INDIAN JOURNAL OF PRACTICAL PEDIATRICS

IJPP

- **IJPP is a quarterly subscription journal of the Indian Academy of Pediatrics committed to presenting practical pediatric issues and management updates in a simple and clear manner**
- **Indexed in Scopus, CABI Publishing and EMCare.**

Vol.27 No.4 (OCT.- DEC.) 2025

CONTENTS

TOPIC OF INTEREST - INBORN ERRORS OF METABOLISM - II

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Published by Dr. T.L.Ratnakumari, Editor-in-Chief, IJPP, on behalf of Indian Academy of Pediatrics, from 1A, Block II, Krsna Apartments, 50, Thamizh Salai (Halls Road), Egmore, Chennai - 600 008. Tamil Nadu, India and Printed by Mr. D.Ramanathan, at Alamu Printing Works, 9, Iyyah Street, Royapettah, Chennai - 600 014.

INBORN ERRORS OF METABOLISM - II

NEWBORN SCREENING FOR INBORN ERRORS OF METABOLISM IN INDIA - PRESENT STATUS, GAPS AND FUTURE DIRECTIONS

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****Neerja Gupta**
*****Madhulika Kabra**
******Seema Kapoor**

Abstract: *Newborn screening (NBS) is a proven public health intervention enabling early detection and management of treatable metabolic and genetic disorders. In India, NBS has evolved from isolated pilot projects to structured state-led initiatives like NEEV (Delhi) and Shalabham (Kerala). Despite demonstrated feasibility, nationwide implementation faces challenges of infrastructure, cost and workforce limitations. A tiered, resource-based strategy integrating NBS with existing maternal-child health programs is proposed to ensure equity, sustainability and long-term reduction in preventable morbidity and mortality.*

Keywords: *Newborn screening, Inborn errors of metabolism, India, Public health.*

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Points to Remember

- ***There is significant experience in India for NBS on DBS of core disorders (CH, CAH, G6PD, Galactosemia, Biotinidase deficiency) primarily through large multicentric, funded projects and some state programs establishing the feasibility and need for a national program.***
- ***Ongoing state programs (e.g. NEEV and Shalabham under RBSK) have initiated comprehensive screening which in addition to DBS (disorders tested variable) include externally visible birth defects, hearing and CCHD screening. This strategy seems to be appropriate providing one time approach , easier implementation and avoids running multiple parallel programs thus saving cost.***
- ***Experience with expanded NBS using TMS is limited though diagnostic facilities are available both in public and private laboratories. The testing is primarily utilised in high-risk scenarios. Some national pilot programs may be initiated in larger experienced institutions.***
- ***FSMPs are now manufactured in India (barring few) at a much lower cost and treatment for small molecule IEMs is supported under the National Rare Disease Policy 2021. There is a need to have more centres with metabolic physicians and a robust referral system.***
- ***There is an urgent need to roll out a national NBS program in a phased manner beginning from states with better health statistics. Start with Tier I (essential, universal), expand to Tier II in capable states and aspire for Tier III in future as health financing improves.***
- ***A tiered, pragmatic framework aligns with India's public health priorities, economic realities, and infrastructure.***

Cite as: Amit Kumar Gupta, Neerja Gupta, Madhulika Kabra, Seema Kapoor. Newborn screening for inborn errors of metabolism in india - Present status, gaps and future directions, Indian J Pract Pediatr. 2025; 27(4):309-314.

