript variant X4, mRNA
PREDICTED: Homo sapiens F7, transcript variant X2, mRNA
Primates, 2 leaves
B


C (protein)
BLAST RID SD0BHXED014
Query ID lcl|Query_12469652
Database nr_cluster_seq
Tree method
Neighbor Joining
Max Seq Difference
0.85
Distance
Grishin (protein)
Sequence Label
Sequence Title (if availa
Mouse over an internal node for a subtree or alignment. Click on tree label to select sequence to download
Hide legend
Label color map
query
from type material
Blast names color map
rodents
other sequences
rabbits & hares
primates
placentals
unknown
insectivores
even-toed ungulates & whales
whales & dolphins
carnivores
bats
odd-toed ungulates
F7 [Ctenodactylus gundi]
Rodents, 3 leaves
F7 [Sciurus carolinensis]
Rodents, 2 leaves
Rodents, 4 leaves
F7 isoform X2 [Castor canadensis]
F7 [Jaculus jaculus]
F7 [Nannospalax galili]
Rodents, 9 leaves
Rodents and other sequences, 3 leaves
Rodents, 3 leaves
Rabbits and hares, 2 leaves
Primates, 2 leaves
Placentals, 2 leaves
Multiple organisms, 18 leaves
Insectivores and placentals, 3 leaves
Placentals, 2 leaves
Placentals, 6 leaves
Even-toed ungulates, whales, and whales and dolphins, 10 leaves
Placentals, 3 leaves
Carnivores, 4 leaves
Carnivores, 7 leaves
Bats, 4 leaves
Bats, 3 leaves
Bats, 4 leaves
Odd-toed ungulates, 2 leaves
C

(Contd...)

(Contd...)



Figs 9A to D: Neighbor-Joining (NJ) phylogenetic trees showing aerial views of the evolution of F7 at (A) Gene; (B) mRNA; and (C) Protein levels. The NJ tree is an unrooted, distance-based depiction of iterative clustering of the most closely related taxa (species/sequences). This method minimizing the total branch length in estimating evolutionary divergence; the distance matrix is seen as input. There is some correction for unequal evolutionary rates. The branch lengths are proportional to evolutionary distance. From this figure, the mRNA could have been more conserved than the DNA or protein;
(D) Shows a detailed pie-chart phylogram down to the species level constructed with currently available data. The large number of branches could just be an artifact arising from the inclusion of more taxa, but may also indicate rapid evolutionary splitting and adaptive radiation due to new ecological opportunities/environmental changes. Branch lengths are still an estimation of the evolutionary changes, but the tips/nodes simultaneously display both divergence and distribution patterns

activity and specificity, reinforcing its central role as the molecular trigger of the extrinsic coagulation pathway in vertebrates.[1,45]

The evolution of TF is closely linked to the emergence of the vertebrate coagulation system and the development of a closed, high-pressure circulatory system. Comparative sequence analyses reveal strong conservation of residues involved in FVIIa docking and catalytic enhancement, indicating early optimization of the TF–FVIIa interface.[29] The acquisition of a transmembrane domain and short cytoplasmic tail enabled spatial restriction of TF activity to sites of vascular injury, while later evolutionary refinements allowed TF–FVIIa to participate in cell signaling via PARs.[37]

The TF–FVII-based extrinsic pathway provided a rapid and localized mechanism for hemostasis in response to vascular injury, offering a significant selective advantage as vertebrates evolved larger body sizes and more complex vasculature.[29] Structurally, TF is conserved as a transmembrane protein with extracellular fibronectin type III-like domains, reflecting its essential role in initiating coagulation.[53] Over evolutionary time, TF also acquired signaling functions through interactions with FVIIa and PARs, integrating coagulation with inflammation, immunity, and tissue repair, and highlighting its dual role as a hemostatic trigger and a signaling molecule.[87]

The evolution of TFPI in early vertebrates reflects the need for precise molecular control over the extrinsic coagulation pathway.[88] Tissue factor pathway inhibitor likely evolved in jawed vertebrates, evolving alongside TF and FVII as a counter-regulatory mechanism to limit excessive thrombin generation.[79] At the molecular level, TFPI arose through the incorporation and duplication of Kunitz-type protease inhibitor domains, a conserved inhibitory scaffold found across metazoans.[89] Subsequent evolutionary refinements, including a basic *C*-terminal region mediating endothelial surface localization, optimized TFPI for spatially restricted anticoagulant control.[90] Together, these adaptations position TFPI as a critical molecular brake on TF-initiated coagulation, ensuring hemostatic balance in vertebrates with high-pressure circulatory systems.[91]

Therapeutic Importance of rFVIIa

Recombinant FVIIa (eptacog alfa) has been in use for over the last two decades.[92,93] In the United States, the Food and Drug Administration (FDA)-approved rFVIIa is a vitamin K-dependent 406 amino-acid glycoprotein with a molecular mass of 50 kD.[94,95] It is structurally similar to human plasma-derived FVIIa.[96] It was originally developed for controlling bleeding in hemophilic patients who had inhibitors to FVIII or FIX.[97] It has also been used to treat bleeding in acquired bleeding disorders.[98]

There are regional differences in licensing and use in various countries:[99–101]

- United States FDA: Approved for hemophilia A or B with inhibitors, acquired hemophilia, congenital FVII deficiency, and Glanzmann's thrombasthenia with refractoriness to platelets.
- European Union (EMA): Similar to the US, but in May 2022, approved for severe postpartum hemorrhage if uterotonics are insufficient. In many European countries, it is also licensed for use in patients with Glanzmann's thrombasthenia.[95]
- Canada: More restricted; generally limited to congenital hemophilia with inhibitors, acquired hemophilia, and congenital FVII deficiency.

Table 1: Components of lyophilized recombinant FVII available for clinical use

Contents	*1.2 mg (60 KIU) vial*	*2.4 mg (120 KIU) vial*	*4.8 mg (240 KIU) vial*
rFVIIa	1,200 µg	2,400 µg	4,800 µg
Sodium chloride*	5.84 mg	11.68 mg	23.36 mg
Calcium chloride dihydrate*	2.94 mg	5.88 mg	11.76 mg
Glycylglycine	2.64 mg	5.28 mg	10.56 mg
Polysorbate 80	0.14 mg	0.28 mg	0.56 mg
Mannitol	60 mg	120 mg	240 mg

*per mg of rFVIIa: 0.44 mEq sodium, 0.06 mEq calcium

- Japan: Approved for hemophilia A/B with inhibitors, acquired hemophilia, congenital FVII deficiency, and Glanzmann's thrombasthenia.
- Off-label usage: Use for trauma, intracranial hemorrhage (ICH), and liver failure is widespread, but often "off-label" and varies significantly, with high usage in Australia and the US to stop life-threatening bleeding refractory to conventional treatment with fresh frozen plasma (FFP) and cryoprecipitate in adults, children and infants.[102] The most important challenge is the lack of randomized controlled trials in neonates.

Preparation and Storage

The gene for human FVII has been cloned and expressed in baby hamster kidney cells.[103] Recombinant activated FVII is secreted into the culture media (containing newborn calf serum) in its single-chain form and then proteolytically converted by autocatalysis to the active two-chain form, rFVIIa, during a chromatographic purification process. The concentrates are purified to remove any infectious agents. No human serum or other proteins are used in the production or formulation of most currently available commercial products. It is supplied in a sterile, white lyophilized powder in single-use vials. After reconstitution, it is administered intravenously as frequent boluses (every 2–4 hours) or as a continuous infusion.[104]

The components of each vial of lyophilized drug typically contain the following (Table 1):

Clinical Usage

Recombinant activated FVII was first developed for the treatment of inhibitor-complicated hemophilia.[105] Additional indications subsequently emerged, including its use in liver disease, platelet-related bleeding disorders, and in patients who bleed extensively after major surgery or trauma.[106] Factor VII-activated thrombin activates factors V, VIII, and XI, as well as platelets, thereby extending its impact into the intrinsic pathway of coagulation.[107,108] It also binds activated platelets at the site(s) of bleeding. In Europe, it has also been approved for post-surgical bleeding, hemophilia home treatment, FVII deficiency and Glanzmann thrombasthenia. Factor VII is increasingly being viewed as a "universal hemostatic agent" as it has been used in many non-hemophilic conditions, including congenital FVII deficiencies, quantitative and qualitative platelet disorders, hepatic failure, liver transplantation, major surgery and trauma.

In neonates, rFVIIa (such as eptacog alfa, marketed as NovoSeven) is used off-label for severe, refractory hemorrhage, and dosing is based largely on case reports and small series rather than randomized trials. The most commonly reported regimen is an intravenous bolus of 90–120 µg/kg, which may be repeated every 2–4 hours depending on clinical response and ongoing bleeding. Some clinicians have used lower initial doses (40–60 µg/kg) or higher doses (up to 150–180 µg/kg) in refractory cases, although an optimal dose has not been clearly established.[99,109,110] Before administration, correction of thrombocytopenia, hypofibrinogenemia, acidosis, and hypocalcemia is recommended to maximize efficacy and potentially reduce thrombotic risk. Given limited safety data and the potential for thromboembolic complications, dosing should be individualized and reserved for life-threatening bleeding unresponsive to standard therapy.

Neonates have naturally low levels of vitamin K-dependent factors, including FVII, which typically reach adult values within 6 months, but sometimes not until 16 years. Congenital FVII deficiency in newborns is a rare, autosomal recessive disorder that can present as life-threatening ICH or umbilical bleeding. Gene mutations such as FVII rs6046 polymorphism, and intra-uterine growth restriction, with certain alleles increasing the risk.[111,112] Interestingly, hepatocyte growth factor (HGF) and FVII are closely linked in liver homeostasis, with HGF expression directly correlating with FVII transcription during liver regeneration and in response to injury.[113,114] We are currently studying HGF as an early predictor of bleeding manifestations in critically ill neonates.

Evidence regarding the impact of rFVIIa on maternal and fetal safety is limited to case reports and small series, since pregnant women are excluded from most clinical trials.[115] Treatment of pregnant women with rFVIIa should be reserved for life-threatening hemorrhage to conventional obstetric hemostatic measures, such as uterotonics, surgical control of bleeding, blood component replacement, and correction of coagulopathy.[116,117] Recombinant activated FVIIa can be life-saving in severe, refractory postpartum hemorrhage but concerns remain regarding potential maternal venous or arterial thromboembolic complications and risks to uteroplacental circulation, although documented fetal adverse effects are rare.[118] As pregnancy is a hypercoagulable state in itself, use of rFVIIa during gestation/ peripartum period requires multidisciplinary decision-making, individualized risk-benefit assessment, and close monitoring.[119] Routine use in pregnancy is not recommended.

Hemophilia

Recombinant activated FVII has been approved by the FDA and in Europe for use in hemophilia A and B patients who have inhibitory antibodies against FVIII or FIX.[120,121] Recombinant activated FVIIa acts by enhancing thrombin generation by both TF-dependent and TF-independent mechanisms; the effects are largely independent of FVIII or FIX, and it is effective in patients who have developed inhibitors to FVIII and FIX.[122] The main disadvantage is short half-life, which necessitates frequent infusions at short intervals. For hemophilia A or B patients with inhibitors, the FDA recommends a standard dose of 90 µg/kg given as 2-hourly intravenous boluses until the bleeding ceases. No transmission of infectious agents has been reported, and thrombotic events are rare.

Alternative dosing regimens have been explored for patients with inhibitors.[123] A thrombin burst can be optimized at an rFVIIa concentration of 150 nM. This is achieved by dosing rFVIIa at

300 µg/kg every 6 hours. The two doses have been shown to have equal hemostatic efficacy, with no additional safety issues. Obviously, the high-dose regimen was reported by patients and families as more convenient.

Cardiopulmonary Bypass (CPB)

Cardiac surgery with CPB is routinely performed in neonates who require early surgical repair of congenital heart diseases.[124,125] Bleeding after the procedure is a serious complication of congenital cardiac surgery and often requires significant transfusion of blood products to achieve hemostasis.[126] Because neonates have immature coagulation system, factors such as massive hemodilution from large circuit primes or extensive suture lines that accompany complex congenital cardiac repairs can potentiate bleeding. In neonates, the half -life of rFVIIa is shorter than in adults, possibly due to faster clearance, and higher doses are often needed to achieve hemostasis.[127]

High doses of rFVIIa are postulated to act via two mechanisms. It can directly activate FX on the surface of activated platelets. During or after cardiac surgery, rFVIIa can also increase the concentrations of circulating FVIIa/TF complexes to activate FIX and FX.[128] Both mechanisms can enhance thrombin generation at the site of injury and facilitate the formation of fibrin clots.[122] The evidence for the use of rFVIIa in neonates is limited, but existing studies in neonates undergoing CPB show that it can reduce the need for packed red blood cells (PRBCs), platelets, FFP, and cryoprecipitate.[109] Recombinant activated FVIIa administration significantly reduced the prothrombin time (PT).[129,130]

The assessment of the efficacy of rFVIIa in neonates with uncontrolled bleeding post-CPB has several limitations. First, data are limited, including the lack of monitoring parameters other than PT values.[109] Dosing remains uncertain. Additionally, rFVIIa activity is influenced by pH and temperature. Many critically ill neonates are hypothermic or acidotic, which may influence the effectiveness of rFVIIa. However, no mortality benefit has been demonstrated. There is increasing, reassuring evidence about the efficacy of rFVIIa in controlling excessive bleeding in patients undergoing cardiac surgery (Table 1).[131] However, there is a need for caution when using rFVIIa with ECMO circuits.

Refractory Hemorrhage in Infants

Recombinant FVIIa has been used "off-label" to treat critical bleeding refractory to conventional replacement therapy such as FFP and cryoprecipitate in adults, children and infants.[132] However, reports on the use in neonates and particularly premature neonates are not well defined. A cohort of newborns with rFVIIa showed 65–70% had a good response with a mean reduction in transfusions for red blood cells, platelets, FFP and cryoprecipitate.[109,133]

Premature and critically ill neonates receiving intensive care may have uncontrolled bleeding due to various causes.[99] The common causes can be disseminated intravascular coagulation (DIC), post-surgical hemorrhage, ICH, gastrointestinal hemorrhage, pulmonary hemorrhage and trauma.[134] A case series by Hünseler et al. has documented three cases of life-threatening bleeding (pulmonary, gastrointestinal and subgaleal bleeding) in two term newborns and one premature infant.[135] These patients received vitamin K, FFP, and platelets, but there was no effect on the extent of bleeding. Then, rFVIIa intravenous bolus was given in a dose range of 90–200 µg/kg, which led to quick control of bleeding.[135] There was a clinically significant hemostatic effect observed with no side effects.

The management of severe coagulopathies in infants can be challenging, especially if the use of FFP is contraindicated or limited.[136] Therefore, the use of rFVII has shown hemostatic benefit in infants who are unresponsive to FFP, platelet concentrates, or prothrombin complex concentrates.[137–143] Early case reports have also shown efficacy in infants with pulmonary hemorrhage.[144–146] The importance of using rFVIIa in neonates has been shown, with encouraging results, although there is a need for randomized trials.

A retrospective data analyzing 29 neonates with intractable bleeding or severe coagulation disturbances received 100 µg/kg of rFVIIa per intravenous bolus as a rescue procedure after other interventions failed to achieve hemostasis.[147] These data showed that rFVIIa can be beneficial in early intervention as rescue therapy without notable adverse events. These findings suggest that early intervention with rFVIIa may be considered in neonates with serious bleeding and coagulation disorders.

Necrotizing Enterocolitis (NEC)

Recombinant activated FVII can help manage post-operative spontaneous hepatic hemorrhage in patients with NEC.[148–151] The actual cause of this complication remains unknown and may be multifactorial, like retractor-induced trauma or excess fluid administration, both before and during surgery. Optimal dosing remains uncertain, but 90–400 µg/kg has been administered once or more. Some infants with multi-system organ failure complicated by persistent peritonitis, intra-abdominal abscesses, septicemia, and coagulopathy have been treated with 2 doses of rFVIIa. Treatment of focal hemorrhages has been more successful than that of multifocal lesions. The likely impact of prophylactic administration of rFVII before surgery is unclear. The ready availability of rFVIIa and other blood products in high-risk infants supports this approach.

Von Willebrand Disease

Factor VIIa has been used in those patients with antibodies to von Willebrand factor (VWF) or due to complications such as angiodysplasia who do not respond to conventional therapy.[152] There is limited evidence as to the use of FVIIa in neonates with vWF disease.

Neonatal Thrombocytopenia

Platelets of newborn infants exhibit impaired function in *in vitro* aggregation measurements.[153] Despite these impairments, the overall phospholipid concentration on their platelet membranes is similar to that of adult platelets.[154] The thrombin generation is also similar to that of adults due to comparable phospholipid composition.[155] Infants with thrombocytopenia are at a significant bleeding risk and need to be treated in NICU, which is even more frequent and severe in preterm babies. If bleeding occurs at platelet counts below 20,000/µL, then platelet concentrates are given to increase the counts.[156] If there is any case of refractory bleeding, rFVIIa is a therapeutic option. However, due to the fragile neonatal hemostatic system, there is an increased risk of thrombosis.[157,158]

Congenital FVIIa Deficiency

Intracranial hemorrhage is considered the most common cause of death in newborns with congenital FVIIa deficiency.[159] Recombinant activated FVIIa has been used effectively to treat ICH in newborns with severe FVIIa deficiency (<1%).[160] Two case reports showed infants presented with convulsions, poor feeding and prolonged PT. Along with therapy, they also received a prophylactic regimen. As

the bleeding recurred, the dose was increased from 20 to 30 µg/kg and indwelling central lines were placed due to poor venous access. Both infants showed improved hemostatic control.[161] Another infant with FVIIa levels at 0% was successfully treated with rFVIIa, maintaining effective hemostasis without hypercoagulation.[162] Recombinant activated FVIIa has also been used in a newborn with ICH due to congenital FVIIa deficiency who presented with ecchymoses. Intracranial hemorrhage was diagnosed in sonographic screening for any internal hemorrhage(s). Imaging of asymptomatic newborns with FVIIa deficiency would pre-emptively detect large asymptomatic hemorrhages and prevent any fatalities.[163] Recombinant activated FVII has been administered prophylactically to prevent ICH in a few asymptomatic newborns with FVIIa deficiency with a weekly dose of 30 µg/kg; these doses were well-tolerated.[101,164–167]

Adverse Effects

Recombinant activated FVII has been used in neonates primarily as rescue therapy for severe, refractory hemorrhage.[99,109,110] Because neonatal hemostasis is developmentally distinct, pharmacologic doses of rFVIIa may generate supraphysiologic thrombin and potentially overcome endogenous regulatory mechanisms. Available evidence, largely derived from case series and small observational studies, suggests that rFVIIa can reduce bleeding and transfusion requirements in selected infants; however, its safety profile warrants caution.[99,109,110] Because neonates with coagulopathies and/or bleeding frequently have indwelling catheters and are extremely ill, they are also at risk for thrombotic events. Larger studies are needed to determine the frequency of such thrombotic events in neonates. Thromboembolic complications, such as catheter-associated thrombosis, intracardiac thrombus, and arterial or venous events, have been reported, with estimated event rates ranging from approximately 5–15%, particularly in extremely preterm or critically ill neonates with central lines, sepsis, or DIC.[110,168] Some existing data show thrombotic events in neonates with bleeding or coagulopathies as around 7%, whether or not they were treated with FFP or rFVIIa.[110,168] Importantly, no clear survival benefit has been demonstrated.[99,109,110] Therefore, rFVIIa should generally be reserved for life-threatening bleeding unresponsive to optimal conventional management, with careful multidisciplinary assessment and vigilant monitoring for thrombotic complications.

In adult patients, there is a clear need to evaluate each case cautiously before off-label use of rFVIIa. Recombinant activated FVIIa can increase the risk of thrombotic complications (myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis) in adults who do not have a congenital bleeding disorder.[105,169] A study showed a 4.3% rate of thrombosis with off-label use, with the highest rate being in neonates.[170] Thrombosis at locations other than the target bleeding site is biologically plausible.[110] *In vitro* studies show that high levels of FVII *in vitro* can accelerate thrombin generation even in the absence of TF.[75] Overall, rFVIIa might be more thrombogenic in patients without hemophilia and in patients with clinical conditions predisposing to thrombosis, such as surgery, liver failure, congestive heart failure, than in patients with hemophilia with inhibitor antibodies.[171,172] There is a need to adopt a cautious approach for off-label use of rFVIIa and restrict it to only when hemorrhages have not responded to transfusion or other conventional therapy, or in specific conditions such as traumatic and postpartum hemorrhages.[96]

The most-concerning adverse post-operative event in neonates after CPB, after administering rFVIIa, is thrombosis.[173] It has been noted in neonates who were placed on ECMO after CPB.[174] These neonates may express TF in areas far beyond the local source of bleeding and are therefore at risk of generalized thrombosis.[109]

Conclusions

The hemostatic agent rFVIIa is generally well tolerated and appears safe and appears safe, and efficacious in neonates.[94,175] It can play a key role not only to amplify the process of coagulation through enhanced thrombin generation, but also to down-regulate fibrinolysis as well.[176] The thrombin generation rate on thrombin-activated platelet surfaces facilitates full activation of thrombin-activable fibrinolytic inhibitor and of factor XIII, promoting the formation of hemostatic plugs with tight fibrin structures that are resistant to premature lysis.[177]

In addition to being approved for refractory bleeding and severe coagulation disorders in neonates, rFVIIa has also been approved for use in patients with Glanzmann's thrombasthenia, with antibodies to GP IIb/IIIa and/or human leukocyte antigen and past or present refractoriness to platelet transfusions.[178,179] It has also been expanded for its use in trauma and surgery-induced coagulopathy and for acute intracerebral hemorrhage.[180] However, the majority of studies were conducted in adult patients, not in infants and children.[152]

A retrospective cohort study (2005–2008)[129] reported that treating critically ill infants with severe acute hemorrhage with rFVIIa at doses of 90 µg/kg improved coagulation studies and decreased the need for plasma transfusions. The authors concluded that rFVIIa can be used as an addition to current treatment modalities for refractory hemorrhage in infants. Other studies have also shown a large increase in the use of rFVIIa in patients without hemophilia in recent years.[96] Nevertheless, the use of rFVIIa for off-label indications is growing significantly in both the number of patients and in their total use of rFVIIa.[105]

The FDA has limited its approval for the use of rFVIIa since 1999, but there have been many case series and reports suggesting potent pro-coagulant benefits for patients with bleeding disorders not included in the FDA endorsement.[96] There remains a need for randomized controlled clinical trials (RCCTs) to evaluate the safety and efficacy of rFVIIa for indications other than genetic FVII deficiencies.[152] The rFVIIa group may have shown more thromboembolic events than placebo, but these findings cannot be directly extrapolated to neonates who do not have coronary, cerebral or other atherosclerotic disease and could therefore be at a lower risk of harmful thrombi after receiving rFVIIa.