References

1. Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organization; 1968. 163 p. (Public health papers).
2. Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bull World Health Organ. 2008 Apr; 86(4):317-9.
3. Singh S, Ojodu J, Kemper AR, Lam WKK, Grosse SD. Implementation of Newborn Screening for Conditions in the United States First Recommended during 2010-2018. Int J Neonatal Screen. 2023 June; 9(2):20.
4. The BabySeq Project - Genomes2People [Internet]. [cited 2025 Dec 29]. Available from: https://www.genomes2people.org/research/babyseq/
5. Smith HS, Zettler B, Genetti CA, Hickingbotham MR, Coleman TF, Lebo M, et al. The BabySeq Project: A clinical trial of genome sequencing in a diverse cohort of infants. Am J Hum Genet. 2024 Oct 3; 111(10):2094-106.
6. Protocol-V8.0-02-December-2025-For-External-Use-1.pdf [Internet]. [cited 2025 Dec 29]. Available from: https://www.genomicsengland.co.uk/assets/documents/Protocol-V8.0-02-December-2025-For-External-Use-1.pdf
7. Rama Devi AR, Naushad SM. Newborn screening in India. Indian J Pediatr. 2004 Feb; 71(2):157-60.
8. ICMR Task Force on Inherited Metabolic Disorders. Newborn Screening for Congenital Hypothyroidism and Congenital Adrenal Hyperplasia. Indian J Pediatr. 2018 Nov; 85(11):935-40.
9. Charting the Course: Towards a Comprehensive Newborn Screening Program in India [Internet]. [cited 2025 Dec 29]. Available from: https://www.mdpi.com/2409-515X/10/3/43
10. Immunization and Child Health | UNICEF India [Internet]. [cited 2025 Dec 29]. Available from: https://www.unicef.org/india/what-we-do/immunization
11. Lodh M, Kerketta A. Inborn errors of metabolism in a tertiary care hospital of eastern India. Indian Pediatr. 2013 Dec; 50(12):1155-6.
12. Kaur G, Thakur K, Kataria S, Singh TR, Chavan BS, Kaur G, et al. Current and future perspective of newborn screening: an Indian scenario. J Pediatr Endocrinol Metab JPEM. 2016 Jan; 29(1): 5-13.
13. Mookken T. Universal Implementation of Newborn Screening in India. Int J Neonatal Screen. 2020 June; 6(2): 24.

INBORN ERRORS OF METABOLISM - II

CLINICAL PRESENTATION AND ENZYME REPLACEMENT THERAPY IN LYSOSOMAL STORAGE DISORDERS - LESSONS FROM INDIA AND GLOBAL CENTRES

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****Sankar VH**

Abstract: *Lysosomal storage disorders are a group of genetic metabolic disorders which usually present with a chronic course and have varied manifestations with multisystemic involvement including hepatosplenomegaly, cytopenias, global developmental delay and/or psychomotor regression, seizures and growth failure. This group consists of around 70 clinically and genetically heterogeneous conditions. The past few decades have witnessed the development of enzyme replacement therapies and other disease-specific treatment strategies for lysosomal storage disorders. This article reviews the clinical presentations, available enzyme replacement therapies and other therapeutic modalities with special reference to some of the relatively common lysosomal storage disorders i.e., Gaucher disease, Pompe disease, mucopolysaccharidoses and Fabry disease.*

Keywords: *Lysosomal storage disorders, Clinical manifestations, Enzyme replacement therapy.*

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Points to Remember

- ***Enzyme replacement therapy (ERT) improves systemic manifestations but cannot cross the blood-brain barrier, so neurological disease generally continues to progress.***
- ***Early initiation of ERT-especially in infantile Pompe disease, severe MPS I and Fabry disease-produces significantly better clinical outcomes.***
- ***ERT requires lifelong weekly or biweekly infusions and remains expensive, making sustained access a major challenge in India.***
- ***Although ERT benefits visceral, cardiac, and skeletal systems, it has limited effect on poorly vascularized tissues such as the cornea and bones.***
- ***Emerging treatments like substrate reduction therapy, chaperone therapy and gene therapy are increasingly important additions where ERT alone is insufficient.***

References

1. Fuller M, Meikle PJ, Hopwood JJ. Epidemiology of lysosomal storage diseases: an overview. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006. Chapter 2. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11603/
2. Penati R, Fumagalli F, Calbi V, Bernardo ME, Aiuti A. Gene therapy for lysosomal storage disorders: recent advances for metachromatic leukodystrophy and mucopolysaccharidosis I. J Inherit Metab Dis. 2017; 40(4):543-554.
3. Sheth J, Nair A, Jee B. Lysosomal storage disorders: from biology to the clinic with reference to India. Lancet Reg Health Southeast Asia. 2022;9:100108.
4. Hughes DA, Pastores GM. Gaucher Disease. 2000 Jul 27 [Updated 2023 Dec 7]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1269/

Cite as: Prajnya Ranganath, Sankar VH, Clinical presentation and enzyme replacement therapy in lysosomal storage disorders - Lessons from india and global centres, Indian J Pract Pediatr. 2025; 27(4):315-322.

5. Sperry E, Leslie N, Berry L, et al. Pompe Disease. 2007 Aug 31 [Updated 2025 Aug 21]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1261/
6. Zhou J, Lin J, Leung WT, Wang L. A basic understanding of mucopolysaccharidosis: Incidence, clinical features, diagnosis, and management. Intractable Rare Dis Res. 2020;9(1):1-9.
7. Clarke LA. Mucopolysaccharidosis Type I. 2002 Oct 31 [Updated 2024 Apr 11]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1162/
8. Scarpa M, Lampe C. Mucopolysaccharidosis Type II. 2007 Nov 6 [Updated 2025 Jan 16]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1274/
9. Mehta A, Hughes DA. Fabry Disease. 2002 Aug 5 [Updated 2024 Apr 11]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1292/
10. Rosenfeld MG, Kreibich G, Popov D, Kato K, Sabatini DD. Biosynthesis of lysosomal hydrolases: their synthesis in bound polysomes and the role of co- and post-translational processing in determining their subcellular distribution. J Cell Biol. 1982; 93(1):135-43.
11. Muro S. New biotechnological and nanomedicine strategies for treatment of lysosomal storage disorders. Wiley Interdiscip Rev NanomedNanobiotechnol. 2010; 2(2):189-204.
12. Fernández-Pereira C, San Millán-Tejado B, Gallardo-Gómez M, Pérez-Márquez T, Alves-Villar M, Melcón-Crespo C,et al. Therapeutic Approaches in Lysosomal Storage Diseases. Biomolecules. 2021;11(12):1775.
13. Elder ME, Nayak S, Collins SW, Lawson LA, Kelley JS, Herzog RW, et al. B-Cell depletion and immunomodulation before initiation of enzyme replacement therapy blocks the immune response to acid alpha-glucosidase in infantile-onset Pompe disease. J Pediatr. 2013; 163(3):847-54.e1.
14. Schiffmann R, Goker-Alpan O, Holida M, Giraldo P, Barisoni L, Colvin RB, et al. Pegunigalsidase alfa, a novel PEGylated enzyme replacement therapy for Fabry disease, provides sustained plasma concentrations and favorable pharmacodynamics: A 1-year Phase 1/2 clinical trial. J Inherit Metab Dis. 2019; 42(3):534-544.
15. Malatack JJ, Consolini DM, Bayever E. The status of hematopoietic stem cell transplantation in lysosomal storage disease. Pediatr Neurol. 2003; 29(5):391-403.
16. Cox T, Lachmann R, Hollak C, Aerts J, van Weely S, Hrebícek M, et al. Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. Lancet. 2000; 355(9214): 1481-1485.
17. Parenti G, Pignata C, Vajro P, Salerno M. New strategies for the treatment of lysosomal storage diseases (review). Int J Mol Med. 2013; 31(1):11-20.
18. Stirnemann J, Belmatoug N, Camou F, Serratrice C, Froissart R, Caillaud C, et al. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. Int J Mol Sci. 2017; 18(2):441.
19. Desnick RJ, Schuchman EH. Enzyme replacement and enhancement therapies: lessons from lysosomal disorders. Nat Rev Genet 2002; 3: 954–966.
20. Donald A, Horgan C, De Castro Lopez MJ, Jones SA, Wynn RF. Gene therapy in neuronopathic lysosomal storage disorders. Eur J Pediatr Neurol. 2025; 57:41-49.
21. Muranjan M, Karande S. Enzyme replacement therapy in India: Lessons and insights. J Postgrad Med. 2018; 64(4):195-199.
22. National Policy for Rare Diseases, 2021. Available at: https://rarediseases.mohfw.gov.in/uploads/Content/1624967837_Final-NPRD-2021.pdf.

INBORN ERRORS OF METABOLISM - II

LONG-TERM FOLLOW-UP AND NEURODEVELOPMENTAL OUTCOMES IN CHILDREN WITH INBORN ERRORS OF METABOLISM

***Umamaheswari Balakrishnan**
****Rangan Srinivasaraghavan**

Abstract : *Inborn errors of metabolism affect 1 in 1000-3000 live births. Without universal newborn screening in India, diagnostic timing varies widely, delaying intervention. Many children experience substantial neurodevelopmental burden despite metabolic stabilization. Outcomes vary widely depending on disorder type, timing of diagnosis, metabolic control and access to care. Effective follow-up requires regular biochemical and clinical monitoring, structured neurodevelopmental assessment using WHO International Classification of Functioning, Disability and Health frameworks, coordinated metabolic clinics and active parental involvement. Strengthening such systems in resource-limited settings is essential to translate survival into meaningful developmental gains. This narrative review outlines a structured follow-up program for children with inborn errors of metabolism, including clinical and biochemical monitoring, neurodevelopmental services, parental roles and establishment of dedicated metabolic clinics.*