References

1. Bernardi F, Mariani G. Biochemical, molecular and clinical aspects of coagulation factor VII and its role in hemostasis and thrombosis. Haematologica 2021;106(2):351–362. DOI: 10.3324/haematol.2020.248542.
2. Park S, Park JK. Back to basics: The coagulation pathway. Blood Res 2024;59(1):35. DOI: 10.1007/s44313-024-00040-8.
3. Shah AM, Kisiel W, Foster DC, et al. Manipulation of the membrane binding site of vitamin K-dependent proteins: Enhanced biological function of human factor VII. Proc Natl Acad Sci U S A 1998;95(8):4229–4234. DOI: 10.1073/pnas.95.8.4229.
4. Stojanovski BM, Di Cera E. Comparative sequence analysis of vitamin K-dependent coagulation factors. J Thromb Haemost 2022;20(12):2837–2849. DOI: 10.1111/jth.15897.

5. Vadivel K, Bajaj SP. Structural biology of factor VIIa/tissue factor initiated coagulation. Front Biosci (Landmark Ed) 2012;17(7):2476–2494. DOI: 10.2741/4066.
6. Mackman N. The role of tissue factor and factor VIIa in hemostasis. Anesth Analg 2009;108(5):1447–1452. DOI: 10.1213/ane.0b013e31819bceb1.
7. Wolberg AS, Campbell RA. Thrombin generation, fibrin clot formation and hemostasis. Transfus Apher Sci 2008;38(1):15–23. DOI: 10.1016/j.transci.2007.12.005.
8. Frandsen TF, Eriksen MB, Hammer DMG, et al. Using Embase as a supplement to PubMed in Cochrane reviews differed across fields. J Clin Epidemiol 2021;133:24–31. DOI: 10.1016/j.jclinepi.2020.12.022.
9. Burnham JF. Scopus database: A review. Biomed Digit Libr 2006;3:1. DOI: 10.1186/1742-5581-3-1.
10. Fremer E. Understanding MeSH for literature searches. JAMA 1995;273(3):184; author reply 184-185. DOI: 10.1001/jama.1995.03520270018013.
11. McVey JH, Boswell E, Mumford AD, et al. Factor VII deficiency and the FVII mutation database. Hum Mutat 2001;17(1):3–17. DOI: 10.1002/1098-1004(2001)17:1<3::AID-HUMU2>3.0.CO;2-V.
12. Tirincsi A, Sicking M, Hadzibeganovic D, et al. The molecular biodiversity of protein targeting and protein transport related to the endoplasmic reticulum. Int J Mol Sci 2021;23(1). DOI: 10.3390/ijms23010143.
13. Hao Z, Jin DY, Stafford DW, et al. Vitamin K-dependent carboxylation of coagulation factors: Insights from a cell-based functional study. Haematologica 2020;105(8):2164–2173. DOI: 10.3324/haematol.2019.229047.
14. Wei FF, Trenson S, Verhamme P, et al. Vitamin K-dependent matrix gla protein as multifaceted protector of vascular and tissue integrity. Hypertension 2019;73(6):1160–1169. DOI: 10.1161/HYPERTENSIONAHA.119.12412.
15. Roumeliotis S, Dounousi E, Eleftheriadis T, et al. Association of the inactive circulating matrix gla protein with vitamin k intake, calcification, mortality, and cardiovascular disease: A review. Int J Mol Sci 2019;20(3):628. DOI: 10.3390/ijms20030628.
16. Peyvandi F, Carew JA, Perry DJ, et al. Abnormal secretion and function of recombinant human factor VII as the result of modification to a calcium binding site caused by a 15-base pair insertion in the F7 gene. Blood 2001;97(4):960–965. DOI: 10.1182/blood.v97.4.960.
17. Hagen FS, Gray CL, O'Hara P, et al. Characterization of a cDNA coding for human factor VII. Proc Natl Acad Sci U S A 1986;83(8):2412–2416. DOI: 10.1073/pnas.83.8.2412.
18. Shahbazi S, Mahdian R. Factor VII gene defects: Review of functional studies and their clinical implications. Iran Biomed J 2019;23(3):165–174. DOI: 10.29252/.23.3.165.
19. Monroe DM, Key NS. The tissue factor-factor VIIa complex: Procoagulant activity, regulation, and multitasking. J Thromb Haemost 2007;5(6):1097–1105. DOI: 10.1111/j.1538-7836.2007.02435.x.
20. Muller MP, Morrissey JH, Tajkhorshid E. Molecular view into preferential binding of the factor VII gla domain to phosphatidic acid. Biochemistry 2022;61(16):1694–1703. DOI: 10.1021/acs.biochem.2c00266.
21. Pike AC, Brzozowski AM, Roberts SM, et al. Structure of human factor VIIa and its implications for the triggering of blood coagulation. Proc Natl Acad Sci U S A 1999;96(16):8925–8930. DOI: 10.1073/pnas.96.16.8925.
22. Nedergaard H, Vestergaard S, Jensen PT, et al. In vitro stability of lyophilized and reconstituted recombinant activated factor VII formulated for storage at room temperature. Clin Ther 2008;30(7):1309–1315. DOI: 10.1016/s0149-2918(08)80055-0.
23. Broze GJ Jr, Majerus PW. Purification and properties of human coagulation factor VII. J Biol Chem 1980;255(4):1242–1247. PMID: 7354023.
24. Lins L, Thomas A, Brasseur R. Analysis of accessible surface of residues in proteins. Protein Sci 2003;12(7):1406–1417. DOI: 10.1110/ps.0304803.
25. Mbaye MN, Hou Q, Basu S, et al. A comprehensive computational study of amino acid interactions in membrane proteins. Sci Rep 2019;9(1):12043. DOI: 10.1038/s41598-019-48541-2.
26. Latour RA. Fundamental principles of the thermodynamics and kinetics of protein adsorption to material surfaces. Colloids Surf B Biointerfaces 2020;191:110992. DOI: 10.1016/j.colsurfb.2020.110992.
27. Leonard BJ, Clarke BJ, Sridhara S, et al. Activation and active site occupation alter conformation in the region of the first epidermal growth factor-like domain of human factor VII. J Biol Chem 2000;275(45):34894–34900. DOI: 10.1074/jbc.M001166200.
28. Ndonwi M, Broze G Jr, Bajaj SP. The first epidermal growth factor-like domains of factor Xa and factor IXa are important for the activation of the factor VII–tissue factor complex. J Thromb Haemost 2005;3(1):112–118. DOI: 10.1111/j.1538-7836.2004.01051.x.
29. Beeler DL, Aird WC, Grant MA. Evolutionary conservation of the allosteric activation of factor VIIa by tissue factor in lamprey. J Thromb Haemost 2018;16(4):734–748. DOI: 10.1111/jth.13968.
30. Wouters MA, Rigoutsos I, Chu CK, et al. Evolution of distinct EGF domains with specific functions. Protein Sci 2005;14(4):1091–103. DOI: 10.1110/ps.041207005.
31. Wildgoose P, Jorgensen T, Komiyama Y, et al. The role of phospholipids and the factor VII Gla-domain in the interaction of factor VII with tissue factor. Thromb Haemost 1992;67(6):679–685. PMID: 1509409.
32. Soriano-Garcia M, Padmanabhan K, de Vos AM, et al. The calcium ion and membrane binding structure of the Gla domain of calcium-prothrombin fragment 1. Biochemistry 1992;31(9):2554–2566. DOI: 10.1021/bi00124a016.
33. Muller MP, Mortenson A, Sedzro JC, et al. Membrane-bound model of the ternary complex between factor VIIa/tissue factor and factor X. Blood Adv 2025;9(4):729–740. DOI: 10.1182/bloodadvances.2024014845.
34. Morrissey JH, Tajkhorshid E, Sligar SG, et al. Tissue factor/factor VIIa complex: Role of the membrane surface. Thromb Res 2012;129 Suppl 2(Suppl 2):S8–10. DOI: 10.1016/j.thromres.2012.02.019.
35. Persson E, Olsen OH, Ostergaard A, et al. Ca^{2+} binding to the first epidermal growth factor-like domain of factor VIIa increases amidolytic activity and tissue factor affinity. J Biol Chem 1997;272(32):19919–19924. DOI: 10.1074/jbc.272.32.19919.
36. Kelly CR, Dickinson CD, Ruf W. Ca^{2+} binding to the first epidermal growth factor module of coagulation factor VIIa is important for cofactor interaction and proteolytic function. J Biol Chem 1997;272(28):17467–17472. DOI: 10.1074/jbc.272.28.17467.
37. Rao LVM, Pendurthi UR. Tissue factor-factor VIIa signaling. Arterioscler Thromb Vasc Biol 2005;25(1):47–56. DOI: 10.1161/01.ATV.0000151624.45775.13.
38. Madsen JJ, Persson E, Olsen OH. The intricate allostery in factor VIIa: Triggering the trigger. J Thromb Haemost 2025;23(1):1–10. DOI: 10.1016/j.jtha.2024.08.026.
39. Raman S, Taylor N, Genuth N, et al. Engineering allostery. Trends Genet 2014;30(12):521–528. DOI: 10.1016/j.tig.2014.09.004.
40. Chu AJ. Tissue factor, blood coagulation, and beyond: An overview. Int J Inflam 2011;2011:367284. DOI: 10.4061/2011/367284.
41. Kamikubo Y, Mendolicchio GL, Zampolli A, et al. Selective factor VIII activation by the tissue factor-factor VIIa-factor Xa complex. Blood 2017;130(14):1661–1670. DOI: 10.1182/blood-2017-02-767079.
42. Rao LV, Pendurthi UR. Regulation of tissue factor coagulant activity on cell surfaces. J Thromb Haemost 2012;10(11):2242–2253. DOI: 10.1111/jth.12003.
43. Goettig P, Brandstetter H, Magdolen V. Surface loops of trypsin-like serine proteases as determinants of function. Biochimie 2019;166:52–76. DOI: 10.1016/j.biochi.2019.09.004.
44. Di Cera E. Serine proteases. IUBMB Life 2009;61(5):510–515. DOI: 10.1002/iub.186.
45. Sorensen AB, Madsen JJ, Svensson LA, et al. Molecular basis of enhanced activity in factor VIIa-trypsin variants conveys insights into tissue factor-mediated allosteric regulation of factor VIIa activity. J Biol Chem 2016;291(9):4671–4683. DOI: 10.1074/jbc.M115.698613.

46. Madsen JJ, Persson E, Olsen OH. Tissue factor activates allosteric networks in factor VIIa through structural and dynamic changes. J Thromb Haemost 2015;13(2):262–267. DOI: 10.1111/jth.12791.
47. Song H, Olsen OH, Persson E, et al. Sites involved in intra- and interdomain allostery associated with the activation of factor VIIa pinpointed by hydrogen-deuterium exchange and electron transfer dissociation mass spectrometry. J Biol Chem 2014;289(51):35388–35396. DOI: 10.1074/jbc.M114.614297.
48. Soeda T, Nogami K, Matsumoto T, et al. Mechanisms of factor VIIa-catalyzed activation of factor VIII. J Thromb Haemost 2010;8(11):2494–2503. DOI: 10.1111/j.1538-7836.2010.04042.x.
49. Ayombil F, Camire RM. Insights into vitamin K-dependent carboxylation: Home field advantage. Haematologica 2020;105(8):1996–1998. DOI: 10.3324/haematol.2020.253690.
50. Berkner KL, Runge KW. Vitamin K-dependent protein activation: Normal gamma-glutamyl carboxylation and disruption in disease. Int J Mol Sci 2022;23(10). DOI: 10.3390/ijms23105759.
51. Tie JK, Stafford DW. Structural and functional insights into enzymes of the vitamin K cycle. J Thromb Haemost 2016;14(2):236–247. DOI: 10.1111/jth.13217.
52. DelGiudice LA, White GA. The role of tissue factor and tissue factor pathway inhibitor in health and disease states. J Vet Emerg Crit Care (San Antonio) 2009;19(1):23–29. DOI: 10.1111/j.1476-4431.2008.00380.x.
53. Butenas S. Tissue factor structure and function. Scientifica (Cairo) 2012;2012:964862. DOI: 10.6064/2012/964862.
54. Dickinson CD, Kelly CR, Ruf W. Identification of surface residues mediating tissue factor binding and catalytic function of the serine protease factor VIIa. Proc Natl Acad Sci U S A 1996;93(25):14379–14384. DOI: 10.1073/pnas.93.25.14379.
55. McCallum CD, Su B, Neuenschwander PF, et al. Tissue factor positions and maintains the factor VIIa active site far above the membrane surface even in the absence of the factor VIIa Gla domain. A fluorescence resonance energy transfer study. J Biol Chem 1997;272(48):30160–30166. DOI: 10.1074/jbc.272.48.30160.
56. Gajsiewicz JM, Morrissey JH. Structure-function relationship of the interaction between tissue factor and factor VIIa. Semin Thromb Hemost 2015;41(7):682–690. DOI: 10.1055/s-0035-1564044.
57. Margetic S. Inflammation and haemostasis. Biochem Med (Zagreb) 2012;22(1):49–62. PMID: 22384519.
58. Kespohl M, Goetzke CC, Althof N, et al. TF-FVIIa PAR2-β-arrestin signaling sustains organ dysfunction in coxsackievirus B3 infection of mice. Arterioscler Thromb Vasc Biol 2024;44(4):843–865. DOI: 10.1161/ATVBAHA.123.320157.
59. Demetz G, Seitz I, Stein A, et al. Tissue factor-factor VIIa complex induces cytokine expression in coronary artery smooth muscle cells. Atherosclerosis 2010;212(2):466–471. DOI: 10.1016/j.atherosclerosis.2010.07.017.
60. Heuberger DM, Schuepbach RA. Protease-activated receptors (PARs): Mechanisms of action and potential therapeutic modulators in PAR-driven inflammatory diseases. Thromb J 2019;17:4. DOI: 10.1186/s12959-019-0194-8.
61. Maheshwari A, Lacson A, Lu W, et al. Interleukin-8/CXCL8 forms an autocrine loop in fetal intestinal mucosa. Pediatr Res 2004;56(2):240–249. DOI: 10.1203/01.PDR.0000133196.25949.98.
62. Norman MU, Lister KJ, Yang YH, et al. TNF regulates leukocyte-endothelial cell interactions and microvascular dysfunction during immune complex-mediated inflammation. Br J Pharmacol 2005;144(2):265–274. DOI: 10.1038/sj.bjp.0706081.
63. Aithabathula RV, Kumar S, Singla B. Role of matricellular proteins in endothelial cell inflammation and atherosclerosis. Antioxidants (Basel) 2025;14(11). DOI: 10.3390/antiox14111338.
64. Egorina EM, Sovershaev MA, Hansen JB. The role of tissue factor in systemic inflammatory response syndrome. Blood Coagul Fibrinolysis 2011;22(6):451–456. DOI: 10.1097/MBC.0b013e328346ef3f.
65. Kondreddy V, Wang J, Keshava S, et al. Factor VIIa induces anti-inflammatory signaling via EPCR and PAR1. Blood 2018;131(21):2379–2392. DOI: 10.1182/blood-2017-10-813527.
66. Osterud B. Tissue factor/TFPI and blood cells. Thromb Res 2012;129(3):274–278. DOI: 10.1016/j.thromres.2011.11.049.
67. Mast AE, Ruf W. Regulation of coagulation by tissue factor pathway inhibitor: Implications for hemophilia therapy. J Thromb Haemost 2022;20(6):1290–1300. DOI: 10.1111/jth.15697.
68. Ahnstrom J, Petri A, Crawley JTB. Tissue factor pathway inhibitor—cofactor-dependent regulation of the initiation of coagulation. Curr Opin Hematol 2024;31(6):315–320. DOI: 10.1097/MOH.0000000000000838.
69. Dockal M, Hartmann R, Fries M, et al. Small peptides blocking inhibition of factor Xa and tissue factor-factor VIIa by tissue factor pathway inhibitor (TFPI). J Biol Chem 2014;289(3):1732–1741. DOI: 10.1074/jbc.M113.533836.
70. Piro O, Broze GJ Jr. Role for the Kunitz-3 domain of tissue factor pathway inhibitor-alpha in cell surface binding. Circulation 2004;110(23):3567–3572. DOI: 10.1161/01.CIR.0000148778.76917.89.
71. Ahamed J, Belting M, Ruf W. Regulation of tissue factor-induced signaling by endogenous and recombinant tissue factor pathway inhibitor 1. Blood 2005;105(6):2384–2391. DOI: 10.1182/blood-2004-09-3422.
72. Wolberg AS, Allen GA, Monroe DM, et al. High dose factor VIIa improves clot structure and stability in a model of haemophilia B. Br J Haematol 2005;131(5):645–655. DOI: 10.1111/j.1365-2141.2005.05820.x.
73. Lisman T, Adelmeijer J, Cauwenberghs S, et al. Recombinant factor VIIa enhances platelet adhesion and activation under flow conditions at normal and reduced platelet count. J Thromb Haemost 2005;3(4):742–751. DOI: 10.1111/j.1538-7836.2005.01227.x.
74. Dargaud Y, Prevost C, Lienhart A, et al. Evaluation of the overall haemostatic effect of recombinant factor VIIa by measuring thrombin generation and stability of fibrin clots. Haemophilia 2011;17(6):957–961. DOI: 10.1111/j.1365-2516.2011.02526.x.
75. Escobar MA, Hoffman M, Castaman G, et al. Recombinant factor VIIa: New insights into the mechanism of action through product innovation. Res Pract Thromb Haemost 2025;9(1):102670. DOI: 10.1016/j.rpth.2024.102670.
76. Sun Y, Myers DR, Nikolov SV, et al. Platelet heterogeneity enhances blood clot volumetric contraction: An example of asynchrono-mechanical amplification. Biomaterials 2021;274:120828. DOI: 10.1016/j.biomaterials.2021.120828.
77. Wu G, Krebs CR, Lin FC, et al. High sensitivity micro-elastometry: Applications in blood coagulopathy. Ann Biomed Eng 2013;41(10):2120–2129. DOI: 10.1007/s10439-013-0817-3.
78. Zhu YA, Li Q, Lu J, et al. The oldest complete jawed vertebrates from the early Silurian of China. Nature 2022;609(7929):954–958. DOI: 10.1038/s41586-022-05136-8.
79. Davidson CJ, Tuddenham EG, McVey JH. 450 million years of hemostasis. J Thromb Haemost 2003;1(7):1487–1494. DOI: 10.1046/j.1538-7836.2003.00334.x.
80. Servais T, Harper DAT, Munnecke A, et al. Understanding the Great Ordovician Biodiversification Event (GOBE): Influences of paleogeography, paleoclimate, or paleoecology? GSA Today 2009;19(4/5):4–10. DOI: 10.1130/GSATG37A.1.
81. Benton MJ. The origins of modern biodiversity on land. Philos Trans R Soc Lond B Biol Sci 2010;365(1558):3667–3679. DOI: 10.1098/rstb.2010.0269.
82. Higdon J. Vitamin K Corvallis, Oregon, USA: Oregon State University Linus Pauling Institute Micronutrient Information Center; 2000 Available from: https://lpi.oregonstate.edu/mic/vitamins/vitamin-K.
83. Jiang Y, Doolittle RF. The evolution of vertebrate blood coagulation as viewed from a comparison of puffer fish and sea squirt genomes. Proc Natl Acad Sci U S A 2003;100(13):7527–7532. DOI: 10.1073/pnas.0932632100.
84. Coban A, Bornberg-Bauer E, Kemena C. Domain evolution of vertebrate blood coagulation cascade proteins. J Mol Evol 2022;90(6):418–428. DOI: 10.1007/s00239-022-10071-3.
85. Maroney SA, Hansen KG, Mast AE. Cellular expression and biological activities of alternatively spliced forms of tissue factor pathway