Keywords : *Treatable IEMs, Follow up, Metabolic clinic, Biochemical monitoring, Growth, Neurodevelopmental outcome.*

Points to Remember

- ***Neurodevelopmental outcomes in IEMs are variable and influenced by disease type, timing of diagnosis, metabolic control, and access to care.***
- ***Multidisciplinary, longitudinal follow-up is essential for optimizing developmental outcomes. General pediatrician should understand the importance of long term follow-up.***
- ***An ICF-guided neurodevelopmental approach emphasizes functional abilities, participation and quality of life beyond biochemical control.***
- ***Strengthening follow-up systems and continued research are crucial to improving long-term outcomes, particularly in resource-limited settings.***

References

1. Zhang H, Tian H, Dai W, Zhang L, Guo G, Ding G. Expanded newborn screening for inborn errors of metabolism and genetic variants in Xinjiang, China. Front Genet. 2025; 16:1617418.
2. Kapoor S, Gupta AK, Thelma BK. Charting the Course: Towards a Comprehensive Newborn Screening Program in India. Int J Neonatal Screen. 2024;10(3):43.
3. Saudubray JM, Garcia-Cazorla A. An overview of inborn errors of metabolism affecting the brain: from neurodevelopment to neurodegenerative disorders. Dialogues Clin Neurosci. 2018; 20(4):301-25.
4. Saudubray JM, Nassogne MC, de Lonlay P, Touati G. Clinical approach to inherited metabolic disorders in neonates: an overview. Semin Neonatol. 2002;7(1):3-15.
5. Aggarwal A, Sharma A, Dhiman S, Halder P. Equity for the rare: a review on India's rare disease challenges and policy responses. International Journal Of Community Medicine And Public Health. 2025; 12(12):5871-8.
6. Matuszewska E, Matysiak J, Kaluzny L, Walkowiak D, Plewa S, Dus-Zuchowska M, et al. Amino Acid Profile Alterations in Phenylketonuria: Implications for Clinical Practice. Metabolites. 2024; 14(7):397.

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Cite as: Umamaheswari Balakrishnan, Rangan Srinivasaraghavan. Long-term follow-up and neurodevelopmental outcomes in children with inborn errors of metabolism, Indian J Pract Pediatr. 2025; 27(4):323-335.

7. Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. Pediatrics. 2002; 109(6):999-1008. doi: 10.1542/peds.109.6.999.
8. Kenneson A, Osara Y, Pringle T, Youngborg L, Singh RH. Natural history of children and adults with maple syrup urine disease in the NBS-MSUD Connect registry. Mol Genet Metab Rep. 2018;15:22-7.
9. Häberle J, Boddaert N, Burlina A, Chakrapani A, Dixon M, Huemer M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis. 2012; 7:32.
10. Summar M. Current strategies for the management of neonatal urea cycle disorders. J Pediatr. 2001;138(1): S30-9.
11. Clark JF, Cecil KM. Diagnostic methods and recommendations for the cerebral creatine deficiency syndromes. Pediatr Res. 2015; 77(3):398-405.
12. Arning E, Bottiglieri T. LC-MS/MS Analysis of Cerebrospinal Fluid Metabolites in the Pterin Biosynthetic Pathway. JIMD Rep. 2016; 29:1-9.
13. Umamaheshwari Balakrishnan. Dietary management in inborn errors of metabolism. Indian J Pract Pediatr. 2024; 26(1):44-52.
14. Ratnaike TE, Elkhateeb N, Lochmüller A, Gilmartin C, Schon K, Horváth R, et al. Evidence for sodium valproate toxicity in mitochondrial diseases: a systematic analysis. BMJ Neurol Open. 2024; 6(1):e000650.
15. van Egmond ME, Eggink H, Kuiper A, Sival DA, Verschuuren-Bemelmans CC, Tijssen MAJ, et al. Crossing barriers: a multidisciplinary approach to children and adults with young-onset movement disorders. J Clin Mov Disord. 2018; 5:3.
16. Arnold GL, Van Hove J, Freedenberg D, Strauss A, Longo N, Burton B, et al. A Delphi clinical practice protocol for the management of very long chain acyl-CoA dehydrogenase deficiency. Mol Genet Metab. 2009; 96(3):85-90.
17. Göbel T, Schadewaldt-Tümmers J, Greiner L, Poremba C, Häussinger D, Erhardt A. Transient elastography improves detection of liver cirrhosis compared to routine screening tests. World J Gastroenterol. 2015; 21(3):953-60.
18. Welling L, Bernstein LE, Berry GT, Burlina AB, Eyskens F, Gautschi M, et al. International clinical guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up. J Inherit Metab Dis. 2017; 40(2):171-6.
19. Tumienë B, Del Toro Riera M, Grikiniene J, Samaitiene-Aleknienë R, Praninskienë R, Monavari AA, et al. Multidisciplinary Care of Patients with Inherited Metabolic Diseases and Epilepsy: Current Perspectives. J Multidiscip Health. 2022; 15:553-66.
20. Juneja M, Gupta A, Sairam S, Jain R, Sharma M, Thadani A, et al. Diagnosis and Management of Global Development Delay: Consensus Guidelines of Growth, Development and Behavioral Pediatrics Chapter, Neurology Chapter and Neurodevelopment Pediatrics Chapter of the Indian Academy of Pediatrics. Indian Pediatr. 2022; 59(5):401-15.
21. International Classification of Functioning, Disability and Health (ICF) [Internet]. [cited 2025 Nov 28]. Available from: https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health
22. Nair MKC, Ahmed S, Multani KS, Mohamed Ismail PM, Kamath SS, Dalwai SH, et al. Consensus Statement of the IAP - Neurodevelopmental Chapter On Neuro developmental Disorders Habilitation Process: Strategic Plan for Prevention, Early Detection and Early Intervention. Indian Pediatr. 2024 15; 61(1):10-23.
23. Al Imam MH, Jahan I, Khan N, Akbar D, Islam S, Muhit M, et al. Sustainable Model of Early Intervention and Telerehabilitation for Children With Cerebral Palsy in Rural Bangladesh: The SMART-CP Randomized Clinical Trial. JAMA Pediatr. 2025; 179(6):621-9.
24. Balakrishnan U, Chandrasekaran A, Amboiram P, Ninan B, Ignatious S. Outcome of Inherited Metabolic Disorders Presenting in the Neonatal Period. Indian J Pediatr. 2021; 88(5):455-462. doi: 10.1007/s12098-020-03522-6.
25. Mütze U, Garbade SF, Gramer G, Lindner M, Freisinger P, Grünert SC, et al. Long-term Outcomes of Individuals With Metabolic Diseases Identified Through Newborn Screening. Pediatrics. 2020; 146(5): e20200444.
26. Miller W, Wothe J, Wang Q, Vock D, Bhatt H, Salunke A, et al. Long-term Outcomes of Liver Transplantation for Inborn Errors of Metabolism in Children. Transplantation Proceedings. 2024; 56(6): 1359-64.
27. JainGhai S, Joffe AR, Bond GY, Siriwardena K, Chan A, Yap JYK, et al. Preschool neurocognitive and functional outcomes after liver transplant in children with early onset urea cycle disorders, maple syrup urine disease, and propionic acidemia: An inception cohort matchedcomparison study. JIMD Rep. 2020; 52(1): 43-54.
28. Bösch F, Landolt MA, Baumgartner MR, Zeltner N, Kölker S, Gleich F, et al. Health-related quality of life in paediatric patients with intoxication-type inborn errors of metabolism: Analysis of an international data set. J Inherit Metab Dis. 2021; 44(1):215-25.

29. Bösch F, Zeltner NA, Baumgartner MR, Huemer M, Landolt MA. Key patient-reported outcomes in children and adolescents with intoxication-type inborn errors of metabolism: an international Delphi-based consensus. Orphanet J Rare Dis. 2022; 17(1):26. doi: 10.1186/s13023-022-02183-2.

30. Reischl-Hajiabadi AT, Garbade SF, Gleich F, Schnabel-Besson E, Posset R, Zielonka M, et al. Impact of Newborn Screening on Survival and Developmental Outcome in Classic Isovaleric Aciduria: A Meta-Analysis. J Inherit Metab Dis. 2025; 48(6):e70090. doi: 10.1002/jimd.70090.

31. Welsink-Karssies MM, Ferdinandusse S, Geurtsen GJ, Hollak CEM, Huidekoper HH, Janssen MCH, et al. Deep phenotyping classical galactosemia: clinical outcomes and biochemical markers. Brain Commun. 2020; 2(1): fcaa006. doi: 10.1093/braincomms/fcaa006.

32. Pereira D, Loftus E, Thompson CE, Boyle F, McNulty J, Boruah R, et al. Clinical and Developmental Outcomes After 50Years of Newborn Bloodspot Screening for Classical Galactosaemia in the Republic of Ireland. JIMD Rep. 2025;66(3):e70022. doi: 10.1002/jmd2.70022.

33. Balakrishnan U. Inborn Errors of Metabolism-Approach to Diagnosis and Management in Neonates. Indian J Pediatr. 2021; 88(7):679-89.

INBORN ERRORS OF METABOLISM - II

EMERGENCY MANAGEMENT OF METABOLIC CRISES IN INTENSIVE CARE SETTINGS

(Acute Decompensation Protocols, Hyperammonemia, Hypoglycemia, Metabolic acidosis)

***Rajakumar Padur Sivaraman**
****Prakash Amboiram**
*****Thangavelu Sangaralingam**

Abstract: *Acute metabolic crises in Inborn Errors of Metabolism (IEM) are life-threatening emergencies warranting prompt management to optimize outcomes. These crises typically manifest as sudden deterioration following a healthy interval in neonates and triggered by stressors like infection or fasting in children. Management includes immediate stabilization followed by specific therapeutic strategies: substrate reduction by withholding feeding for 48 hours; toxic metabolite elimination; provision of adequate calories and deficient nutrients and enhancement of enzyme activity by cofactor supplementation. Clinical protocols recommend restarting enteral feeding with breast milk or special formula milk within 48 hours, barring specific contraindications. This review comprehensively details these essential principles and strategies for managing IEM crisis.*

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Points to Remember

- ***Early recognition and timely intensive care for metabolic crises in IEM are crucial for preventing mortality.***
- ***Initial investigations of 'GALAKS' - glucose, arterial blood gases, lactate, ammonia, ketones, and urine reducing substances help in guiding further approach.***
- ***Stabilization with airway, breathing, circulation support and correction of hypoglycemia, seizures, and metabolic acidosis form the foundation of acute management.***
- ***Substrate reduction is the key and is achieved by nil per oral route, adequate glucose infusion to prevent catabolism and initiation of special formulas if the IEM diagnosis is known.***
- ***Elimination of toxic metabolites should be done by scavengers like sodium benzoate in hyperammonemia and followed by extracorporeal detoxification techniques.***
- ***Supplementation with cofactors and vitamins, such as biotin, thiamine and riboflavin will help in specific IEMs.***
- ***Prevention of recurrent crises is by multidisciplinary long-term management involving metabolic specialist, pediatrician, dietician and neurologist.***
- ***Genetic counselling and metabolic autopsy in critical end stage cases is important for preventing recurrence of the disorder in future pregnancies.***

Cite as: Rajakumar Padur Sivaraman, Prakash Amboiram, Thangavelu Sangaralingam. Emergency management of metabolic crises in intensive care settings (Acute decompensation protocols, hyperammonemia, hypoglycemia, metabolic acidosis), Indian J Pract Pediatr. 2025; 27(4):336-346.