inhibitor. Curr Opin Hematol 2013;20(5):403–409. DOI: 10.1097/MOH.0b013e3283634412.
86. Godzik A, Sander C. Conservation of residue interactions in a family of Ca-binding proteins. Protein Eng 1989;2(8):589–596. DOI: 10.1093/protein/2.8.589.
87. Mackman N. The many faces of tissue factor. J Thromb Haemost 2009;7(Suppl 1):136-139. DOI: 10.1111/j.1538-7836.2009.03368.x.
88. Mast AE. Tissue factor pathway inhibitor: Multiple anticoagulant activities for a single protein. Arterioscler Thromb Vasc Biol 2016;36(1):9–14. DOI: 10.1161/ATVBAHA.115.305996.
89. Maroney SA, Mast AE. Platelet tissue factor pathway inhibitor modulates intravascular coagulation. Thromb Res 2012;129(Suppl 2):S21–S22. DOI: 10.1016/j.thromres.2012.02.023.
90. Ellery PE, Maroney SA, Martinez ND, et al. Translation of human tissue factor pathway inhibitor-β-mRNA is controlled by alternative splicing within the 5′ untranslated region. Arterioscler Thromb Vasc Biol 2014;34(1):187–195. DOI: 10.1161/ATVBAHA.113.302660.
91. Maroney SA, Mast AE. New insights into the biology of tissue factor pathway inhibitor. J Thromb Haemost 2015;13 Suppl 1(0 1):S200–S207. DOI: 10.1111/jth.12897.
92. Lyseng-Williamson KA, Plosker GL. Recombinant factor VIIa (eptacog alfa): A pharmacoeconomic review of its use in haemophilia in patients with inhibitors to clotting factors VIII or IX. Pharmacoeconomics 2007;25(12):1007–1029. DOI: 10.2165/00019053-200725120-00004.
93. Georgieva R. Application of activated recombinant factor VII (rFVIIa, NovoSeven) in neonatology. Akush Ginekol (Sofiia) 2008;47(3):46–50. PMID: 18756832.
94. Roberts HR. Recombinant factor VIIa: How safe is the stuff? Can J Anaesth 2005;52(1):8–11. DOI: 10.1007/BF03018573.
95. Lloyd JV, Joist JH. Recombinant factor VIIa: A universal hemostatic agent? Curr Hematol Rep 2002;1(1):19–26. PMID: 12901121.
96. Dutta TK, Verma SP. Rational use of recombinant factor viia in clinical practice. Indian J Hematol Blood Transfus 2014;30(2):85–90. DOI: 10.1007/s12288-013-0240-9.
97. Hedner U. Recombinant activated factor VII: 30 years of research and innovation. Blood Rev 2015;29(Suppl 1):S4–S8. DOI: 10.1016/S0268-960X(15)30002-3.
98. Kinra P, Kumar H. Recombinant Factor VIIA. Med J Armed Forces India 2009;65(1):59–61. DOI: 10.1016/S0377-1237(09)80058-0.
99. Davenport P, Sola-Visner M. Hemostatic challenges in neonates. Front Pediatr 2021;9:627715. DOI: 10.3389/fped.2021.627715.
100. Ostilla L, Knopoff K, Myers P, et al. Disorders of coagulation in the newborn. Neoreviews 2024;25(11):e694–e709. DOI: 10.1542/neo.25-11-e694.
101. Mathijssen NCJ, Masereeuw R, Verbeek K, et al. Prophylactic effect of recombinant factor VIIa in factor VII deficient patients. Br J Haematol 2004;125(4):494–499. DOI: 10.1111/j.1365-2141.2004.04942.x.
102. Alten JA, Benner K, Green K, et al. Pediatric off-label use of recombinant factor VIIa. Pediatrics 2009;123(3):1066–72. DOI: 10.1542/peds.2008-1685.
103. Thim L, Bjoern S, Christensen M, et al. Amino acid sequence and posttranslational modifications of human factor VIIa from plasma and transfected baby hamster kidney cells. Biochemistry 1988;27(20):7785–7793. DOI: 10.1021/bi00420a030.
104. Lindley CM, Sawyer WT, Macik BG, et al. Pharmacokinetics and pharmacodynamics of recombinant factor VIIa. Clin Pharmacol Ther 1994;55(6):638–648. DOI: 10.1038/clpt.1994.80.
105. Heller M, Lau W, Pazmino-Canizares J, et al. A comprehensive review of rFVIIa use in a tertiary care pediatric center. Pediatr Blood Cancer 2008;50(5):1013–1017. DOI: 10.1002/pbc.21375.
106. Lisman T, De Groot PG. Mechanism of action of recombinant factor VIIa. J Thromb Haemost 2003;1(6):1138–1139. DOI: 10.1046/j.1538-7836.2003.00225.x.
107. Maheshwari A. Role of platelets in neonatal necrotizing enterocolitis. Pediatr Res 2021;89(5):1087–1093. DOI: 10.1038/s41390-020-1038-8.
108. Sang Y, Roest M, de Laat B, et al. Interplay between platelets and coagulation. Blood Rev 2021;46:100733. DOI: 10.1016/j.blre.2020.100733.
109. Guzzetta NA, Huch S, Fernandez JD, et al. Use of recombinant factor VIIa for uncontrolled bleeding in neonates after cardiopulmonary bypass. Paediatr Anaesth 2009;19(4):364–370. DOI: 10.1111/j.1460-9592.2008.02905.x.
110. Puetz J, Darling G, Brabec P, et al. Thrombotic events in neonates receiving recombinant factor VIIa or fresh frozen plasma. Pediatr Blood Cancer 2009;53(6):1074–1078. DOI: 10.1002/pbc.22160.
111. Donda KT, Torres BA, Khashu M, et al. Single nucleotide polymorphisms in neonatal necrotizing enterocolitis. Curr Pediatr Rev 2022;18(3):197–209. DOI: 10.2174/1573396318666220117091621.
112. Jain S, Maheshwari A, Jain SK. Maternal Nutrition and Fetal/Infant Development. Clin Perinatol 2022;49(2):313–330. DOI: 10.1016/j.clp.2022.02.005.
113. Jain SK, Baggerman EW, Mohankumar K, et al. Amniotic fluid-borne hepatocyte growth factor protects rat pups against experimental necrotizing enterocolitis. Am J Physiol Gastrointest Liver Physiol 2014;306(5):G361–G369. DOI: 10.1152/ajpgi.00272.2013.
114. Chiu B, Melin-Aldana H, Pillai S, et al. Factor VII transcription correlates with hepatocyte proliferation and hepatocyte growth factor expression in a rodent extrahepatic portal vein obstruction model. J Am Coll Surg 2007;205(2):277–283. DOI: 10.1016/j.jamcollsurg.2007.04.005.
115. Zur RL. Protected from harm, harmed by protection: Ethical consequences of the exclusion of pregnant participants from clinical trials. Res Ethics 2023;19(4):536–545. DOI: 10.1177/17470161231189843.
116. Welsh A, McLintock C, Gatt S, et al. Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. Aust N Z J Obstet Gynaecol 2008;48(1):12–16. DOI: 10.1111/j.1479-828X.2007.00823.x.
117. Acs N, Korte WC, von Heymann CC, et al. Rationale for the potential use of recombinant activated factor VII in severe post-partum hemorrhage. J Clin Med 2024;13(10):2928. DOI: 10.3390/jcm13102928.
118. Cortis PA. FT13 Guideline driven management of obstetric haemorrhage. Reg Anesth Pain Med 2025;50(1):A366–A368. DOI: 10.1136/rapm-2025-ESRA.632.
119. Struble E, Harrouk W, DeFelice A, et al. Nonclinical aspects of venous thrombosis in pregnancy. Birth Defects Res C Embryo Today 2015;105(3):190–200. DOI: 10.1002/bdrc.21111.
120. Alexander WA, Jensen I, Hathway J, et al. Bleeding in patients with hemophilia who have inhibitors: Modeling US medical system utilization and cost avoidance between recombinant factor VIIa products with different clinical dosing requirements. J Manag Care Spec Pharm 2022;28(5):518–527. DOI: 10.18553/jmcp.2022.21197.
121. Watson N, Al-Samkari H. Eptacog beta, a novel recombinant factor VIIa, for the treatment of hemophilia. Drugs Today (Barc) 2022;58(3):105–116. DOI: 10.1358/dot.2022.58.3.3381593.
122. Keshava S, Pendurthi UR, Esmon CT, et al. Therapeutic doses of recombinant factor VIIa in hemophilia generates thrombin in platelet-dependent and -independent mechanisms. J Thromb Haemost 2020;18(8):1911–1921. DOI: 10.1111/jth.14881.
123. Kenet G. High-dose recombinant factor VIIa therapy in hemophilia patients with inhibitors. Semin Hematol 2006;43(1 Suppl 1):S108– S110. DOI: 10.1053/j.seminhematol.2005.11.006.
124. Morrison S, Lacey C, Attard C, et al. Recombinant Factor VIIa in Pediatric Cardiac Surgery. J Cardiothorac Vasc Anesth 2022;36(3):684–689. DOI: 10.1053/j.jvca.2021.08.002.
125. Roychaudhuri S, Grewal G, Vijayashankar SS, et al. Necrotizing Enterocolitis Associated with Congenital Heart Disease-A Review Article. Newborn (Clarksville) 2022;1(1):170–176. DOI: 10.5005/jp-journals-11002-0016.
126. Pychynska-Pokorska M, Moll JJ, Krajewski W, et al. The use of recombinant coagulation factor VIIa in uncontrolled postoperative bleeding in children undergoing cardiac surgery with cardiopulmonary bypass. Pediatr Crit Care Med 2004;5(3):246–250. DOI: 10.1097/01.pcc.0000123546.78900.67.
127. Mathew P, Young G. Recombinant factor VIIa in paediatric bleeding disorders–a 2006 review. Haemophilia 2006;12(5):457–472. DOI: 10.1111/j.1365-2516.2006.01321.x.

128. Shibeko AM, Woodle SA, Lee TK, et al. Unifying the mechanism of recombinant FVIIa action: Dose dependence is regulated differently by tissue factor and phospholipids. Blood 2012;120(4):891–899. DOI: 10.1182/blood-2011-11-393371.
129. Dang CN, Katakam LI, Smith PB, et al. Recombinant activated factor VIIa treatment for refractory hemorrhage in infants. J Perinatol 2011;31(3):188–192. DOI: 10.1038/jp.2010.85.
130. Harrison TD, Laskosky J, Jazaeri O, et al. "Low-dose" recombinant activated factor VII results in less blood and blood product use in traumatic hemorrhage. J Trauma 2005;59(1):150–154. DOI: 10.1097/01.ta.0000171470.39742.8e.
131. Okonta KE, Edwin F, Falase B. Is recombinant activated factor VII effective in the treatment of excessive bleeding after paediatric cardiac surgery? Interact Cardiovasc Thorac Surg 2012;15(4):690–694. DOI: 10.1093/icvts/ivs309.
132. Brady KM, Easley RB, Tobias JD. Recombinant activated factor VII (rFVIIa) treatment in infants with hemorrhage. Paediatr Anaesth 2006;16(10):1042–1046. DOI: 10.1111/j.1460-9592.2006.02039.x.
133. Tyagi M, Guaragni B, Dendi A, et al. Use of Cryoprecipitate in Newborn Infants. Newborn (Clarksville) 2023;2(1):11–18. DOI: 10.5005/jp-journals-11002-0045.
134. Budnik I, Shenkman B, Morozova O, et al. In-vitro assessment of the effects of fibrinogen, recombinant factor VIIa and factor XIII on trauma-induced coagulopathy. Blood Coagul Fibrinolysis 2020;31(4):253–257. DOI: 10.1097/MBC.0000000000000910.
135. Hünseler C, Kribs A, Eifinger F, et al. Recombinant activated factor seven in acute life-threatening bleeding in neonates: Report on three cases and review of literature. J Perinatol 2006;26(11):706–713. DOI: 10.1038/sj.jp.7211588.
136. Fontaine MJ, Lazarchick J, Taylor S, et al. Use of recombinant factor VIIa in infants with severe coagulopathy. J Perinatol 2004;24(5):310–311. DOI: 10.1038/sj.jp.7211086.
137. Burnett JW. Seabather's eruption. Cutis 1992;50(2):98. PMID: 1511625.
138. Tobias JD, Groeper K, Berkenbosch JW. Preliminary experience with the use of recombinant factor VIIa to treat coagulation disturbances in pediatric patients. South Med J 2003;96(1):12–16. DOI: 10.1097/01.SMJ.0000047629.79538.82.
139. Chuansumrit A, Nuntnarumit P, Okascharoen C, et al. The use of recombinant activated factor VII to control bleeding in a preterm infant undergoing exploratory laparotomy. Pediatrics 2002;110(1 Pt 1):169–171. DOI: 10.1542/peds.110.1.169.
140. Greisen G, Andreasen RB. Recombinant factor VIIa in preterm neonates with prolonged prothrombin time. Blood Coagul Fibrinolysis 2003;14(1):117–120. DOI: 10.1097/00001721-200301000-00021.
141. Barro C, Wrobleski I, Piolat C, et al. Successful use of recombinant factor VIIa for severe surgical liver bleeding in a 5 month-old baby. Haemophilia 2004;10(2):183–185. DOI: 10.1046/j.1365-2516.2003.00845.x.
142. Abdullah F, Hunter C, Hargrove C, et al. Recombinant factor VIIa for treatment of massive liver fracture in a premature infant. J Pediatr Surg 2006;41(10):1764–1767. DOI: 10.1016/j.jpedsurg.2006.05.054.
143. Mitsiakos G, Papaioannou G, Giougi E, et al. Is the use of rFVIIa safe and effective in bleeding neonates? A retrospective series of 8 cases. J Pediatr Hematol Oncol 2007;29(3):145–150. DOI: 10.1097/MPH.0b013e3180335bcb.
144. Olomu N, Kulkarni R, Manco-Johnson M. Treatment of severe pulmonary hemorrhage with activated recombinant factor VII (rFVIIa) in very low birth weight infants. J Perinatol 2002;22(8):672–674. DOI: 10.1038/sj.jp.7210787.
145. Cosar H, Isik H, Cakir SC, et al. Recombinant activated factor VIIa (rFVIIa) treatment in very-low-birth-weight (VLBW) premature infants with acute pulmonary hemorrhage: A single-center, retrospective study. Paediatr Drugs 2017;19(1):53–58. DOI: 10.1007/s40272-016-0203-3.
146. Cetin H, Yalaz M, Akisu M, et al. The use of recombinant activated factor VII in the treatment of massive pulmonary hemorrhage in a preterm infant. Blood Coagul Fibrinolysis 2006;17(3):213–216. DOI: 10.1097/01.mbc.0000220245.20036.2d.
147. Gkiougki E, Mitsiakos G, Chatziioannidis E, et al. Predicting response to rFVIIa in neonates with intractable bleeding or severe coagulation disturbances. J Pediatr Hematol Oncol 2013;35(3):221–226. DOI: 10.1097/MPH.0b013e318286d27e.
148. Filan PM, Mills JF, Clarnette TD, et al. Spontaneous liver hemorrhage during laparotomy for necrotizing enterocolitis: A potential role for recombinant factor VIIa. J Pediatr 2005;147(6):857–859. DOI: 10.1016/j.jpeds.2005.07.034.
149. Young G, Nugent DJ. Prevention of bleeding complications in neonates with liver failure undergoing surgery using recombinant factor VIIa. Hematology 2001;6(5):341–346. DOI: 10.1080/10245332.2001.11746589.
150. Maheshwari A. Immunologic and hematological abnormalities in necrotizing enterocolitis. Clin Perinatol 2015;42(3):567–585. DOI: 10.1016/j.clp.2015.04.014.
151. MohanKumar K, Namachivayam K, Song T, et al. A murine neonatal model of necrotizing enterocolitis caused by anemia and red blood cell transfusions. Nat Commun 2019;10(1):3494. DOI: 10.1038/s41467-019-11199-5.
152. Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. Blood 2004;104(13):3858–3864. DOI: 10.1182/blood-2004-06-2223.
153. Del Vecchio A, Motta M, Romagnoli C. Neonatal Platelet Function. Clin Perinatol 2015;42(3):625–638. DOI: 10.1016/j.clp.2015.04.015.
154. Bernhard H, Rosenkranz A, Petritsch M, et al. Phospholipid content, expression and support of thrombin generation of neonatal platelets. Acta Paediatr 2009;98(2):251–255. DOI: 10.1111/j.1651-2227.2008.01075.x.
155. Namachivayam K, MohanKumar K, Shores DR, et al. Targeted inhibition of thrombin attenuates murine neonatal necrotizing enterocolitis. Proc Natl Acad Sci U S A 2020;117(20):10958–10969. DOI: 10.1073/pnas.1912357117.
156. Maheshwari A. Thrombocytopenia. In: Maheshwari A, editor. Principles of Neonatology. Maryland Heights, Missouri, United States;2024. pp. 387–398.
157. Haidl H, Pohl S, Leschnik B, et al. Neonatal thrombocytopenia: Thrombin generation in presence of reduced platelet counts and effects of rFVIIa in cord blood. Sci Rep 2019;9(1):8014. DOI: 10.1038/s41598-019-44199-y.
158. Almeida AM, Khair K, Hann I, et al. The use of recombinant factor VIIa in children with inherited platelet function disorders. Br J Haematol 2003;121(3):477–481. DOI: 10.1046/j.1365-2141.2003.04286.x.
159. Ucsel R, Savasan S, Coban A, et al. Fatal intracranial hemorrhage in a newborn with factor VII deficiency. Turk J Pediatr 1996;38(2):257–260. PMID: 8701495.
160. Chuansumrit A, Visanuyothin N, Puapunwattana S, et al. Outcome of intracranial hemorrhage in infants with congenital factor VII deficiency. J Med Assoc Thai 2002;85(Suppl 4):S1059–S1064. PMID: 12549776.
161. Karimi M. Successful control of central nervous system bleeding in two newborns with severe factor VII deficiency using rFVIIa administered via Port-a-Cath. Semin Hematol 2008;45(2 Suppl 1):S74. DOI: 10.1053/j.seminhematol.2008.03.010.
162. Wong WY, Huang WC, Miller R, et al. Clinical efficacy and recovery levels of recombinant FVIIa (NovoSeven) in the treatment of intracranial haemorrhage in severe neonatal FVII deficiency. Haemophilia 2000;6(1):50–54. DOI: 10.1046/j.1365-2516.2000.00345.x.
163. Ince Z, Bulut O, Tugrul-Aksakal M, et al. Asymptomatic intracranial hemorrhage in a newborn with congenital factor VII deficiency and successful treatment with recombinant activated factor VII. Turk J Pediatr 2018;60(5):562–565. DOI: 10.24953/turkjped.2018.05.014.
164. Farah RA, Hamod D, Melick N, et al. Successful prophylaxis against intracranial hemorrhage using weekly administration of activated recombinant factor VII in a newborn with severe factor VII deficiency. J Thromb Haemost 2007;5(2):433–434. DOI: 10.1111/j.1538-7836.2007.02318.x.

165. Michaels LA, Philipp CS, Eisele J, et al. Prophylactic treatment of a small child with severe factor VII deficiency using repeat dosing from a single vial of recombinant activated factor VII. Pediatr Blood Cancer 2007;49(5):736–739. DOI: 10.1002/pbc.20688.
166. Napolitano M, Giansily-Blaizot M, Dolce A, et al. Prophylaxis in congenital factor VII deficiency: Indications, efficacy and safety. Results from the Seven Treatment Evaluation Registry (STER). Haematologica 2013;98(4):538–544. DOI: 10.3324/haematol.2012.074039.
167. Kankirawatana S, Mahasandana C, Veerakul G, et al. Successful prophylaxis of intracranial hemorrhage in infants with severe congenital factor VII deficiency. Southeast Asian J Trop Med Public Health 2000;31(4):795–800. PMID: 11414431.
168. Puetz J, Darling G, McCormick KA, et al. Fresh frozen plasma and recombinant factor VIIa use in neonates. J Pediatr Hematol Oncol 2009;31(12):901–906. DOI: 10.1097/MPH.0b013e3181c29c25.
169. Levi M, Levy JH, Andersen HF, et al. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med 2010;363(19):1791–800. DOI: 10.1056/NEJMoa1006221.
170. Young G, Wicklund B, Neff P, et al. Off-label use of rFVIIa in children with excessive bleeding: A consecutive study of 153 off-label uses in 139 children. Pediatr Blood Cancer 2009;53(2):179–183. DOI: 10.1002/pbc.22053.
171. O'Connell KA, Wood JJ, Wise RP, et al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. JAMA 2006;295(3):293–298. DOI: 10.1001/jama.295.3.293.
172. Ferraris VA, Boral LI, Cohen AJ, et al. Consensus review of the treatment of cardiovascular disease in people with hemophilia A and B. Cardiol Rev 2015;23(2):53–68. DOI: 10.1097/CRD.0000000000000045.
173. Downey L, Brown ML, Faraoni D, et al. Recombinant factor VIIa Is associated with increased thrombotic complications in pediatric cardiac surgery patients. Anesth Analg 2017;124(5):1431–1436. DOI: 10.1213/ANE.0000000000001947.
174. Chambers NA, Andrews D, Frew E, et al. rFV11a and paediatric open-heart surgery: Thrombosis in the cardiopulmonary bypass circuit in spite of adequate markers of anticoagulation. Anaesthesia 2009;64(6):683–686. DOI: 10.1111/j.1365-2044.2009.05897.x.
175. Roberts HR. Recombinant factor VIIa (Novoseven) and the safety of treatment. Semin Hematol 2001;38(4 Suppl 12):48–50. DOI: 10.1016/s0037-1963(01)90148-9.
176. Lisman T, Mosnier LO, Lambert T, et al. Inhibition of fibrinolysis by recombinant factor VIIa in plasma from patients with severe hemophilia A. Blood 2002;99(1):175–179. DOI: 10.1182/blood.v99.1.175.
177. He S, Blomback M, Ekman GJ, et al. The role of recombinant factor VIIa (FVIIa) in fibrin structure in the absence of FVIII/FIX. J Thromb Haemost 2003;1(6):1215–1219. DOI: 10.1046/j.1538-7836.2003.00242.x.
178. Monroe DM, Hoffman M, Allen GA, et al. The factor VII-platelet interplay: Effectiveness of recombinant factor VIIa in the treatment of bleeding in severe thrombocytopathia. Semin Thromb Hemost 2000;26(4):373–377. DOI: 10.1055/s-2000-8455.
179. Poon MC. The use of Recombinant activated factor VII in patients with Glanzmann's thrombasthenia. Thromb Haemost 2021;121(3):332–340. DOI: 10.1055/s-0040-1718373.
180. Dutton RP, Stein DM. The use of factor VIIa in haemorrhagic shock and intracerebral bleeding. Injury 2006;37(12):1172–1177. DOI: 10.1016/j.injury.2006.09.001.

EXPERT VIEW/REVIEW PAPER

Unseen Children: Risks and Anticipatory Management

Colin Michie[1,2]

Received on: 19 April 2026; *Accepted on*: 20 May 2026; *Published on*: 22 June 2026

Abstract

"Unseen children" represent a persistent global public health concern, encompassing infants and children who fail to attend scheduled healthcare or educational encounters and are frequently coded as "Did Not Attend" (DNA) or more appropriately "Was Not Brought" (WNB). These children are vulnerable by definition, as missed appointments may result in delayed immunization, impaired growth monitoring, and unmet developmental needs. Non-attendance may also signal broader safeguarding concerns, including social disadvantage, family dysfunction, mobility, and exposure to neglect, abuse, or displacement. Importantly, WNB is associated with substantial service-level impacts, including increased healthcare costs, inefficiencies, and delayed identification of children requiring medical attention, with a significant proportion of non-attenders later presenting to acute services. Rates of pediatric non-attendance vary across health systems, generally lower in coordinated universal care systems and higher in fragmented or socioeconomically unequal contexts. Socioeconomic deprivation, language barriers, and access difficulties are key determinants. In some cases, cultural, religious, or trust-related factors may further influence engagement with healthcare systems. System-level factors, including fragmented communication, inadequate follow-up processes, and normalization of non-attendance, may contribute to some children becoming invisible within healthcare pathways. Reframing DNA as WNB emphasizes caregiver responsibility while reinforcing professional accountability to identify and support at-risk families. Effective responses require proactive, community-based strategies, including outreach nursing, integrated social and health services, flexible scheduling, and culturally sensitive engagement. Strengthening safeguarding frameworks, improving interagency coordination, and promoting visibility of vulnerable children are essential. Ultimately, addressing unseen children requires a shift toward compassionate, child-centered systems that recognize absence itself as a clinically and socially meaningful signal requiring action.

Keywords: Child abuse, Child labor, Child-centered safeguarding, Community outreach, Coordinated sibling scheduling, Did not attend, Disabilities, Family-centered care models, First Nations children, Flexible appointment times, Housing instability, Infant, Language barriers, Migration, Nursing engagement, Pediatric clinic non-attendance rates, Podcast-discussion, Poverty, Reminder systems, Telemedicine options, Trafficking, Transportation support, Ultra-orthodox or separatist communities, United National Children's Fund, Violence.

Newborn (2026): 10.5005/jp-journals-11002-0158

Key Points

- "Unseen children" represent a persistent global public health concern, encompassing infants and children who fail to attend scheduled healthcare or educational encounters and are frequently coded as "Did Not Attend" (DNA) or more appropriately "Was Not Brought" (WNB).
- These children are vulnerable by definition, as missed appointments may result in delayed immunization, impaired growth monitoring, and unmet developmental needs. Non-attendance may also signal broader safeguarding concerns, including social disadvantage, family dysfunction, mobility, and exposure to neglect, abuse, or displacement.
- WNB is associated with substantial service-level impacts, including increased healthcare costs, inefficiencies, and delayed identification of children requiring medical attention, with a significant proportion of non-attenders later presenting to acute services.
- Effective responses require proactive, community-based strategies, including outreach nursing, integrated social and health services, flexible scheduling, and culturally sensitive engagement. Strengthening safeguarding frameworks, improving interagency coordination, and promoting visibility of vulnerable children are essential.

Introduction

"Unseen children" live in all countries.[1–5] This has been a recognized, major public health concern; the magnitude of this problem was again clearly evident in a recent podcast discussion I had with Professor Monica Lakhanpaul from the Integrated Community Child Health, UCL Great Ormond Street Institute of Child Health, London, United Kingdom.[6,7]

Unseen infants and children are often grouped and coded by services as "Did Not Attend" (DNA) because they were not seen in a clinic, service, or educational activity.[5,8] These children constitute minorities, but they deserve careful evaluation for several reasons.[5] Firstly, they are vulnerable, by definition.[9] If unseen children miss a vaccination or follow-up assessment of their growth and

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

[2]Global Newborn Society, Laurel, Greater Washington Metropolitan Region, Washington, D.C., United States of America

Corresponding Author: Colin Michie, Department of Population, Policy, and Practice Research and Teaching, Institute of Child Health, University College, London, United Kingdom; Global Newborn Society, Laurel, Greater Washington Metropolitan Region, Washington, D.C., United States of America, Phone: +44 7590620293, e-mail: c.michie@ucl.ac.uk

How to cite this article: Michie C. Unseen Children: Risks and Anticipatory Management. Newborn 2026;5(2):104–108.

Source of support: Nil

Conflict of interest: Dr Colin Michie is associated as the Editorial Board Member of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of Editorial Board Member and his research group.

development, for example, they have been disadvantaged.[10–12] Secondly, missing a clinic may be a red flag signaling that, in some respect, their care is not optimal.[12] Thirdly, by definition, the number of children involved can be difficult to calibrate.[13] And finally, non-attenders cause financial costs to services, increasing waiting times for other attenders.[9,14,15] Up to 60% in this subgroup in a Hospital clinic are likely to require medical attention; some will present subsequently to alternative services, including casualties.[14]

Pediatric clinic non-attendance rates may be lower in countries with highly coordinated universal child health systems and strong community outreach, but higher in fragmented or socioeconomically unequal systems.[16,17] For example, published rates in the UK are often reported between 3 and 12%, while some US pediatric services report much wider ranges, from 5% to over 30%, depending on the population studied.[15,18] Denmark has reported comparatively lower rates in pediatric clinics.[19]

United National Children's Fund (UNICEF) reports show that globally, millions of children remain "uncounted" or "invisible" without sufficient data to measure their well-being or development.[20] More than 500 million children live in nations where progress toward child-related development goals cannot be adequately tracked.[21] Societies work better with children who are visible and reachable; the vulnerable often remain overlooked.[22] Medical risks in such marginalized, mobile groups are readily demonstrated in hospitalized cases of measles.[23] A report from the Czech Republic documenting cases from 2018 to 2024 noted that of 791 cases, 109 were imported, 62 from Ukraine, and the others from 25 countries. Substantial numbers of cases were unvaccinated or partially vaccinated.[24]

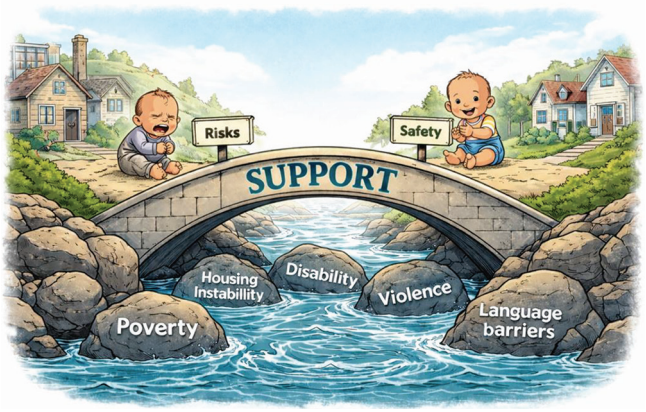


Fig. 1: A graphic illustration showing an "was not brought" infant sitting in the midst of numerous risks, on one bank of a difficult-to-navigate river of social barriers. The flow in this river is clearly turbulent and is seen passing between rocky difficulties such as poverty, housing instability, disability, violence, and language barriers. A bridge built of much-needed social-medical support does exist, and the other bank seems safer, but the infant needs support to navigate the hurdles. The figure was created using artificial intelligence–assisted image generation (OpenAI 2026. ChatGPT version 5. https://chat.openai.com). A detailed figure legend describing the desired visual elements and conceptual framework was used as the initial prompt. Subsequent iterative modifications were performed through serial text-based refinements to adjust composition, symbolism, labeling, and visual emphasis until the final illustration met the intended design objectives

Why Was This Patient Not Brought to Clinic?

The reasons for children not being brought to a Hospital clinic require identification, consideration, and appropriate responses.[25] This should ideally be part of their clinical journey.[13,25] There are likely to be differences between an initial and a follow-up clinic visit, and the explanations will depend on the type of visit.[9] In the UK, for instance, the issues of transport, waiting times, and administrative errors are common in audits of neonatal follow-up clinic visits.[26] However, these can hide other, more significant problems (Fig. 1).[27] Most frequently, "WNB" is associated with lower household incomes, greater family dysfunction, forgetfulness, and varied perceptions of carers as to the importance of appointments for their children.[9] Large family sizes, for instance, can make clinic attendance challenging for caregivers, as can a history of previous poor experiences in Hospitals or fears of a potentially tragic diagnosis.[28]

Less obvious explanations and associations with WNB can be geographical; for instance, infants, children, and young people may live in temporary accommodation.[29] Disabilities, abuse, violence in the home, child labor, and trafficking may exist, unseen, in such environments.[30] With increasing frequency, clinicians will be managing families seeking asylum or refuge, displaced by war.[31] In our clinic, we have seen these families carrying significant suspicions of our data-sharing and safeguarding procedures.[32]

Patient characteristics such as gender or ethnicity do not yield a powerful association with WNB very frequently. A large pediatric ophthalmology study from New Zealand found that missed appointments were only slightly more common among boys overall, particularly among Māori and Pacific populations.[33] A pediatric dental study has reported slightly higher WNB rates among male children.[34] Conditions such as female genital mutilation may be becoming less frequent, but there is a possibility that such cases have been underreported.[35]

Ethnicity itself is rarely a driver for missed appointments.[36] Rather, WNB in different ethnic groups are more likely to reflect socioeconomic challenges, linguistic barriers, and historical mistrust.[37] For instance, studies in Australia showed substantially higher pediatric non-attendance rates among First Nations children compared with non-indigenous children.[38] In these situations, language barriers and a shortage of interpreters can contribute to a variety of breakdowns in communications, misperceptions, and mistrust of a clinical system.[39]

Trust is a Major Determinant of Clinical Care of Infants

The evaluation of an infant in a clinic appointment can be complicated by issues related to trust, modesty, gender, or religious traditions in a family.[40] One cannot generalize or stigmatize, but awareness is important, as some carers prefer prayer or spiritual healing and emphasize traditional/community-based healing practices.[41] Some examples discussed in medical and public health literature include groups within Christian Science, which historically emphasize spiritual healing and prayer rather than conventional medical treatment.[42] Some ultra-orthodox or separatist communities across multiple religions may limit institutional contact.[43,44] Some communities rely heavily on traditional healing systems alongside or instead of biomedical care.[45]

Professional Communications can Contribute to Losing Sight of Children

If an infant or a toddler WNB to a neonatal follow-up appointment, was their primary care team or community contact informed?[2,46]

What was recorded by the neonatologist, and were steps taken to try to re-establish a clinical journey?[47] If such a family were in temporary accommodation, who might reach out and communicate effectively with them? When repeated missed appointments are documented as administrative failures rather than potential indicators of vulnerability, the focus may shift away from the child and their underlying needs.[48] Wording in professional correspondence can normalize non-attendance, reducing the sense of urgency around follow-up and missing opportunities to identify children at risk.[49,50] Over time, fragmented records, poor interagency communication, and repeated "DNAs" without escalation can result in a child disappearing from professional attention.[51]

Making Children More Visible

Modern safeguarding frameworks encourage the use of the more accurate abbreviation of "WNB" rather than "DNA" when referring to children.[4,5] This wording recognizes that responsibility for accessing care usually lies with caregivers, not the child, and it prompts professionals to consider a family-based approach in the community to the WNBs.[52]

Community Outreach

Communications between healthcare professionals and the community are important determinants for ensuring that children are seen. Employing experienced nurses in local healthcare is effective.[53] They can connect with disadvantaged mothers and their families, or those in temporary accommodation, when home visiting.[54] This reduces fear and suspicions. Community nurses are well-positioned to engage effectively with charities or religious organizations; they will be aware of local influencers and can build trust. This promotes child safety and clinical services.[55, 56] Pediatric supports, including health visitors and migrant support workers, provided in communities, rather than through clinics, improve attendances at outpatients and reduce casualty numbers.[57]

Staff Training

Having well-trained and experienced staff is likely to be beneficial in the management of unseen children, both in the clinic and community.[58,59] Services can improve attendance by offering flexible appointment times, reminder systems, telemedicine options, transportation support, coordinated sibling scheduling, community outreach, and family-centered care models.[60] Healthcare professionals have dual responsibilities: Protecting children from harm while also maintaining trust and access to care.[61,62] Child-centered safeguarding is generally most effective when combined with compassion, cultural understanding, and sustained community engagement.[63]

Future Global Challenges

Pandemics, climate-driven migration, antimicrobial resistance, conflict, and urbanization are likely to increase the number of children living in temporary, unstable, or marginalized circumstances.[64] In these environments, healthcare systems must become more proactive, coordinated, and community-focused.[61] If we are to deploy effective vaccination programs, for instance, we are more likely to be successful by first promoting the visibility of children and young people in these at-risk, mobile populations.[65]

Conclusion

The unseen child is not always absent from society. More often, society is absent from the child. Vulnerable children can gradually disappear from professional attention. Transition from "DNA" to "WNB" is an important ethical shift toward child-centered thinking and professional accountability. Safeguarding unseen children needs more than efficient appointment systems; it requires curiosity, compassion, continuity, and meaningful outreach. Nurses, pediatricians, educators, social workers, community leaders, charities, and faith organizations can all ensure that absence itself is recognized as clinically and socially significant.

Ultimately, every missed contact should prompt an important question: What might this child's absence be telling us? A just and effective healthcare system can be calibrated both by the quality of care delivered to attending populations and also its ability to identify, protect, and advocate for the visibility of all children.

Acknowledgment

The authors would like to acknowledge the persistent encouragement provided by Professor Akhil Maheshwari to me in the writing of this article.

References

1. Spray J, Hunleth J. Where have all the children gone? Against children's invisibility in the COVID-19 pandemic. Anthropol Now 2020;12(2):39–52. DOI: 10.1080/19428200.2020.1824856.
2. Ahmar S, Clarke A, Kanyuuru L. Challenges and inequities of healthcare in meeting the growing needs of urban children in sub-Saharan Africa. BMJ Paediatr Open 2025;9(1). DOI: 10.1136/bmjpo-2025-003901.
3. Amoako E, Jumbam DT, Bediako Y. Unseen and unheard: African children with cancer are consistently excluded from clinical trials. BMJ Glob Health 2021;6(1). DOI: 10.1136/bmjgh-2020-004750.
4. Weld GR, Coghlan R, Pereira H, et al. Uncounted and Unreached: The Unseen Children Who Could be Saved by Better Data. Uxbridge: World Vision International; 2014. Available from: https://www.wvi.org/sites/default/files/Uncounted%20and%20Unreached-%20%20LOWRES.pdf.
5. Calvo R, Hawkins SS. Disparities in quality of healthcare of children from immigrant families in the US. Matern Child Health J 2015;19(10):2223–2232. DOI: 10.1007/s10995-015-1740-z.
6. Michie C. Unseen Children. London: Excellence in Pediatrics Institute; 2025. Available from: https://www.ineip.org/announcements/interview-monica-lakhanpaul-unseen-children.
7. University College London;2026. Available from: https://profiles.ucl.ac.uk/35294-monica-lakhanpaul.
8. Arai L, Stephenson T, Roberts H. The unseen child and safeguarding: 'Did not attend' guidelines in the NHS. Arch Dis Child 2015;100(6):517–520. DOI: 10.1136/archdischild-2014-307294.
9. French LR, Turner KM, Morley H, et al. Characteristics of children who do not attend their hospital appointments, and GPs' response: A mixed methods study in primary and secondary care. Br J Gen Pract 2017;67(660):e483–e489. DOI: 10.3399/bjgp17X691373.
10. Sabnis SS, Pomeranz AJ, Lye PS, et al. Do missed opportunities stay missed? A 6-month follow-up of missed vaccine opportunities in inner city Milwaukee children. Pediatrics 1998;101(5):E5. DOI: 10.1542/peds.101.5.e5.
11. Holt E, Guyer B, Hughart N, et al. The contribution of missed opportunities to childhood underimmunization in Baltimore. Pediatrics 1996;97(4):474–480. PMID: 8632931.
12. Cameron E, Heath G, Redwood S, et al. Health care professionals' views of paediatric outpatient non-attendance: Implications for general practice. Fam Pract 2014;31(1):111–117. DOI: 10.1093/fampra/cmt063.
13. Hirani N, Karafillakis EN, Majeed A. Why children do not attend their appointments: Is there a need for an interface between general practitioners and hospitals allowing for the exchange of patients'

contact details? JRSM Open 2016;7(8):2054270416648046. DOI: 10.1177/2054270416648046.
14. Andrews R, Morgan JD, Addy DP, et al. Understanding non-attendance in outpatient paediatric clinics. Arch Dis Child 1990;65(2):192–195. DOI: 10.1136/adc.65.2.192.
15. Bech M. The economics of non-attendance and the expected effect of charging a fine on non-attendees. Health Policy 2005;74(2):181–191. DOI: 10.1016/j.healthpol.2005.01.001.
16. Buckley L, Gibson L, Harford K, et al. Community paediatric clinics and their role in supporting developmental outcomes and services for children living in disadvantaged communities. J Child Health Care 2024;28(3):658–674. DOI: 10.1177/13674935221146008.
17. Ukpeh H. Community paediatrics: Ideas for the way forward. Paediatr Child Health 2009;14(5):299–302. DOI: 10.1093/pch/14.5.299.
18. Goldbart AD, Dreiher J, Vardy DA, et al. Nonattendance in pediatric pulmonary clinics: an ambulatory survey. BMC Pulm Med 2009;9:12. DOI: 10.1186/1471-2466-9-12.
19. Norgard BM, Iachina M, Ammentorp J, et al. Non-attendance in hospital appointments based on data from the entire region of southern Denmark: Descriptive analyses and predictive factors. Clin Epidemiol 2025;17:303–314. DOI: 10.2147/CLEP.S512971.
20. UNICEF. Progress for Every Child in the SDG Era: Data and Analytics Section. New York: Division of Data, Research and Policy in UNICEF HQ; 2019. Available from: https://bjgp.org/content/bjgp/early/2017/06/19/bjgp17X691373.full.pdf.
21. Lufadeju YAU. UNICEF report: Over half a billion 'uncounted' children live in countries unable to measure SDG progress. New York: UNICEF; 2018. Available from: https://www.unicef.org/eca/press-releases/over-half-billion-uncounted-children.
22. Hart J. The child as vulnerable victim: Humanitarianism constructs its object. Int J Environ Res Public Health 2023;20(6). DOI: 10.3390/ijerph20065102.
23. Chovatiya R, Silverberg JI. Inpatient morbidity and mortality of measles in the United States. PLoS One 2020;15(4):e0231329. DOI: 10.1371/journal.pone.0231329.
24. Liptakova M, Maly M, Spackova M, et al. Measles: Retrospective study of cases reported in a national notification system, Czech Republic, 2018–2024. BMC Public Health 2026;26(1). DOI: 10.1186/s12889-026-27042-8.
25. Gibson J, Evennett J. Child not brought to appointment. Br J Gen Pract 2017;67(662):397. DOI: 10.3399/bjgp17X692285.
26. Lee KS. Neonatal transport metrics and quality improvement in a regional transport service. Transl Pediatr 2019;8(3):233–245. DOI: 10.21037/tp.2019.07.04.
27. Karlsen KA, Trautman M, Price-Douglas W, et al. National survey of neonatal transport teams in the United States. Pediatrics 2011;128(4):685–691. DOI: 10.1542/peds.2010-3796.
28. Riffin C, Wolff JL, Butterworth J, et al. Challenges and approaches to involving family caregivers in primary care. Patient Educ Couns 2021;104(7):1644–1651. DOI: 10.1016/j.pec.2020.11.031.
29. Kirby J, Harris JC. Development and evaluation of a 'was not brought' pathway: A team approach to managing children's missed dental appointments. Br Dent J 2019;227(4):291–297. DOI: 10.1038/s41415-019-0621-z.
30. Jagoe C, Toh PYN, Wylie G. Disability and the risk of vulnerability to human trafficking: An analysis of case law. J Hum Trafficking 2025;11(2):220–234. DOI: 10.1080/23322705.2022.2111507.
31. Iqbal MP, Walpola R, Harris-Roxas B, et al. Improving primary health care quality for refugees and asylum seekers: A systematic review of interventional approaches. Health Expect 2022;25(5):2065–2094. DOI: 10.1111/hex.13365.
32. Jolly A, Gupta A. Children and families with no recourse to public funds: Learning from case reviews. Children Soc 2024;38(1):16–31. DOI: 10.1111/chso.12646.
33. Mpe D, Niederer RL, Low J, et al. Predictors of missed pediatric ophthalmology appointments in a New Zealand cohort: The impact of gender, ethnicity, and socioeconomic deprivation. J AAPOS 2025:104646. DOI: 10.1016/j.jaapos.2025.104646.
34. Laforgia A, Inchingolo AM, Inchingolo F, et al. Paediatric dental trauma: Insights from epidemiological studies and management recommendations. BMC Oral Health 2025;25(1):6. DOI: 10.1186/s12903-024-05222-5.
35. Galgano AC, Kikuchi JY. Female genital mutilation or cutting. Treasure Island: StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK606106/.
36. Malloy M, Tarima S, Canales B, et al. Identifying risk factors for appointment no-shows in a pediatric orthopaedic surgery clinic. J Pediatr Soc North Am 2023;5(3):695. DOI: 10.55275/JPOSNA-2023-695.
37. Pardhan S, Sehmbi T, Wijewickrama R, et al. Barriers and facilitators for engaging underrepresented ethnic minority populations in healthcare research: An umbrella review. Int J Equity Health 2025;24(1):70. DOI: 10.1186/s12939-025-02431-4.
38. Cleary M, Edwards C, Mitchell-Watson J, et al. Benchmarking non-attendance patterns in paediatric medical imaging: A retrospective cohort study spotlighting First Nations children. Radiography (Lond) 2024;30(2):492–499. DOI: 10.1016/j.radi.2024.01.002.
39. Steinberg EM, Valenzuela-Araujo D, Zickafoose JS, et al. The "battle" of managing language barriers in health care. Clin Pediatr (Phila) 2016;55(14):1318–1327. DOI: 10.1177/0009922816629760.
40. Dickens R, Leroy P, Eppich W, et al. Trustful relationships between healthcare professionals and children: A concept analysis using Rodgers' evolutionary approach. Eur J Pediatr 2025;184(7):464. DOI: 10.1007/s00431-025-06297-0.
41. Puchalski CM. The role of spirituality in health care. Proc (Bayl Univ Med Cent) 2001;14(4):352–357. DOI: 10.1080/08998280.2001.11927788.
42. Swihart DL, Yarrarapu SNS, Martin RL. Cultural Religious Competence in Clinical Practice; 2023. Treasure Island: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493216/
43. Velan B, Tawil Y, Marciano A, et al. Disaffiliation from Jewish ultra-orthodox communities: Life trajectories shaped by the axes of rigidity-fluidity and alterity-inclusion. Contemp Jew 2022;42(2):293–314. DOI: 10.1007/s12397-022-09452-z.
44. Gemara N. "The feeling is what counts": Fathers' perspectives on child risk and protection within the ultra-orthodox context. Int J Environ Res Public Health 2023;20(5). DOI: 10.3390/ijerph20054385.
45. Selvaraj K, Deshmukh PR, Yadav P. Role of traditional healers in health and healthcare access: A multi stakeholder perspective from a tribal block of central India. Discov Health Syst 2026;5(1):18. DOI: 10.1007/s44250-026-00345-8.
46. Swearingen C, Simpson P, Cabacungan E, et al. Social disparities negatively impact neonatal follow-up clinic attendance of premature infants discharged from the neonatal intensive care unit. J Perinatol 2020;40(5):790–797. DOI: 10.1038/s41372-020-0659-4.
47. Chandrasekaran SA, John HB, Ross BJ, et al. Torn between two worlds: Parental experiences of neonatal follow-up for infants with hypoxic ischaemic encephalopathy in India-a qualitative study using interpretative phenomenological analysis. BMJ Open 2022;12(11):e063732. DOI: 10.1136/bmjopen-2022-063732.
48. Byrne AL, Baldwin A, Harvey C, et al. Understanding the impact and causes of 'failure to attend' on continuity of care for patients with chronic conditions. PLoS One 2021;16(3):e0247914. DOI: 10.1371/journal.pone.0247914.
49. Gorsky KG, Butala S, House M, et al. Uncertainty and the NICU experience: A qualitative evaluation of family and provider perspectives. Children (Basel) 2023;10(11). DOI: 10.3390/children10111745.
50. Zeitlin W, McInerney M, Balser G, et al. Communication is key: At-risk families' perspectives on follow-up in New Jersey's early hearing detection and intervention program. Soc Work Health Care 2024;63(2):74–88. DOI: 10.1080/00981389.2023.2292547.
51. Crawford M, Fleming P, Moghal N. The fragmented clinical record: A risk to at-risk children. Lancet 2009;373(9657):25. DOI: 10.1016/S0140-6736(08)61945-5.
52. Woodman J, Allister J, Rafi I, et al. A simple approach to improve recording of concerns about child maltreatment in primary care

records: Developing a quality improvement intervention. Br J Gen Pract 2012;62(600):e478–e486. DOI: 10.3399/bjgp12X652346.
53. Goldberg L, Rankine J, Devlin B, et al. School nurse perspectives on collaboration with primary care providers. J Sch Health 2023;93(8):717–725. DOI: 10.1111/josh.13325.
54. Landy CK, Jack SM, Wahoush O, et al. Mothers' experiences in the Nurse-Family Partnership program: A qualitative case study. BMC Nurs 2012;11:15. DOI: 10.1186/1472-6955-11-15.
55. Bawah RK, Osman W, Pireh D, et al. Nursing staff involvement of children in care activities: A cross-sectional study. Int J Nurs Stud Adv 2023;5:100160. DOI: 10.1016/j.ijnsa.2023.100160.
56. Burt S, Lewis R, Braithwaite Y. Faith community nursing: Impacting community-based care. J Christ Nurs 2024;41(3):160–165. DOI: 10.1097/CNJ.0000000000001178.
57. Bird C, Dutton F, Kaur S, et al. Early activity and impact of a neighbourhood multidisciplinary team that integrates health and social support for underserved children and young people in Birmingham, UK: An observational study. BMJ Paediatr Open 2025;23:9(1). DOI: 10.1136/bmjpo-2025-003935.
58. Boustani MM, Frazier SL, Marin D, et al. A qualitative review of community health workers' training, supervision, and service delivery needs. Adm Policy Ment Health 2025;52(6):1061–1075. DOI: 10.1007/s10488-025-01439-w.
59. Coker TR, Gregory EF, McCord M, et al. Integrating community health workers in early childhood well-child care: A statement from the Pediatric Academic Societies Maternal Child Health: First 1,000 days Special Interest Group. BMC Prim Care 2024;25(1):345. DOI: 10.1186/s12875-024-02582-3.
60. Crable EL, Biancarelli DL, Aurora M, et al. Interventions to increase appointment attendance in safety net health centers: A systematic review and meta-analysis. J Eval Clin Pract 2021;27(4):965–975. DOI: 10.1111/jep.13496.
61. Agonafer EP, Carson SL, Nunez V, et al. Community-based organizations' perspectives on improving health and social service integration. BMC Public Health 2021;21(1):452. DOI: 10.1186/s12889-021-10449-w.
62. Joh-Carnella N, Livingston E, Kagan-Cassidy M, et al. Understanding the roles of the healthcare and child welfare systems in promoting the safety and well-being of children. Front Psychiatry 2023;14:1195440. DOI: 10.3389/fpsyt.2023.1195440.
63. Buivydaite R, Tsiachristas A, Thomas S, et al. Understanding the impact of a new approach to the safeguarding of children at risk: An evaluation protocol. Int J Integr Care 2022;22(4):9. DOI: 10.5334/ijic.5980.
64. Sharma M, Akhter MS, Roy S, et al. Future issues in global health: Challenges and conundrums. Int J Environ Res Public Health 2025;22(3). DOI: 10.3390/ijerph22030325.
65. de Koning R, Gonzalez Utrilla M, Spanaus E, et al. Strategies used to improve vaccine uptake among healthcare providers: A systematic review. Vaccine X 2024;19:100519. DOI: 10.1016/j.jvacx.2024.100519.

EXPERT VIEW/REVIEW PAPER

Fetal Hydrops, Meconium Peritonitis, and Distal Ileal Atresia in a Neonate with a Homozygous Fanconi Anemia *FANCG* Splice Variant: A Case Report

Kanithi Ravishankar[1], Kambham Rishika[2]

Received on: 01 May 2026; *Accepted on*: 10 June 2026; *Published on*: 22 June 2026

Abstract

Fanconi anemia (FA) is a clinically heterogeneous disorder of DNA repair associated with bone marrow failure, malignancies, and congenital malformations. While gastrointestinal (GI) anomalies such as duodenal and anal atresias are recognized in the FA spectrum, jejunoileal atresias presenting with fetal hydrops are rare. We report the case of a male infant born to consanguineous parents who presented prenatally with non-immune hydrops fetalis and postnatally with meconium peritonitis. Surgical exploration revealed distal ileal atresia with necrosis. The patient also exhibited left preaxial polydactyly. Whole exome sequencing (WES) identified a homozygous likely pathogenic 5′ splice site variant in the Fanconi anemia complementation group gene (*FANCG)* (c.307+1G>T). Fanconi anemia complementation group mutations are associated with a severe clinical phenotype and high risk of early-onset bone marrow failure. This case highlights the rare presentation of distal ileal atresia and meconium peritonitis in *FANCG*-associated FA, supporting the hypothesis that defective DNA repair and endothelial fragility may predispose fetuses to vascular disruption sequences. Early genetic diagnosis in neonates with atypical GI atresias and skeletal anomalies is critical for guiding perioperative management and initiating long-term hematologic surveillance.

Keywords: Atypical gastrointestinal atresias, Bone marrow failure, Congenital anemia, DNA repair, Endothelial fragility, ERCC1-XPF endonuclease, *FANCG* gene, *FANCG* gene (c.307+1G>T; ENST00000378643.8), Fanconi anemia complementation group G, Hematologic surveillance, Hydrops fetalis, Intestinal necrosis, Meconium peritonitis, Monoubiquitination of the FANCD2/FANCI heterodimer, Neonate, Newborn, Polydactyly, Repair of DNA interstrand cross-links, Skeletal anomalies, VACTERL-H association (vertebral, anal, cardiac, tracheo-esophageal, renal, limb anomalies, and hydrocephalus), Vascular disruption sequences.

Newborn (2026): 10.5005/jp-journals-11002-0159

Keypoints

- Fanconi anemia (FA) is a clinically heterogeneous disorder of DNA repair associated with bone marrow failure, malignancies, and congenital malformations.
- The authors report a case of a male infant born to consanguineous parents who showed non-immune hydrops fetalis prior to birth and postnatally with meconium peritonitis. Surgical exploration after birth revealed distal ileal atresia with necrosis.
- Whole exome sequencing (WES) identified a homozygous likely pathogenic 5′ splice site variant in the FA complementation group gene (*FANCG)* (c.307+1G>T).
- This case highlights the rare presentation of distal ileal atresia and meconium peritonitis in *FANCG*-associated FA, supporting the hypothesis that defective DNA repair and endothelial fragility may predispose fetuses to vascular disruption sequences.

Introduction

Fanconi anemia (FA) is an inherited disorder characterized by genomic instability due to defects in the repair of DNA interstrand cross-links (ICLs).[1,2] The *FANCG* (complementation group G) encodes a critical scaffold protein that stabilizes the FA core complex, which is required for the monoubiquitination of the FANCD2/FANCI heterodimer.[3] Pathogenic variants in *FANCG* account for approximately 10–16% of all FA cases globally, with higher proportions reported in Indian (11.7–16.5%) and Japanese (25%) cohorts.[4,5] Fanconi anemia complementation group gene mutations are disproportionately associated with a severe clinical phenotype, including an elevated incidence of congenital malformations, early-onset bone marrow failure, and a very high risk of leukemia.[6–10]

Gastrointestinal (GI) anomalies, particularly duodenal atresia and anal atresia, are frequently observed in FA, often overlapping with the vertebral, anal, cardiac, tracheoesophageal, renal, limb anomalies, and hydrocephalus (VACTERL-H) association.[11] However, jejunoileal atresia is the least common GI defect in this population.[12] In this report, we describe a neonate presenting with hydrops fetalis, meconium peritonitis, distal ileal atresia, and preaxial polydactyly, who was diagnosed with a homozygous splice variant in the *FANCG* gene.[13,14]

Written informed consent for publication of this case report and accompanying nonidentifying clinical information was obtained from the patient's parents.

[1,2]Department of Pediatrics/Neonatology, Sowmya Children's Hospital, Hyderabad, Telangana, India

Corresponding Author: Kambham Rishika, Department of Pediatrics/Neonatology, Sowmya Children's Hospital, Hyderabad, Telangana, India, Phone: +91 9848014641, e-mail: rishikakambham@gmail.com

How to cite this article: Ravishankar K, Rishika K. Fetal Hydrops, Meconium Peritonitis, and Distal Ileal Atresia in a Neonate with a Homozygous Fanconi Anemia *FANCG* Splice Variant: A Case Report. Newborn 2026;5(2):109–112.

Source of support: Nil

Conflict of interest: None

Clinical Report

Our patient was a male infant born to a 19-year-old primigravida mother of consanguineous descent. The pregnancy was uncomplicated until an ultrasound at 35 weeks and 3 days of gestation revealed gross fetal ascites, mild pericardial and pleural effusions, and increased fetal abdominal wall thickness (12–13 mm). Due to non-reassuring cardiotocography (CTG) and hydrops fetalis, the infant was delivered via emergency lower segment cesarean section (LSCS) at 35 weeks and 4 days.

The proband weighed 1.92 kg at birth and required extensive resuscitation. Apgar scores were 0 at 1 minute, 0 at 5 minutes, and 6 at 10 minutes. Intubation, cardiopulmonary resuscitation, and intravenous adrenaline were administered before spontaneous efforts were regained. Physical examination revealed gross abdominal distension and pre-axial polydactyly of the left hand. An echocardiogram demonstrated a patent ductus arteriosus (PDA) with left-to-right shunt, a patent *foramen ovale* (PFO), poor cardiac output, and mild pericardial and pleural effusions. Abdominal ultrasound identified gross ascites with dense internal echoes, suggesting meconium peritonitis, and an abdominal tap yielded fluid with elevated amylase and lipase.

On postnatal day 3, the proband underwent an exploratory laparotomy. Surgical findings revealed a single distal ileal atresia with focal necrosis and frank meconium peritonitis. The necrotic ileal segment was resected, and an end ileostomy was created, followed by peritoneal lavage. Histopathological examination of the resected ileum confirmed ulceration, pigment-laden macrophages, calcification, and distended mucous cells consistent with meconium ileus/atresia (Fig. 1). Crucially, ganglion cells were present throughout the resected segment, ruling out Hirschsprung disease.

Given the combination of GI atresia, meconium peritonitis, and skeletal anomalies (polydactyly), WES was performed when the proband was 2 months old. Sequencing identified a homozygous 5′ splice site variant in intron 3 of the *FANCG* gene (c.307+1G>T; ENST00000378643.8).[15] This variant affects the invariant GT donor splice site and was classified as Likely Pathogenic [Pathogenic Moderate (PM2), (Pathogenic Very Strong (PVS1)].[16] The diagnosis of FA, complementation group G, was confirmed, and the parents received genetic counseling regarding the autosomal recessive inheritance pattern, the 25% recurrence risk, and the lifetime risks of hematological malignancy and bone marrow failure.[10]

Discussion

We report a severe case of *FANCG*-associated FA presenting unusually with hydrops fetalis, meconium peritonitis secondary to distal ileal atresia, and preaxial polydactyly. The pathogenesis of intestinal atresia in FA differs from sporadic cases. Gastrointestinal anomalies occur in approximately 7% of FA patients; the most common include esophageal atresia, duodenal atresia, and anorectal malformations, frequently embedded within the broader VACTERL-H spectrum.[17] While duodenal atresia in FA is believed to stem from uncontrolled apoptosis and failure of gut recanalization due to extreme cellular sensitivity to oxidative stress in rapidly proliferating cells, jejunoileal atresia is traditionally attributed to vascular disruption *in utero*.[18] The most widely accepted pathogenic mechanism for jejunoileal atresia posits that an intrauterine vascular accident causes ischemia to a segment of the fetal intestine, leading to resorption of the affected segment and subsequent atresia.[19] Contributing precipitants include intussusception, volvulus, perforation, and thromboembolism; placental vascular compromise has also been identified as an additional factor in atresias associated with low birth weight and multiple congenital anomalies.[14,20–23]

The *FANCG* splice-site variant c.307+1G>T is usually expected to produce an altered/truncated protein with subnormal/non-functional protein, although the exact outcome depends on how the RNA is spliced (one example can be seen in Fig. 2).[3–10] The notation "c.307+1G>T" means the mutation occurs at the +1 position of the donor splice site immediately after exon 3 of the *FANCG* gene. The +1 guanine is part of the highly conserved "GT" splice donor sequence required for normal RNA splicing. Such variations typically disrupt exon recognition and may result in exon skipping, intron retention, frameshifts, or premature stop

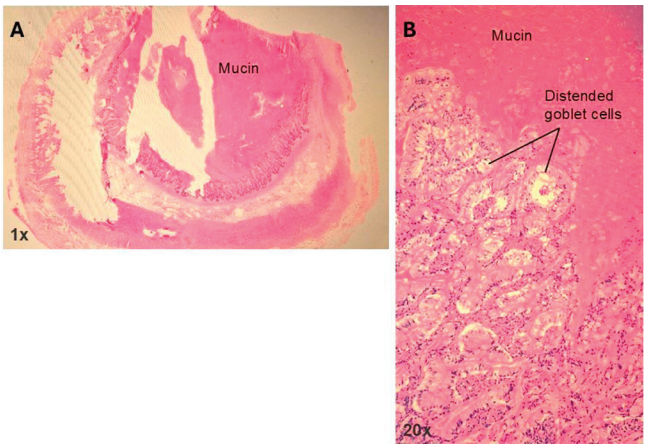
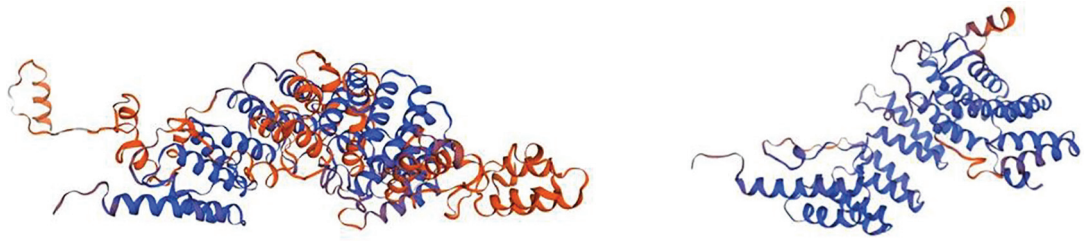


Fig. 1: Hematoxylin and Eosin-stained sections (A) 1x and (B) 20x of resected ileal tissue showing distended goblet cells with overlying mucin



A **Fanconi anemia group G (*FANCG*) protein**

B **Truncated *FANCG* (c.307+1G>T; ENST00000378643.8)**

Fig. 2: *FANCG* protein (A) is a 622 amino-acid-long, 68.6 kDa, predominantly an α-helical protein rich in tetratricopeptide repeat (TPR)-like motifs, which help mediate protein–protein interactions within the FA complex. It is mostly seen in the nucleus. (B) The figure on the right shows a truncated version resulting from the c.307+1G>T mutation

codons. Some closely related variants at the same splice donor site (c.307+1G>C) show skipping of exon 3 or exons 3–4, producing abnormal transcripts predicted to lead to loss of function. Some of these splice-site variants do not appear truncated because they may undergo nonsense-mediated decay, while others may generate shortened or structurally altered proteins.

The role of the FA pathway in vascular and cellular integrity is increasingly recognized. *FANCG* directly interacts with the excision repair cross-complementation group 1 (ERCC1)-xeroderma pigmentosum complementation group F (XPF) endonuclease via its TPRs and the central domain of ERCC1 — an essential component of the ICL incision machinery.[24,25] Loss of *FANCG* in murine models has been shown to cause replicative stress-induced apoptosis in rapidly proliferating progenitor cells, analogous to the mechanism predicted to compromise endothelial progenitors in the developing fetal vasculature.[26,27] Because the FA repair pathway is essential for maintaining genomic integrity in all proliferating cells, including vascular endothelial cells, its loss renders these cells hypersusceptible to oxidative DNA damage.[28] This likely precipitates microscopic vascular insults resulting in ischemic necrosis and subsequent atresia of the ileum.[29] In our patient, this ischemic event likely led to the distal ileal atresia and subsequent in utero bowel perforation, resulting in meconium peritonitis. Meconium peritonitis is a rare form of sterile chemical peritonitis caused by antenatal intestinal perforation; when associated with intestinal atresia, it can progress to non-immune hydrops fetalis. As observed in this case, it can involve massive peritoneal inflammation, lymphatic obstruction, and hypoalbuminemia.[17,21,30,31]

The presence of preaxial polydactyly in our patient strongly aligns with the mesodermal defects (radial ray anomalies) canonically associated with the FA spectrum.[32] A systematic review of 2,245 published FA cases identified an "FA VATER signal" defined by the combined presence of radial ray and renal anomalies.[11] This pattern was uncommon in non-FA VATER patients. Patients with this FA VATER phenotype displayed a worse prognosis, shorter median survival, and earlier onset of malignancy compared with FA patients with milder phenotypes.[33] The identification of intestinal atresia alongside a radial ray or digital defect should therefore immediately prompt evaluation for an FA core complex mutation.[14]

Establishing a genetic diagnosis of *FANCG* deficiency carries profound implications for clinical management.[10] A landmark genotype–phenotype analysis of FA complementation groups demonstrated that FA-G patients exhibit more severe cytopenia, earlier onset of bone marrow failure, and a significantly higher incidence of acute myeloid leukemia (AML) compared with most other complementation groups, placing FA-G among the highest-risk genotypes requiring early intervention and frequent hematologic monitoring.[30] Postoperative care must be meticulously managed: Hyperoxia during anesthesia generates reactive oxygen species that aggravate apoptosis in FA-deficient cells, and therefore high inspired oxygen concentrations, nitrous oxide, and bone marrow–suppressive anesthetic agents should be avoided.[34] Furthermore, these patients must be strictly protected from DNA ICLs chemotherapeutic agents and unnecessary ionizing radiation, which are profoundly toxic to FA-deficient cells.[7,9,10,35,36]

In conclusion, this case underscores that fetal intestinal atresia, including the rare jejunoileal subtype coupled with skeletal anomalies, warrants immediate investigation for FA.[10] Early identification of *FANCG* mutations is important for appropriate clinical management and for planning long-term hematologic and oncologic surveillance.[21]

Authors' Contributions

Kanithi Ravishankar: Conceptualization, formal analysis, and writing - original draft. Rishika: Data curation, medical management, and writing - review and editing.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Support

None for this publication.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request, subject to institutional ethical restrictions to protect patient privacy.

References

1. Fang C, Zhu Z, Cao J, et al. Comprehensive review on Fanconi anemia: Insights into DNA interstrand cross-links, repair pathways, and associated tumors. Orphanet J Rare Dis 2025;20(1):389. DOI: 10.1186/s13023-025-03896-w.
2. Rageul J, Kim H. Fanconi anemia and the underlying causes of genomic instability. Environ Mol Mutagen 2020;61(7):693–708. DOI: 10.1002/em.22358.
3. Nagareddy B, Khan A, Kim H. Acetylation modulates the Fanconi anemia pathway by protecting FAAP20 from ubiquitin-mediated proteasomal degradation. J Biol Chem 2020;295(40):13887–13901. DOI: 10.1074/jbc.RA120.015288.
4. Donovan FX, Solanki A, Mori M, et al. A founder variant in the South Asian population leads to a high prevalence of FANCL Fanconi anemia cases in India. Hum Mutat 2020;41(1):122–128. DOI: 10.1002/humu.23914.
5. Mori M, Hira A, Yoshida K, et al. Pathogenic mutations identified by a multimodality approach in 117 Japanese Fanconi anemia patients. Haematologica 2019;104(10):1962–1973. DOI: 10.3324/haematol.2018.207241.
6. Mehta PA, Ebens CL. Fanconi Anemia. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. Seattle, WA: GeneReviews(R); 1993.
7. Hoover A, Turcotte LM, Phelan R, et al. Longitudinal clinical manifestations of Fanconi anemia: A systematized review. Blood Rev 2024;68:101225. DOI: 10.1016/j.blre.2024.101225.
8. Moreno OM, Paredes AC, Suarez-Obando F, et al. An update on Fanconi anemia: Clinical, cytogenetic and molecular approaches (Review). Biomed Rep 2021;15(3):74. DOI: 10.3892/br.2021.1450.
9. Repczynska A, Ciastek B, Haus O. New insights into the Fanconi anemia pathogenesis: A crosstalk between inflammation and oxidative stress. Int J Mol Sci 2024;25(21):11619. DOI: 10.3390/ijms252111619.
10. Bhandari J, Thada PK, Killeen RB, et al. Fanconi Anemia. Treasure Island, Florida, USA: StatPearls Publishing; 2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559133/.
11. Alter BP, Rosenberg PS. VACTERL-H association and Fanconi anemia. Mol Syndromol 2013;4(1-2):87–93. DOI: 10.1159/000346035.
12. Sharma P, Sharma N, Sharma D. A narrative review on Fanconi anemia: Genetic and diagnostic considerations. Glob Med Genet 2022;9(3):237–241. DOI: 10.1055/s-0042-1751303.
13. Celli J. Genetics of gastrointestinal atresias. Eur J Med Genet 2014;57(8):424–439. DOI: 10.1016/j.ejmg.2014.06.007.

14. Pulliam-Leath AC, Ciccone SL, Nalepa G, et al. Genetic disruption of both Fancc and Fancg in mice recapitulates the hematopoietic manifestations of Fanconi anemia. Blood 2010;116(16):2915–2920. DOI: 10.1182/blood-2009-08-240747.
15. Yamada T, Tachibana A, Shimizu T, et al. Novel mutations of the FANCG gene causing alternative splicing in Japanese Fanconi anemia. J Hum Genet 2000;45(3):159–166. DOI: 10.1007/s100380050203.
16. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405–424. DOI: 10.1038/gim.2015.30.
17. Hays L. Fanconi Anemia: Guidelines for Diagnosis and Management Eugene, Oregon, USA: Fanconi Anemia Research Fund, Inc.; 2014. Available from: https://www.fanconi.org/images/uploads/other/Guidelines_4th_Edition.pdf.
18. Sigmon DF, Eovaldi BJ, Cohen HL. Duodenal Atresia and Stenosis. [Updated 2023 Jun 26] Treasure Island, Florida, USA: StatPearls Publishing; 2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470548/.
19. Oh C. Jejunoileal atresia: A contemporary review. Adv Pediatr Surg 2023;29(2):89–99. DOI: 10.13029/aps.2023.29.2.89.
20. Przychodzen B, Makishima H, Sekeres MA, et al. Fanconi anemia germline variants as susceptibility factors in aplastic anemia, MDS and AML. Oncotarget 2018;9(2):2050–2057. DOI: 10.18632/oncotarget.23328.
21. Kee Y, D'Andrea AD. Molecular pathogenesis and clinical management of Fanconi anemia. J Clin Invest 2012;122(11):3799–3806. DOI: 10.1172/JCI58321.
22. LifeMap_Sciences. Fanconi Anemia, Complementation Group L (FANCL) Rehovot, Israel: LifeMap Sciences, Inc.; 2026. Available from: https://www.malacards.org/card/fanconi_anemia_complementation_group_l.
23. Alam MS, Elghote SE, Kamel SMM, et al. Intestinal atresia leading to intussusception: An unconventional submission. Cureus 2024;16(9):e69723. DOI: 10.7759/cureus.69723.
24. Sumpter R, Jr., Levine B. Emerging functions of the Fanconi anemia pathway at a glance. J Cell Sci 2017;130(16):2657–2662. DOI: 10.1242/jcs.204909.
25. Wang C, Lambert MW. The Fanconi anemia protein, FANCG, binds to the ERCC1-XPF endonuclease via its tetratricopeptide repeats and the central domain of ERCC1. Biochemistry 2010;49(26):5560–5569. DOI: 10.1021/bi100584c.
26. Parmar K, D'Andrea A, Niedernhofer LJ. Mouse models of Fanconi anemia. Mutat Res 2009;668(1-2):133–140. DOI: 10.1016/j.mrfmmm.2009.03.015.
27. Garcia-de-Teresa B, Rodriguez A, Frias S. Chromosome instability in Fanconi anemia: From breaks to phenotypic consequences. Genes (Basel) 2020;11(12):1528. DOI: 10.3390/genes11121528.
28. Du W, Adam Z, Rani R, et al. Oxidative stress in Fanconi anemia hematopoiesis and disease progression. Antioxid Redox Signal 2008;10(11):1909–1921. DOI: 10.1089/ars.2008.2129.
29. Matarneh AS, Matarneh B, Rout P, et al. Fanconi Syndrome. Treasure Island, Florida, USA: StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534872/.
30. Faivre L, Guardiola P, Lewis C, et al. Association of complementation group and mutation type with clinical outcome in fanconi anemia. European Fanconi Anemia Research Group. Blood 2000;96(13):4064–4070. PMID: 11110674.
31. Mehta PA, Ebens CL. Fanconi Anemia Complementation Group G (FANCG). Bethesda, Maryland, USA: National Library of Medicine; 2026. Available from: https://www.ncbi.nlm.nih.gov/medgen/854017.
32. Bourke G, Wilks D, Kinsey S, et al. The incidence and spectrum of congenital hand differences in patients with Fanconi anaemia: Analysis of 48 patients. J Hand Surg Eur Vol 2022;47(7):711–715. DOI: 10.1177/17531934221087521.
33. Alter BP, Rosenberg PS, Brody LC. Clinical and molecular features associated with biallelic mutations in FANCD1/BRCA2. J Med Genet 2007;44(1):1–9. DOI: 10.1136/jmg.2006.043257.
34. Jung M, Ramanagoudr-Bhojappa R, van Twest S, et al. Association of clinical severity with FANCB variant type in Fanconi anemia. Blood 2020;135(18):1588–1602. DOI: 10.1182/blood.2019003249.
35. Maung KZY, Leo PJ, Bassal M, et al. Rare variants in Fanconi anemia genes are enriched in acute myeloid leukemia. Blood Cancer J 2018;8(6):50. DOI: 10.1038/s41408-018-0090-7.
36. Rosenberg PS, Huang Y, Alter BP. Individualized risks of first adverse events in patients with Fanconi anemia. Blood 2004;104(2):350–355. DOI: 10.1182/blood-2004-01-0083.

CASE SERIES

Neonates with Persistent Fever, Omphalitis, and Hepatomegaly Need should be Evaluated for a Liver Abscess

Nikhil Jain

Received on: 11 May 2026; *Accepted on*: 12 June 2026; *Published on*: 22 June 2026

Abstract

Background: Liver abscess is a rare diagnosis in neonates but it can be associated with serious complications and high mortality. Very little is known about the risk factors, management, and complications; and hence, a high level of suspicion and careful screening is needed.

Objectives: We present a retrospective case-series of six infants with fever, sepsis, omphalitis, and liver abscess.

Study design: These infants were admitted in our newborn unit between March 2020 and February 2025 for persistent fever, omphalitis, hepatomegaly, and signs of sepsis were found to have one/more liver abscess(es). We present their demographics and clinical presentation, predisposing factors, laboratory investigations, imaging findings, and clinical course/outcomes.

Observations: The six neonates admitted with fever, omphalitis, and hepatomegaly were born at a gestational age of average 36.6 weeks (range 34–39) with a birth weight of 3.3 (3.1–4.2 kg). The postnatal age at admission was average 18.5 (10–27 days). None had a history of umbilical catheterization. Abdominal distension with paralytic ileus was noted in four and signs of inflammation on the abdominal wall were evident in one. Three had clinical features of peritonitis. One had septic shock at admission. Sonography showed multiple liver abscesses in three patients and a one abscess was notable in the other three. The right lobe was involved in five patients with abscesses measuring 1–5 cm. Four patients tested positive for *Staphylococcus aureus* in blood or pus; the isolates were methicillin-resistant in four and methicillin-sensitive in one. All infants were initiated empirically on vancomycin with clindamycin at admission, which was then later modified on the basis of sensitivity reports. Three infants who showed clinical findings suggestive of peritonitis had at least one ruptured liver abscess and underwent operative management. All patients were followed sonographically for abscess resolution; two developed portal cavernomas.

Conclusion: Neonates admitted with fever, omphalitis, and hepatomegaly should be evaluated for a liver abscess. A high index of suspicion is required for timely diagnosis. Long-term follow-up is required to monitor the risk of portal cavernomas and portal hypertension.

Keywords: Community-acquired *Staphylococcus aureus*, Infant, Methicillin-resistant staphylococcus aureus (MRSA), Methicillin-sensitive staphylococcus aureus (MSSA), Neonatal liver abscess, Neonate, Newborn, Omphalitis, Portal cavernoma, Portal hypertension.

Newborn (2026): 10.5005/jp-journals-11002-0155

Key Points

- Liver abscess is a rare diagnosis in neonates but it can be associated with serious complications and high mortality.
- The patients were admitted with fever, omphalitis, and hepatomegaly. The diagnosis was confirmed on sonography. There were no frequently-associated risk factors such as umbilical catheters.
- Four patients tested positive for *Staphylococcus aureus* in blood or pus; the isolates were methicillin-resistant in four and methicillin-sensitive in one.
- Neonates admitted with fever, omphalitis, and hepatomegaly should be evaluated for a liver abscess. A high index of suspicion is required for timely diagnosis. Long-term follow-up is required to monitor the risk of portal cavernomas and portal hypertension.

Department of Neonatology, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India

Corresponding Author: Nikhil Jain, Department of Neonatology, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India, Phone: +91 7987808638, e-mail: nikhiljain1791@gmail.com

How to cite this article: Jain N. Neonates with Persistent Fever, Omphalitis, and Hepatomegaly Need should be Evaluated for a Liver Abscess. Newborn 2026;5(2):113–117.

Source of support: Nil

Conflict of interest: None

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

Introduction

Liver abscess in neonates is a rare clinical entity with serious complications and high mortality.[1,2] The rarity of liver abscesses may be explained partly by the rich blood supply, unique architecture, and extensive reticuloendothelial system of the liver.[3] Neonatal liver abscesses could be idiopathic, or secondary to sepsis or omphalitis, some of which may be related to umbilical vein catheterization.[4] Other predisposing factors include central parenteral nutrition lines (central venous lines), necrotizing enterocolitis (NEC), umbilical and gallbladder or liver surgery, prematurity, and neutrophil defects.[5] Potential routes of hepatic infection include portal vein, biliary ducts, hepatic artery during sepsis, or direct spread from infected contiguous structures.[6,7] Signs such as lethargy, fever, intolerance to feeding, vomiting, abdominal distention, abdominal tenderness, and hepatomegaly are non-specific, as are laboratory findings such as leukocytosis, neutropenia, thrombocytopenia, increased erythrocyte sedimentation rates (ESR), elevated C-reactive protein (CRP) and elevated or normal liver enzymes.[8–10] Conservative management involve rational use of antibiotic for 3–4 weeks,

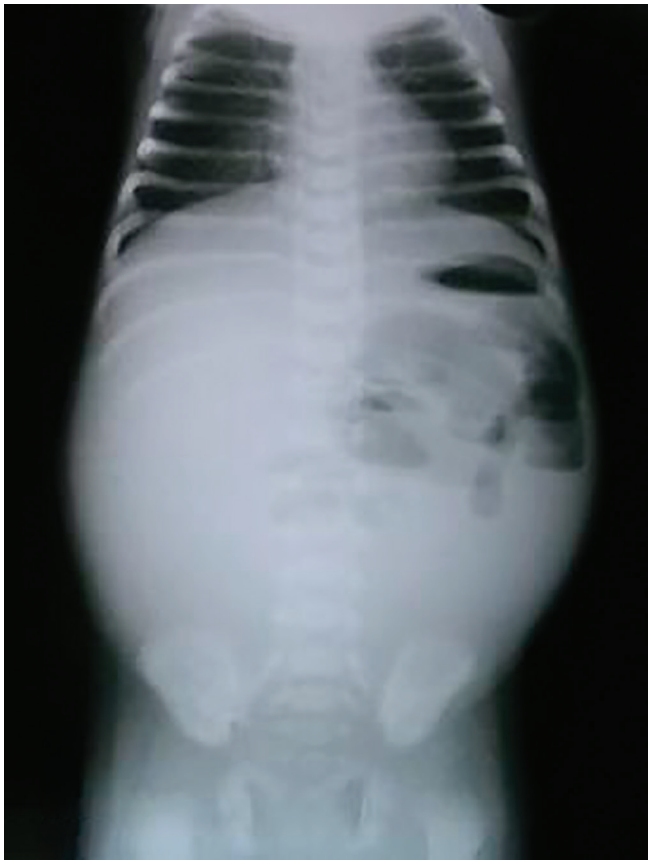


Fig. 1: X-ray of chest and abdomen of an infant with a ruptured liver abscess and peritonitis. The abdominal opacification was due to hepatomegaly and ascites that was confirmed on ultrasound examination

while patients having features of ruptured abscess require surgical management. Common complications are sepsis, peritonitis, NEC, bowel perforation, portal vein thrombosis, and portal hypertension (Figs 1 to 3).[11,12]

We still do not have specific information about the predisposing factors or clinical presentations associated with neonatal liver abscesses, and consequently the diagnosis is frequently delayed. This patient cluster with liver abscesses was seen in our neonatal unit within a span of few months, and the fact that none had received an umbilical catheter, evoked interest in the team to analyze the clinical presentation, laboratory investigations, radiological findings, possible risk factors, management, and the final outcomes in newborns with liver abscess (Table 1).

Materials and Methods

This retrospective study was performed in a single tertiary center over 5 years period between March 2020 and February 2025, after taking institutional clearance. It included all patients till the corrected gestational age of 44 weeks of life, who were admitted in our newborn unit with persistent fever, omphalitis, hepatomegaly, and signs of sepsis. The patients were analyzed for gestational age at birth, birth weight age, sex, mode of delivery, presentation, predisposing factors, and laboratory investigations. Liver abscesses were studied for location, number, and size. The clinical course and outcome were recorded. In abscesses, sonographic findings ranged between a heterogenous hypoechoic lesion with or without internal echoes, to hyperechoic lesions.[13]

All patients were started on empirical broad-spectrum intravenous antibiotics to cover both gram-positive and gram-negative aerobic organisms until a culture report was finalized. Irrespective of the size of the abscess, all clinically-stable patients were treated conservatively with an empirical course of intravenous antibiotic. Critically-ill patients underwent an exploratory laparotomy and examined for ruptured abscess(es) and the antibiotic management was modified based on blood/pus culture reports. Once stable, the route of antibiotic administration was changed from intravenous to oral and the vital signs were monitored closely for 48–72 hours. Most infants were received antibiotics for 3–4 weeks, until sonographic resolution of the abscess lesions. These patients were followed closely after discharge and were followed for the development of complications like portal cavernomas and portal hypertension.[14]

Observations

We identified six neonates with persistent fever, omphalitis, hepatomegaly, and signs of sepsis. They were found to have one/more liver abscess(es). These infants were born at a gestational age of average 36.6 weeks (range 34–39) with a birth weight of 3.37 (3.1–4.2 kg). The postnatal age at admission was average 18.5 (10–27 days). Four of six patients were male.

None of the patients had a history of umbilical catheterization. All had presented with fever, a notable umbilical abscesses/discharge, and hepatomegaly. Four showed notable abdominal distension with paralytic ileus, and one showed with abdominal wall swelling. Three were admitted with features of peritonitis. One had septic shock, seizures, and a notable pustule on the back.

All six patients had leukocytosis and raised CRP levels. The infant with septic shock showed hyponatremia. All other biochemical tests, including liver function panels, were within normal limits. Ultrasound examination showed multiple liver abscesses in three and one abscess in three patients. The abscesses ranged between 1 and 5 cm diameter in the patients. The lesion was seen in the right lobe in five infants. Blood/pus cultures showed *S. aureus* in four patients; the other two remained culture negatives. Three patients grew methicillin-resistant organisms, whereas the 4th had methicillin-sensitive Staphylococcus spp.

On admission, all patients were treated empirically with vancomycin and clindamycin, and the antibiotic regimens were modified once the sensitivity reports became available. The three infants with features of peritonitis underwent operative management and were found to have ruptured liver abscesses. Antibiotics were continued based on improvement in clinical status (fever and activity), laboratory markers of sepsis (leukocytosis and CRP), and sonographic features of the liver abscesses. The median duration of stay in hospital was 18.5 (12–28 days) and antibiotics were given for 24 (21–29 days). All patients were followed on ultrasound for abscess resolution. Two developed portal cavernomas.

Discussion

Neonatal liver abscess is a rare complication of neonatal sepsis with serious clinical sequelae.[1,2] A high index of suspicion is needed for

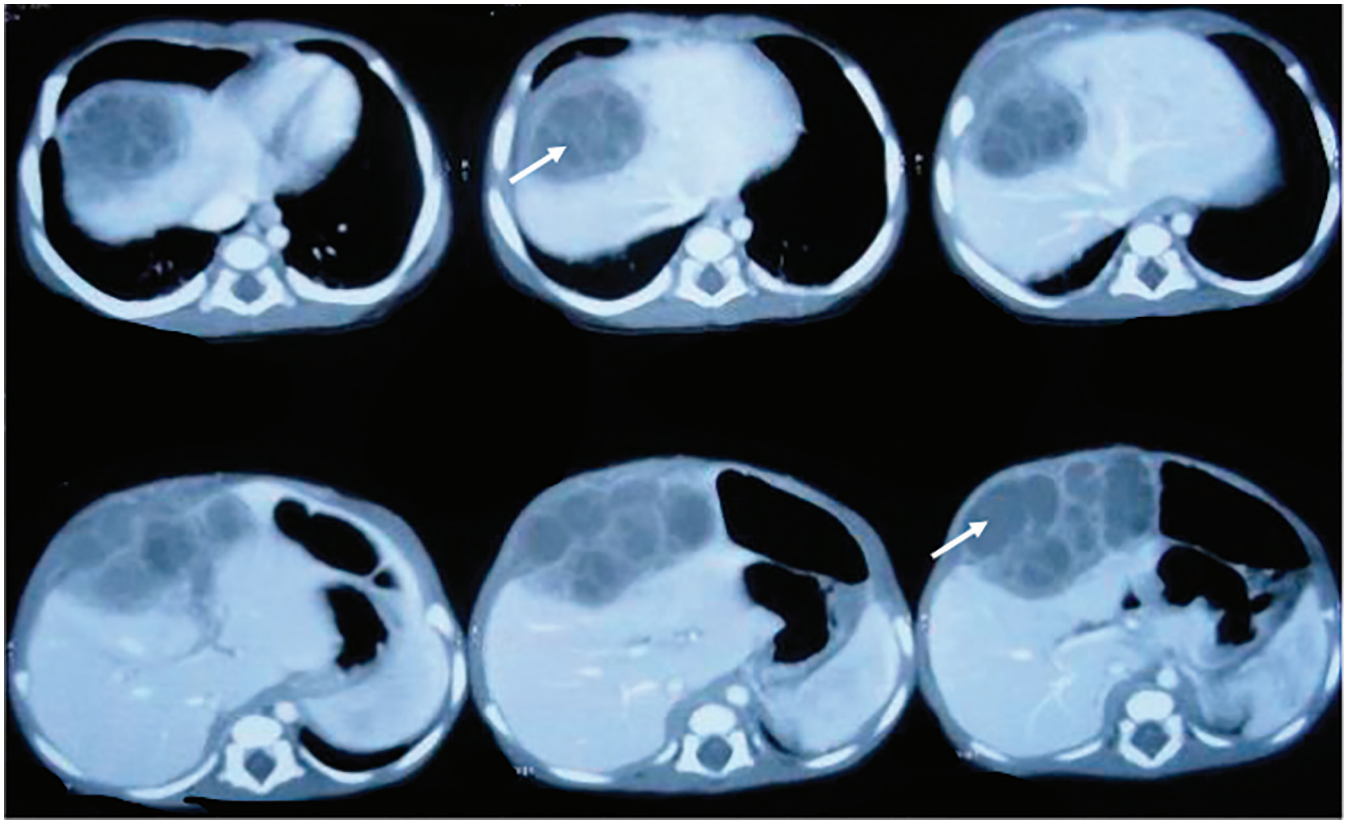


Fig. 2: Abdominal CT scans of a patient showing liver abscesses (arrow)

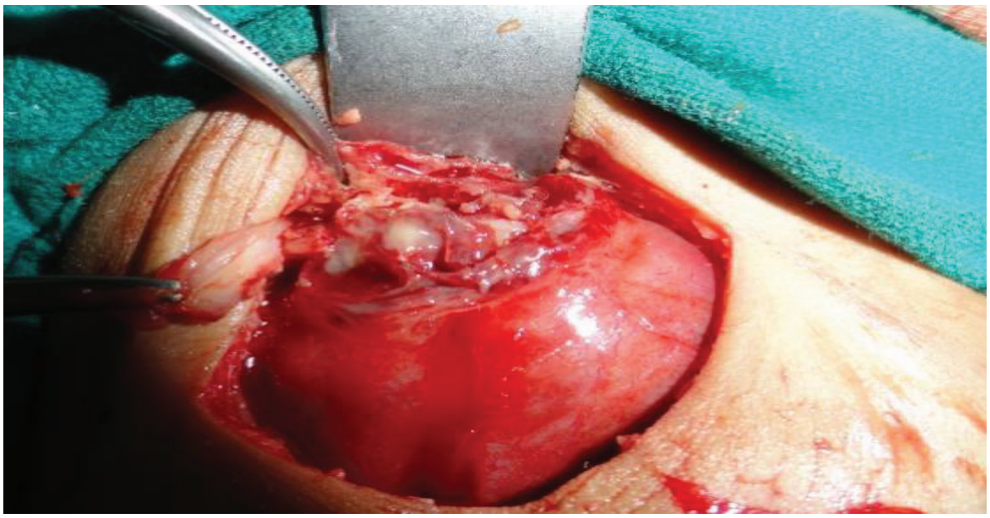


Fig. 3: Intra-operative image of a ruptured neonatal liver abscess

this diagnosis. Timely identification and appropriate management are crucial to minimize the morbidity and mortality from liver abscess. Neonates with fever, lethargy, feeding intolerance, hepatomegaly/abdominal mass(es), leukocytosis, and elevated CRP should be evaluated. A delay in diagnosis can lead to increased morbidity and life-threatening complications.[15]

Previous studies have identified incorrect placement of umbilical vein catheters as the most frequent predisposing factor for liver abscesses. Central lines placed to administer parenteral nutrition, NEC, surgery, and prematurity have also been associated.[4,8] However, these risk factors have not been identified consistently.[16] In our series, none of the patients had received an umbilical line. The association with omphalitis and portal vein thrombosis suggests that community-acquired umbilical sepsis cannot be excluded as an important cause of liver abscess in neonates.

Table 1: Demographic, clinical presentation, microbiology, imaging findings of abscess, management, and final outcome

Case	*I*	*II*	*III*	*IV*	*V*	*VI*
Age at presentation (days)	25	27	12	10	17	20
Weight at presentation (kg)	3.1	4.2	3.3	3.2	3.3	3.1
Gestational age at birth	38 weeks	34 weeks	36 weeks	35 weeks	38 weeks	39 weeks
Mode of delivery (LSCS/NVD)	LSCS	LSCS	LSCS	LSCS	NVD	NVD
Birth weight (kg)	3.2	2.8	3.3	2.4	3.3	3.4
Sex (M-male/F-female)	M	M	M	F	M	F
Clinical features	Fever, history of umbilical discharge, abdominal wall swelling	Fever, Abdominal distension, and ileus history of umbilical discharge	Fever, history of umbilical discharge, abdominal distension, ileus seizures, hyponatremia shock	Fever, history of umbilical discharge, abdominal distension, and ileus lethargy	Fever Abdominal distension, and ileus lethargy history of umbilical discharge	Fever, umbilical discharge with erythema and induration
Preoperative diagnosis (ultrasound of abdomen)	Liver abscess	Liver abscess	Septic shock with liver abscess	Perforated abscess with peritonitis	Intestinal obstruction related to perforation and peritonitis	Liver abscess
Number (multiple/single)	Multiple	Multiple	Multiple	Single	Single	Single
Size (cm)	4 and 5 cm	1–2 cm	1–3 cm	5 cm	2 cm	1 cm
Lobe of liver (R-right/L-left)	Right	Right	Right	Left	Right	Right
Cultures						
Blood	Sterile	Sterile	MRSA	MRSA	MRSA	Sterile
Pus	*S. aureus*	N/A	N/A	MRSA	MRSA	N/A
Management	Surgical (ruptured abscess)	Conservative	Conservative	Surgical (ruptured abscess)	Surgical (ruptured abscess)	Conservative
Hospital stay	20 days	7 days	29 days	17 days	14 days	25 days
Development of portal vein thrombosis/cavernoma	No	No	Yes – started on LMWH	Yes	No	No

LMWH, low molecular weight heparin; LSCS, lower Segment Caesarean Section; MRSA, methicillin-resistant staphylococcus aureus; MSSA, methicillin-sensitive staphylococcus aureus; NVD, normal vaginal delivery

Ultrasound is the main modality for the diagnosis of the liver abscess.[11] It can also help in localizing and enumerating the lesion(s), assessing the severity (hepatomegaly, size of lesions, ruptured lesions, and ascites) and resolution of the lesions, and in the overall clinical management.

The most common causative pathogens are *S. aureus*, *Streptococcus pyogenes*, and *Escherichia coli*. Klebsiella spp., Pseudomonas spp., *Corynebacterium acnes*, anaerobes, and *Candida albicans* have also been cultured from neonatal liver abscesses. Polymicrobial infection is found in up to 50% of abscesses.[17–19] As noted in our study, community-acquired *S. aureus* is an important cause of liver abscess in neonates.

Conclusion

Liver abscess in neonates is an uncommon clinical entity with serious complications and high mortality. As in our series, the lesions were not associated with plausible clinical risk factors and there is a need for more data from tropical/peri-equatorial regions. Omphalitis is possibly an important risk factor for neonatal liver abscess(es) and should be treated aggressively to prevent its complications. Community-acquired *S. aureus* has been associated with liver abscess. Unfortunately, Staphylococcal sepsis can result in vague/indeterminate clinical signs and a high index of suspicion is required to identify liver abscesses. Timely diagnosis and management are needed; rational antibiotics use and surgical drainage has been found to improve survival. Long-term follow-up with repeated ultrasonography is required to monitor for the risk of portal cavernoma and portal hypertension.[20]

Ethical Approval

Yes.

Informed Consent

An informed consent was obtained from all families.

References

1. Sharma D, Choudhary M, Shastri S, et al. Neonatal liver abscesses due to Candida infection in a preterm infant, secondary to malpositioned umbilical lines–a rare entity. Pathog Glob Health 2015;109(2):84–87. DOI: 10.1179/2047773215Y.0000000008.
2. Shah SI, Hudak J, Meng HD. Meta-analysis of factors associated with survival of neonatal hepatic abscess. J Pediatr Infect Dis 2010;5(3): 215–220. DOI: 10.3233/JPI-2010-0263.
3. Feigin RD, Cherry J, Demmler-Harrison GJ, et al. Textbook of pediatric infectious diseases. Els Health Sci 2009;49:492–495. ISBN: 978-1416040446.
4. Bosnali O, Moralioglu S, Pektas O. Liver abscess: Increasing occurrence in premature newborns. J Neonatal Surg 2013;2(2):23. PMID: 26023443.
5. Tan NW, Sriram B, Tan-Kendrick AP, et al. Neonatal hepatic abscess in preterm infants: A rare entity? Ann Acad Med Singap 2005;34(9): 558–564. PMID: 16284678.
6. Freij BJ, Robinson-Dunn BE, Schlievert PM. Detection of enterotoxin Gene Cluster in *Staphylococcus epidermidis* Recovered from Neonatal Liver Abscess. Poster. American Society for Microbiology ASM Microbe: Washington, D.C; 2022.
7. Amachawadi RG, Nagaraja TG. Pathogenesis of liver abscesses in cattle. Vet Clin North Am Food Anim Pract 2022;38(3):335–346. DOI: 10.1016/j.cvfa.2022.08.001.
8. Liu KW, Fitzgerald RJ, Blake NS. An alternative approach to pyogenic hepatic abscess in childhood: An alternative approach to pyogenic hepatic abscess in childhood. J Paediatr Child Health 1990;26(2): 92–94. DOI: 10.1111/j.1440-1754.1990.tb02394.x.
9. Sethi SK, Dewan P, Faridi MM, et al. Liver abscess, portal vein thrombosis and cavernoma formation following umbilical vein catherisation in two neonates. Trop Gastroenterol 2007;28(2):79–80. PMID: 18050847.
10. Lam HS, Li AM, Chu WC, et al. Mal-positioned umbilical venous catheter causing liver abscess in a preterm infant. Neonatology 2005;88(1):54–56. DOI: 10.1159/000084718.
11. Singh D, Venkateshwar V, Bhatia M. Neonatal hepatic abscess with resolving portal vein thrombosis. Med J Armed Forces India 2015;71(1):82–74. DOI: 10.1016/j.mjafi.2012.07.020.
12. Aggarwal S, Mathur NB, Garg A. Portal vein thrombosis complicating neonatal hepatic abscess. Indian Pediatr 2003;40(10):997–1001. PMID: 14581740.
13. Ahmed M, Chowdhary S, Kumar A, et al. Solitary sterile neonatal liver abscess in an infant. Int J Contemp Pediatr 2017;1(3):187–189. DOI: 10.5455/2349-3291.ijcp20141116.
14. Yogi BR, Basnet BM, Thapa S, et al. A rare case report on neonatal complications from Nepal: Solitary neonatal hepatic abscess. Ann Med Surg (Lond) 2023;85(5):2034–2036. DOI: 10.1097/MS9.0000000000000468.
15. Semerci SY, Babayigit A, Cebeci B, et al. Hepatic abscesses in preterm infants: Report of three cases and review of the literature. J Trop Pediatr 2016;62(3):255–260. DOI: 10.1093/tropej/fmv103.
16. Anand M, Kaur Sahi P, Mantan M. Liver abscess in early infancy with no underlying risk factors: A case series. Trop Doct 2021;51(2):223–226. DOI: 10.1177/0049475520959937.
17. Sharma S, Mohta A, Sharma P. Hepatic abscess in a preterm neonate. Indian Pediatr 2007;44(3):226. PMID: 17413202.
18. Bari S, Sheikh KA, Malik AA, et al. Percutaneous aspiration vs open drainage of liver abscess in children. Pediatr Surg Int 2007;23:69–74. DOI: 10.1007/s00383-006-1812-7.
19. Filippi L, Poggi C, Gozzini E, et al. Neonatal liver abscesses due to Candida infection effectively treated with caspofungin. Acta Paediatr 2009;98(5):906–909. DOI: 10.1111/j.1651-2227.2009.01225.x.
20. Al-Qurashi FO, Aladsani AA, Al Qanea FK, et al. Portal hypertension of a delayed onset following liver abscesses in a 12-month-old infant: A case report and review of the literature. Pediatr Gastroenterol Hepatol Nutr 2019;22(4):400–406. DOI: 10.5223/pghn.2019.22.4.400.

CASE REPORT

Radiological Case Report: Duodenal Atresia in Down Syndrome

Nitasha Bagga[1,2], Monika Kaushal[2,3], Prathik Bandiya[2,4], Satyanam Bhartiya[2,5], Moisés Q Corona[2,6]

Received on: 11 May 2026; *Accepted on*: 12 June 2026; *Published on*: 22 June 2026

Abstract

Down syndrome (DS) has a strong and well-established epidemiologic association with duodenal atresia, making it one of the classic congenital anomalies linked to chromosomal disorders. Duodenal atresia occurs in approximately one in 5,000–10,000 live births in the general population, but about 20–30% of all infants born with duodenal atresia have DS. Here, we present our observations from the clinical course of an infant with phenotypic features of DS. He started vomiting at 24 hours after birth, and an abdominal radiograph showed a classical "double bubble" sign. He was treated surgically with a duodenoduodenostomy where the proximal and distal segments of the duodenum were connected to bypass the atretic segment and restore continuity in the small intestine. The infant had a reasonably stable postnatal course. In this article, we have summarized our current understanding of the clinical-radiological correlation and the likely molecular mechanisms of DS-related duodenal atresia, involving the two dosage-sensitive genes on chromosome 21, dual-specificity tyrosine phosphorylation–regulated kinase 1A (*DYRK1A*) and regulator of calcineurin 1 (*RCAN1*); overexpression of these two genes disrupts key developmental pathways involving Wnt/β-catenin, sonic hedgehog (SHH), and fibroblast growth factor (FGF). These disruptions impair epithelial proliferation, apoptosis, and remodeling during embryonic duodenal recanalization, leading to luminal obstruction.

Keywords: BCL-2 homologous antagonist/killer, BCL-2 associated X-protein, B-cell leukemia/lymphoma 2, calcineurin, cell-cycle regulators, Cystic fibrosis transmembrane conductance regulator, chromosome 21, Duodenal recanalization, Dual-specificity tyrosine phosphorylation–regulated kinase 1A, E-cadherin.

Newborn (2026): 10.5005/jp-journals-11002-0156

Key Points

- Down syndrome (DS) has a strong and well-established epidemiologic association with duodenal atresia.
- Duodenal atresia occurs in approximately one in 5,000–10,000 live births in the general population, but about 20–30% of all infants born with duodenal atresia have DS.
- We treated an infant with phenotypic features of DS and intractable vomiting. The radiograph showed a classical "double bubble" sign and was confirmed to have duodenal atresia in surgery.
- We present our understanding of the molecular mechanisms underlying the association of DS with duodenal atresia.

Introduction

Down syndrome (trisomy 21, DS) is associated with a spectrum of congenital anomalies, among which duodenal atresia represents a classic and clinically significant gastrointestinal manifestation.[1–4] The prevalence of duodenal atresia is estimated to be approximately one in 5,000–10,000 live births, and nearly 20–30% of affected infants have DS.[5,6] Conversely, 1–5% of infants with DS show duodenal atresia, reflecting a markedly increased risk compared with the general population.[7]

This strong association provides an important diagnostic clue in both prenatal and postnatal settings. While the clinical and radiological features are well established, the molecular mechanisms linking trisomy 21 to duodenal atresia are still being elucidated.[4,8,9] This report presents a clinical case and integrates current evidence on developmental and molecular pathways involved.

[1]Department of Neonatology, Rainbow Children's Hospital, Hyderabad, Telangana, India

[2]Global Newborn Society, Maryland, United States of America

[3]Department of Pediatrics/Neonatology, Emirates Specialty Hospital, Dubai Healthcare City, United Arab Emirates

[4]Department of Neonatology, Indira Gandhi Institute of Child Health, Bengaluru, Karnataka, India

[5]Department of Surgery, Banaras Hindu University, Varanasi, Uttar Pradesh, India

[6]Pediatrician/Neonatologist, Civil Hospital of Guadalajara Dr. Juan I Menchaca, Guadalajara, Mexico

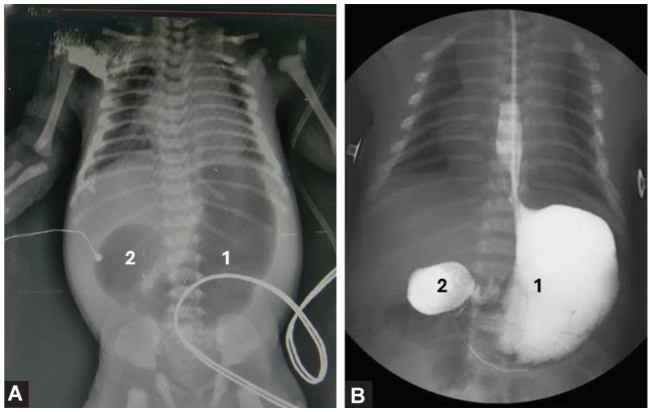
Corresponding Author: Nitasha Bagga, Department of Neonatology, Rainbow Children's Hospital, Hyderabad, Telangana, India; Global Newborn Society, Maryland, United States of America, Phone: +91 9000764206, e-mail: nitashabagga@gmail.com

How to cite this article: Bagga N, Kaushal M, Bandiya P, *et al*. Radiological Case Report: Duodenal Atresia in Down Syndrome. Newborn 2026;5(2):118–122.

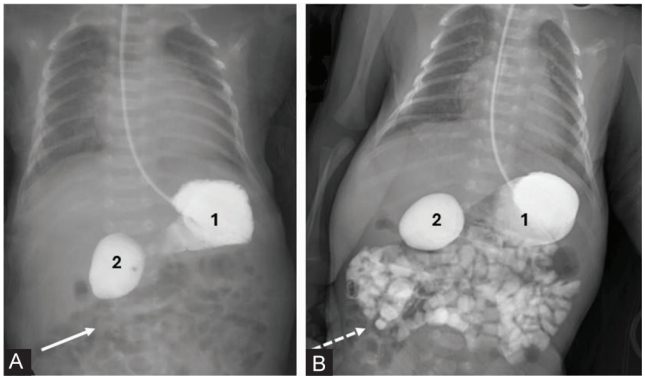
Source of support: Nil

Conflict of interest: Dr Nitasha Bagga is associated as the Editorial board members of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of her association with the Editorial board.

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



Figs 1A and B: (A) Thoraco-abdominal radiograph of the infant with duodenal atresia. The double bubble sign is seen with two bubbles (numbered 1 and 2); (B) The diagnosis was confirmed by using a dye study. The dye study began to show some extra-intestinal gas, indicative of an early intestinal perforation. He was treated surgically soon after the study



Figs 2A and B: (A) An infant with phenotypic features of DS and duodenal stenosis showed two prominent gastric and duodenal gas shadows. Many small gas bubbles were visible beyond the site of obstruction at 24 hours after birth (arrow); (B) These findings were clearly evident (broken arrow) in dye-enhanced radiographs

Case Report

Here, we present our observations from the clinical course of a full-term 38 weeks' gestation/3,400 gm birth weight male infant with phenotypic features of DS. He started vomiting at 24 hours after birth. The radiograph showed a classical "double bubble" sign (Fig. 1), comprised of a dilated stomach and proximal duodenum. These radiologic findings are highly suggestive, though not pathognomonic, of duodenal atresia.[10] The obstruction, typically distal to the ampulla of Vater, results in the accumulation of swallowed amniotic fluid prenatally and gastric secretions postnatally.

The infant underwent surgical exploration and was confirmed to have duodenal atresia. A duodenoduodenostomy was performed, where the proximal and distal segments of the duodenum were connected to bypass the atretic segment and restore continuity in the small intestine.[11] The postoperative course was stable, and further management focused on associated DS comorbidities.

Discussion

Neonatal duodenal obstruction is broadly classified into intrinsic and extrinsic anatomical types, depending on whether the blockage arises from within the duodenal wall or from external compression.[12] These conditions typically present soon after birth with feeding intolerance and bilious vomiting, and many are related to abnormalities in embryologic development of the foregut.[5,13] The intestinal obstruction is seen most frequently distal to the ampulla of Vater.[5] Consequently, swallowed amniotic fluid (prenatally) or gastric secretions (postnatally) accumulate and dilate the stomach and proximal duodenum, while no gas passes into the distal bowel beyond the site of obstruction. These findings can be seen on prenatal ultrasound or postnatal abdominal X-ray. As mentioned above, the double bubble is a highly suggestive but not absolutely specific marker of duodenal atresia.[10] Further evaluation may be needed to confirm the level and cause of obstruction before surgical correction.[7,10]

Intrinsic duodenal obstruction results from failure or incomplete recanalization of the duodenal lumen during fetal life.[5] The most severe form is duodenal atresia, where there is complete obliteration of the lumen. These intrinsic lesions are strongly associated with DS and often produce the classic "double bubble" appearance on imaging. Duodenal atresia has been viewed in three anatomical types:[14] Type I, in which a mucosal diaphragm or web obstructs the lumen while the bowel wall remains intact (often producing a "windsock" deformity); type II, where the proximal and distal segments are separated but connected by a fibrous cord; and type III, characterized by complete separation of the two segments with a gap in the mesentery.

Less severe forms include duodenal stenosis, where the lumen is narrowed but still patent, and duodenal webs, which are thin mucosal membranes that may partially obstruct the lumen.[5,15] The radiological studies in Figure 2 show a dye study from an infant with duodenal stenosis; he had incomplete duodenal obstruction and small gas bubbles can be seen beyond the site of obstruction.

In some infants, extrinsic duodenal obstruction may occur from compression due to abnormal extra-intestinal structures. One of the most important causes is annular pancreas, in which this pancreatic tissue encircles the second part of the duodenum and constricts it.[16,17] Intestinal malrotation is another life-threatening condition, where a midgut volvulus can lead to a life-threatening twisting of the duodenum with luminal obstruction and ischemia.[18,19] In malrotation, fibrous peritoneal attachments known as Ladd's bands can also cross over and compress the duodenum.[20] Rare vascular anomalies, such as a preduodenal portal vein, may pass anterior to the duodenum and cause obstruction.[21] These extrinsic causes are particularly important because some, like volvulus, require urgent surgical intervention. Less commonly, intraluminal causes such as inspissated meconium or debris may contribute to duodenal blockage, although these are rare compared to structural abnormalities.[22] Overall, understanding the anatomical classification of duodenal obstruction is essential for diagnosis and management, as intrinsic lesions often require surgical correction of the lumen, whereas extrinsic causes may demand correction of abnormal anatomy or urgent intervention to prevent ischemic injury.[23]

The molecular mechanisms of DS-associated duodenal atresia have long been a subject of study.[1] During normal embryologic development, the duodenum temporarily becomes solid at about 5–6 weeks' gestation, when its lumen is obliterated by proliferating cells and then undergoes recanalization between approximately

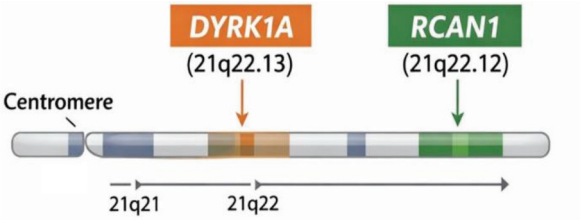


Fig. 3: Location of *DYRK1A* and *RCAN1* genes on chromosome 21

8 and 10 weeks of gestation.[24] In DS, this recanalization process often fails or is incomplete, leading to atresia (complete blockage) or stenosis.[5] These abnormalities typically affect the duodenum at the junction of the foregut and midgut, a region that undergoes a critical solid-to-hollow transition. Two dosage-sensitive genes on chromosome 21, dual-specificity tyrosine phosphorylation–regulated kinase 1A (*DYRK1A*) and regulator of calcineurin 1 (*RCAN1*) (Fig. 3), are overexpressed and contribute to these developmental effects:[25,26]

- Dual-specificity tyrosine phosphorylation–regulated kinase 1A is a kinase involved in regulating cell proliferation, neurodevelopment, and transcriptional control.[27] In trisomy 21, increased *DYRK1A* activity alters phosphorylation of multiple downstream targets, including components of the Wnt/β-catenin pathway and cell-cycle regulators, leading to reduced proliferation and altered differentiation during embryonic development.[27,28]
- Regulator of calcineurin 1 modulates calcineurin signaling, which is calcium-dependent and influences transcription factors such as nuclear factor of activated T-cells (NFAT).[29] Overexpression of *RCAN1* inhibits calcineurin activity, thereby disrupting calcium-mediated gene expression, immune signaling, and aspects of organogenesis.[30] This can indirectly affect multiple developmental pathways, including those involved in epithelial–mesenchymal interactions.[31]

Together, overexpression of *DYRK1A* and *RCAN1* causes signaling imbalance across pathways critical for embryonic patterning and gut morphogenesis such as sonic hedgehog (SHH), Wnt (a hybrid name derived from Wingless + Int, not a traditional acronym), and fibroblast growth factor (FGF).[32–35] These genes/pathways are located on other chromosomes, not chromosome 21, but are important for transcriptional regulation, calcium signaling, and kinase activity, which in turn can affect many distant regulators of developmental signaling networks:

- Sonic hedgehog: A secreted signaling molecule that guides cell fate decisions.[36] During gut development, it is expressed in the endoderm and signals to surrounding mesenchyme, coordinating epithelial proliferation, differentiation, and structural remodeling.[37] Its downstream effects may be altered in DS due to broader disturbances in developmental signaling networks. This is particularly relevant at the foregut–midgut junction, where SHH signaling is critical for patterning and morphogenesis.[37,38]
- Wnt responses: This disrupted signaling balance impairs coordinated epithelial proliferation, apoptosis, and tissue remodeling, contributing to developmental anomalies.[39] β-catenin is a central effector of the Wnt signaling pathway; abnormally high or low β-catenin-mediated signaling alters the balance between epithelial proliferation and apoptosis and consequently, with vacuolization and lumen formation in the duodenum.[40,41]
- Fibroblast growth factor signaling: Even though the FGF genes are not located on chromosome 21, developmental abnormalities arise because upstream regulatory networks and signaling crosstalk are altered. During gut development, FGF signaling normally coordinates epithelial-mesenchymal interactions, mesenchymal proliferation, vascular development, and morphogenesis of the foregut–midgut junction, including the duodenum.[42]

Subsequently, coordinated apoptosis and cellular remodeling create multiple intracellular and intercellular vacuoles within the epithelial plug.[14] These vacuoles enlarge, coalesce, and connect to form a continuous central lumen, a process known as recanalization. Programmed cell death is triggered via both intrinsic (mitochondrial) and extrinsic (death-receptor) pathways, with activation of caspases –3 and –9, downstream of regulators such as B-cell leukemia/lymphoma 2 (BCL-2) family proteins and tumor protein 53 (p53), selectively eliminating centrally located cells within the plug.[43,44] At the same time, surviving epithelial cells undergo polarization and junctional reorganization:

- E-cadherin–mediated adhesion is dynamically modulated, tight junctions are remodeled, and the cytoskeleton reorganizes (actin–myosin contraction via Rho/ROCK signaling), allowing cells to separate and form intercellular spaces.[45]
- Cystic fibrosis transmembrane conductance regulator (CFTR) regulate mucus viscosity and hydration in epithelial tissues.[46] Cystic fibrosis transmembrane conductance regulator and aquaporins promotes luminal fluid accumulation, expanding these spaces into vacuoles.[47]
- Matrix metalloproteinases remodel the basement membrane and extracellular matrix, facilitating tissue reorganization and coalescence of vacuoles into a continuous lumen.[48] These processes are orchestrated by developmental signaling pathways, which coordinate proliferation, apoptosis, and morphogenesis; disruption can contribute to duodenal atresia.[49]

Trisomy 21 does not alter the caspases, BCL-2, and/or p53 directly, but it perturbs these regulatory networks via *DYRK1A* and *RCAN1*.[50,51] These changes can lead to reduced or mistimed programmed cell death in the gastrointestinal embryonic tissues.[52] Since BCL-2 is a key anti-apoptotic protein that controls mitochondrial membrane permeability and caspase activation, its functional balance with pro-apoptotic members such as BCL-2 associated X-protein (BAX) and BCL-2 homologous antagonist/killer (BAK) can be secondarily altered through upstream signaling changes.[53]

To summarize, DS disrupts normal embryonic gut development by altering key signaling and regulatory pathways that control epithelial proliferation, apoptosis, and remodeling.[54] This disturbance affects the precisely timed process of duodenal recanalization, in which the temporarily solid embryonic duodenum must reopen to form a hollow lumen. When this process is impaired, the lumen fails to form properly, resulting in an increased risk of duodenal atresia. The precise molecular mechanisms remain incompletely understood and warrant further investigation.

References

1. Freeman SB, Torfs CP, Romitti PA, et al. Congenital gastrointestinal defects in Down syndrome: A report from the Atlanta and National Down Syndrome Projects. Clin Genet 2009;75(2):180–184. DOI: 10.1111/j.1399-0004.2008.01110.x.

2. Keckler SJ, St Peter SD, Spilde TL, et al. The influence of trisomy 21 on the incidence and severity of congenital heart defects in patients with duodenal atresia. Pediatr Surg Int 2008;24(8):921–923. DOI: 10.1007/s00383-008-2185-x.
3. Pijpers AGH, Eeftinck Schattenkerk LD, Straver B, et al. The incidence of associated anomalies in children with congenital duodenal obstruction-a retrospective cohort study of 112 patients. Children (Basel) 2022;9(12):1814. DOI: 10.3390/children9121814.
4. Atiyat DK, Al-Nusair DA, Alhajahjeh A, et al. Global prevalence of duodenal atresia in trisomy 21: A systematic review and meta-analysis. Eur J Pediatr Surg 2025;35(3):208–218. DOI: 10.1055/a-2471-6435.
5. Sigmon DF, Eovaldi BJ, Cohen HL. Duodenal Atresia and Stenosis. In: StatPearls [Internet]. Treasure Island, Florida, USA: StatPearls Publishing; 2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470548/. [Updated 2023 Jun 26].
6. Morris JK, Springett AL, Greenlees R, et al. Trends in congenital anomalies in Europe from 1980 to 2012. PLoS One 2018;13(4):e0194986. DOI: 10.1371/journal.pone.0194986.
7. Al Shahwani N, Mandhan P, Elkadhi A, et al. Congenital duodenal obstruction associated with Down's syndrome presenting with hematemesis. J Surg Case Rep 2013;2013(12):rjt108. DOI: 10.1093/jscr/rjt108.
8. Tam CW, Patel S, Massoumi J, et al. Atypical presentation of duodenal atresia in a newborn with trisomy 21: A simulated case report and narrative review. Pediatr Ann 2025;54(4):e139–e143. DOI: 10.3928/19382359-20250206-04.
9. Latzman JM, Levin TL, Nafday SM. Duodenal atresia: Not always a double bubble. Pediatr Radiol 2014;44(8):1031–1034. DOI: 10.1007/s00247-014-2896-1.
10. Bishop JC, McCormick B, Johnson CT, et al. The double bubble sign: Duodenal atresia and associated genetic etiologies. Fetal Diagn Ther 2020;47(2):98–103. DOI: 10.1159/000500471.
11. Upadhyay V, Sakalkale R, Parashar K, et al. Duodenal atresia: A comparison of three modes of treatment. Eur J Pediatr Surg 1996;6(2):75–77. DOI: 10.1055/s-2008-1066475.
12. Rattan KN, Singh J, Dalal P. Neonatal duodenal obstruction: A 15-year experience. J Neonatal Surg 2016;5(2):13. PMID: 27123397.
13. Wilson DJ, Bordoni B. Embryology, Bowel. In: StatPearls [Internet]. Treasure Island, Florida, USA: StatPearls Publishing; 2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545247/. [Updated 2023 May 1].
14. Gharpure V. Duodenal atresia. J Neonatal Surg 2014;3(1):14. PMID: 26023485.
15. Ekram K, Razawi F, Jalal SN, et al. Congenital duodenal web causing partial obstruction with recurrent vomiting and abdominal distention in a toddler boy: A case report. J Med Case Rep 2023;17(1):507. DOI: 10.1186/s13256-023-04179-3.
16. Aleem A, Desai H, Shah H. Annular Pancreas. Treasure Island (FL): StatPearls; 2026.
17. Androulakis J, Colborn GL, Skandalakis PN, et al. Embryologic and anatomic basis of duodenal surgery. Surg Clin North Am 2000;80(1):171–199. DOI: 10.1016/s0039-6109(05)70401-1.
18. Adams SD, Stanton MP. Malrotation and intestinal atresias. Early Hum Dev 2014;90(12):921–925. DOI: 10.1016/j.earlhumdev.2014.09.017.
19. Ferrero L, Ahmed YB, Philippe P, et al. Intestinal malrotation and volvulus in neonates: Laparoscopy vs open laparotomy. J Laparoendosc Adv Surg Tech A 2017;27(3):318–321. DOI: 10.1089/lap.2015.0544.
20. Alani M, Rentea RM. Midgut Malrotation. In: StatPearls [Internet]. Treasure Island, Florida, USA: StatPearls Publishing; 2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560888/. [Updated 2026 Jan 31].
21. Kim SH, Cho YH, Kim HY. Preduodenal portal vein: A 3-case series demonstrating varied presentations in infants. J Korean Surg Soc 2013;85(4):195–197. DOI: 10.4174/jkss.2013.85.4.195.
22. Waldhausen JHT, Richards M. Meconium ileus. Clin Colon Rectal Surg 2018;31(2):121–126. DOI: 10.1055/s-0037-1609027.
23. Al-Salem AH. Congenital intrinsic duodenal obstruction: A review of 35 cases. Ann Saudi Med 2007;27(4):289–292. DOI: 10.5144/0256-4947.2007.289.
24. Matsumoto A, Hashimoto K, Yoshioka T, et al. Occlusion and subsequent re-canalization in early duodenal development of human embryos: Integrated organogenesis and histogenesis through a possible epithelial-mesenchymal interaction. Anat Embryol (Berl) 2002;205(1):53–65. DOI: 10.1007/s00429-001-0226-5.
25. Park J, Song WJ, Chung KC. Function and regulation of Dyrk1A: Towards understanding Down syndrome. Cell Mol Life Sci 2009;66(20):3235–3240. DOI: 10.1007/s00018-009-0123-2.
26. Lee SK, Ahnn J. Regulator of calcineurin (RCAN): Beyond Down syndrome critical region. Mol Cells 2020;43(8):671–685. DOI: 10.14348/molcells.2020.0060.
27. Duchon A, Herault Y. DYRK1A, a dosage-sensitive gene involved in neurodevelopmental disorders, is a target for drug development in Down syndrome. Front Behav Neurosci 2016;10:104. DOI: 10.3389/fnbeh.2016.00104.
28. Wegiel J, Gong CX, Hwang YW. The role of DYRK1A in neurodegenerative diseases. FEBS J 2011;278(2):236–245. DOI: 10.1111/j.1742-4658.2010.07955.x.
29. Rotter D, Peiris H, Grinsfelder DB, et al. Regulator of calcineurin 1 helps coordinate whole-body metabolism and thermogenesis. EMBO Rep 2018;19(12):e44706. DOI: 10.15252/embr.201744706.
30. Lao M, Zhang X, Yang H, et al. RCAN1-mediated calcineurin inhibition as a target for cancer therapy. Mol Med 2022;28(1):69. DOI: 10.1186/s10020-022-00492-7.
31. Peiris H, Dubach D, Jessup CF, et al. RCAN1 regulates mitochondrial function and increases susceptibility to oxidative stress in mammalian cells. Oxid Med Cell Longev 2014;2014:520316. DOI: 10.1155/2014/520316.
32. Ishihara K. Genes associated with disturbed cerebral neurogenesis in the embryonic brain of mouse models of Down syndrome. Genes (Basel) 2021;12(10):1598. DOI: 10.3390/genes12101598.
33. Moyer AJ, Fernandez FX, Li Y, et al. Overexpression screen of chromosome 21 genes reveals modulators of sonic hedgehog signaling relevant to Down syndrome. Dis Model Mech 2023;16(4):dmm049712. DOI: 10.1242/dmm.049712.
34. Singh R, Lauth M. Emerging roles of DYRK kinases in embryogenesis and hedgehog pathway control. J Dev Biol 2017;5(4):13. DOI: 10.3390/jdb5040013.
35. Murphy AJ, Wilton SD, Aung-Htut MT, et al. Down syndrome and DYRK1A overexpression: Relationships and future therapeutic directions. Front Mol Neurosci 2024;17:1391564. DOI: 10.3389/fnmol.2024.1391564.
36. Lai K, Robertson MJ, Schaffer DV. The sonic hedgehog signaling system as a bistable genetic switch. Biophys J 2004;86(5):2748–2757. DOI: 10.1016/S0006-3495(04)74328-3.
37. Walton KD, Gumucio DL. Hedgehog signaling in intestinal development and homeostasis. Annu Rev Physiol 2021;83:359–380. DOI: 10.1146/annurev-physiol-031620-094324.
38. Xu J, Iyyanar PPR, Lan Y, et al. Sonic hedgehog signaling in craniofacial development. Differentiation 2023;133:60–76. DOI: 10.1016/j.diff.2023.07.002.
39. Jin X, Wang J, Cao R, et al. Wnt signaling pathway: Biological function, diseases, and therapeutic interventions. MedComm (2020) 2026;7(1):e70580. DOI: 10.1002/mco2.70580.
40. Chen J, Wang X, Zhang J, et al. Effects of the Wnt/beta-catenin signaling pathway on proliferation and apoptosis of gastric cancer cells. Contrast Media Mol Imaging 2022;2022:5132691. DOI: 10.1155/2022/5132691.
41. Fevr T, Robine S, Louvard D, et al. Wnt/beta-catenin is essential for intestinal homeostasis and maintenance of intestinal stem cells. Mol Cell Biol 2007;27(21):7551–7559. DOI: 10.1128/MCB.01034-07.
42. Teague WJ, Jones MLM, Hawkey L, et al. FGF10 and the mystery of duodenal atresia in humans. Front Genet 2018;9:530. DOI: 10.3389/fgene.2018.00530.

43. Kylarova D, Vrchovecky J, Holinka M, et al. The occurrence of c-myc, p53 and Bcl-2 family proteins in the early phase of development of duodenal epithelium. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2004;148(2):229–232. DOI: 10.5507/bp.2004.046.
44. Prochazkova J, Lichnovsky V, Kylarova D, et al. Involvement of p53 and Bcl-2 family proteins in regulating programmed cell death and proliferation in human embryogenesis. Gen Physiol Biophys 2004;23(2):209–229. PMID: 15696860.
45. Kurnit DM, Aldridge JF, Matsuoka R, et al. Increased adhesiveness of trisomy 21 cells and atrioventricular canal malformations in Down syndrome: A stochastic model. Am J Med Genet 1985;20(2):385–399. DOI: 10.1002/ajmg.1320200222.
46. Oweidat M, Qutaina T, Hamdan AA, et al. Novel co-occurrence of trisomy 21 and heterozygous CFTR mutation. Respirol Case Rep 2025;13(4):e70185. DOI: 10.1002/rcr2.70185.
47. Levin MH, Verkman AS. Aquaporins and CFTR in ocular epithelial fluid transport. J Membr Biol 2006;210(2):105–115. DOI: 10.1007/s00232-005-0849-1.
48. Cabral-Pacheco GA, Garza-Veloz I, Castruita-De la Rosa C, et al. The roles of matrix metalloproteinases and their inhibitors in human diseases. Int J Mol Sci 2020;21(24):9739. DOI: 10.3390/ijms21249739.
49. Gupta T, Yang W, Iovannisci DM, et al. Considering the vascular hypothesis for the pathogenesis of small intestinal atresia: A case control study of genetic factors. Am J Med Genet A 2013;161A(4):702–710. DOI: 10.1002/ajmg.a.35775.
50. Jung MS, Park JH, Ryu YS, et al. Regulation of RCAN1 protein activity by Dyrk1A protein-mediated phosphorylation. J Biol Chem 2011;286(46):40401–40412. DOI: 10.1074/jbc.M111.253971.
51. Tramutola A, Pupo G, Di Domenico F, et al. Activation of p53 in Down syndrome and in the Ts65Dn mouse brain is associated with a pro-apoptotic phenotype. J Alzheimers Dis 2016;52(1):359–371. DOI: 10.3233/JAD-151105.
52. Holmes G. Gastrointestinal disorders in Down syndrome. Gastroenterol Hepatol Bed Bench 2014;7(1):6–8. PMID: 25436092.
53. Vogler M, Braun Y, Smith VM, et al. The BCL2 family: From apoptosis mechanisms to new advances in targeted therapy. Signal Transduct Target Ther 2025;10(1):91. DOI: 10.1038/s41392-025-02176-0.
54. Liu Y, Lin Z, Peng Y, et al. Embryonic organizer formation disorder leads to multiorgan dysplasia in Down syndrome. Cell Death Dis 2022;13(12):1054. DOI: 10.1038/s41419-022-05517-x.