References

1. Saudubray JM, Cazorla AG. Clinical approach to inborn errors of metabolism in pediatrics. In: Saudubray JM, Baumgartner MR, Walter J, editors. Inborn metabolic diseases: diagnosis and treatment. Berlin: Springer; 2016. p. 3-70.
2. Sivaraman RP, Balakrishnan U, Chidhambaram S, Tarikare S, Sankaranarayanan S. Profile and outcome of children with inborn errors of metabolism in a tertiary pediatric intensive care unit in South India. Indian J Child Health. 2019; 6(3):104-9.
3. Saudubray JM, Nassogne MC, de Lonlay P, Touati G. Clinical approach to inherited metabolic disorders in neonates: an overview. Semin Neonatol. 2002; 7:3-15.
4. Champion MP. An approach to the diagnosis of inherited metabolic disease. Arch Dis Child Educ Pract Ed. 2010; 95:40-6.
5. Ratnakumari TL. Evaluation and management of a sick infant with suspected inborn error of metabolism. Indian J Pract Pediatr. 2010; 12(2):109-30.
6. Balakrishnan U. Inborn errors of metabolism-approach to diagnosis and management in neonates. Indian J Pediatr. 2021; 88(7):679-89.
7. British Inherited Metabolic Disease Group. Emergency guidelines. Available from: https://www.bimdg.org.uk/guidelines/guidelines-adult.asp. Accessed October 28, 2021.
8. Solares I, Heredia-Mena C, Castelbón FJ, et al. Diagnosis and management of inborn errors of metabolism in adult patients in the emergency department. Diagnostics (Basel). 2021; 11:2148.
9. Häberle J. Clinical practice: the management of hyperammonemia. Eur J Pediatr. 2011; 170:21–34.
10. van Karnebeek CDM, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review. Mol Genet Metab. 2012; 105:368-81.
11. Alfadhel M, Al Mutairi F, Makhseed N, Al Jasmi F, Al-Thihli K, Al-Jishi E, et al. Guidelines for acute management of hyperammonemia in the Middle East region. Ther Clin Risk Manag. 2016;12:479-87.
12. Weinstein DA, Steuerwald U, De Souza CFM, Derks TGJ. Inborn errors of metabolism with hypoglycemia: glycogen storage diseases and inherited disorders of gluconeogenesis. Pediatr Clin North Am. 2018; 65(2):247-65.
13. Ratnaike TE, Elkhateeb N, Lochmüller A, Gilmartin C, Schön K, Horváth R, et al. Evidence for sodium valproate toxicity in mitochondrial diseases: a systematic analysis. BMJ Neurol Open. 2024; 6(1):e000650.
14. Baxter P. Epidemiology of pyridoxine-dependent and pyridoxine-responsive seizures in the UK. Arch Dis Child. 1999; 81:431-3.
15. Balakrishnan U. Inborn errors of metabolism. In: Balakrishnan U, editor. Genetic and inherited metabolic disorders in children. Chennai: Paras Medical Publisher; 2021. p. 193-224.
16. Thompson GN, Chalmers RA, Walter JH, Bresson JL, Lyonnet SL, Reed PJ, et al. The use of metronidazole in management of methylmalonic and propionic acidaemias. Eur J Pediatr. 1990; 149(11):792-6.
17. Ninkovic D, Mustapic •, Bartonicek D, Benjak V, Cuk M, Buljevic A, et al. Therapeutic hypothermia in hyperammonemic encephalopathy due to urea cycle disorders and organic acidemias. Klin Padiatr. 2019; 231(2):74-9.
18. Umamaheswari Balakrishnan, Shiv Sajan Saini, James Daniel, Aleesha K Aliyar. Inborn errors of metabolism. In: Hansen AR, Eichenwald EC, Stark AR, Jain N, editors. Manual of neonatal care. 2nd South Asian ed. New Delhi: Wolters Kluwer India; 2023. p. 897-929.
19. Balakrishnan U. Dietary management in inborn errors of metabolism. Indian J Pract Pediatr. 2024; 26(1): 44-52.
20. Das A. Clinical utility of nitisinone for the treatment of hereditary tyrosinemia type 1. Appl Clin Genet. 2017; 10:43-8.
21. Vockley J, Burton BK, Berry G, Longo N, Phillips J, Sanchez-Valle A, et al. Triheptanoin for the treatment of long-chain fatty acid oxidation disorders: final results of an open-label, long-term extension study. J Inherit Metab Dis. 2023; 46(5):943-55.
22. Nyhan WL, Rice-Kelts M, Klein J, Barshop BA. Treatment of the acute crisis in maple syrup urine disease. Arch Pediatr Adolesc Med. 1998; 152(6):593-8.
23. Häberle J, Boddaert N, Burlina A, Chakrapani A, Dixon M, Huemer M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis. 2012; 7:32.
24. Gupta S, Fenves AZ, Hootkins R. The role of renal replacement therapy in hyperammonemic patients. Clin J Am Soc Nephrol. 2016; 11(10):1872-8.
25. Raina M, Doshi K, Myneni A, Tibrewal A, Gillen M, Hu J, et al. Inborn errors of metabolism in neonates and pediatrics on varying dialysis modalities: a systematic review and meta-analysis. Pediatr Nephrol. 2024; 40(7): 2177-88.
26. Ribas GS, Lopes FF, Deon M, Vargas CR. Hyperammonemia in inherited metabolic diseases. Cell Mol Neurobiol. 2022; 42(8):2593-610.
27. Summar ML, Mew NA. Inborn errors of metabolism with hyperammonemia. Pediatr Clin North Am. 2018; 65(2): 231-46.

28. Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. Pediatrics. 2002; 109(6):999-1008.
29. MacDonald A, Depondt E, Evans S, Daly A, Hendriksz C, Chakrapani A, et al. Breast feeding in inherited metabolic disorders. J Inherit Metab Dis. 2006; 29:299-303.
30. Tumiene B, Del Toro Riera M, Grikiniene J, Samaitiene-Alekniene R, Praninskiene R, Monavari AA, et al. Multidisciplinary care of patients with inherited metabolic diseases and epilepsy. J Multidiscip Healthc. 2022; 15:553-66.
31. Miller W, Wothe J, Wang Q, Vock D, Bhatt H, Salunke A, et al. Long-term outcomes of liver transplantation for inborn errors of metabolism in children. Transplant Proc. 2024; 56(6):1359-64.
32. Balakrishnan U, Chandrasekaran A, Amboiram P, Ninan B, Ignatious S. Outcome of inherited metabolic disorders presenting in the neonatal period. Indian J Pediatr. 2021; 88(5):455-62.
33. Bösch F, Landolt MA, Baumgartner MR, Zeltner N, Kölker S, Gleich F, et al. Health-related quality of life in pediatric patients with intoxication-type inborn errors of metabolism. J Inherit Metab Dis. 2021; 44(1):215-25.

INBORN ERRORS OF METABOLISM - II

NUTRITIONAL MANAGEMENT IN INBORN ERRORS OF METABOLISM - PRINCIPLES AND PRACTICAL PITFALLS

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Abstract: *Inborn Errors of Metabolism constitute a heterogeneous group of genetic disorders, resulting from an enzyme defect in biochemical and metabolic pathways affecting proteins, fats, carbohydrates metabolism or impaired organelle function presenting as complicated medical conditions involving several human organ systems. Their successful long-term clinical outcome is fundamentally dependent upon prompt and precise nutritional intervention. In majority of inborn errors of metabolism, the key therapeutic strategy is nutritional management which primarily is structured around the restriction of toxic substrates, supplementation of deficient products and strict prevention of catabolism. This comprehensive review systematically delineates the key principles of nutritional management, emphasizing the necessity of highly individualized, dynamic and rigorously monitored dietary regimens. Specific emphasis is placed on the tailored nutritional strategies and prevalent practical challenges associated with Maple Syrup Urine Disease, Organic Acidemias, Fatty Acid Oxidation Disorders, Glycogen Storage Diseases, Galactosemia and Urea Cycle Defects. Furthermore, this article articulates critical operational pitfalls pertaining to the reliable procurement of specialized medical foods, accurate biochemical monitoring and ensuring patient adherence in resource-constrained environments. Consequently, an anticipatory and highly coordinated multidisciplinary team approach, incorporating the expertise of the pediatrician, metabolic specialist and specialized dietitian, is deemed indispensable for optimizing somatic growth, neurodevelopmental outcomes and the overall quality of life for affected pediatric populations.*

Keywords: *Inborn errors of metabolism, Nutritional management, Acute metabolic crisis, Specialized medical foods.*

Points to Remember

- ***Acute illness necessitates the immediate cessation of the restricted substrate and aggressive high-dose carbohydrate administration to prevent catabolism and neurotoxicity.***
- ***Monitoring is dynamic and must prioritize tracking the specific toxic metabolite while urgently checking urine ketones for signs of catabolism during illness.***
- ***For FAOD and GSD, the primary therapy is the absolute prevention of fasting, often maintained via strict nocturnal slow-releasing carbohydrate administration.***
- ***The availability of indigenous low cost specialized medical formulae has made the treatment of IEMs accessible in India. However long-term adherence and requirement of dietician, specialized in the management of IEM are the challenges for the successful outcome.***

References

1. Enns GM, et al. Inborn errors of metabolism: Emerging therapies and ongoing challenges. Pediatr Clin North Am. 2020; 67(3):477-493.
2. Balasubramaniam S, Ponnusundar S, Murugesan R, Suresh S. Challenges in the diagnosis and management of inborn errors of metabolism in India. Indian J Pediatr. 2018; 85(1):6-13.
3. Kapoor S, Agarwal R, Raghunathan M, et al. Newborn Screening in India: Current Status and Challenges. Indian Pediatr. 2021; 58(Suppl 1):S21-S26.

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Cite as: Sanjeeva GN. Nutritional management in inborn errors of metabolism (IEM) - Principles and practical pitfalls, Indian J Pract Pediatr. 2025; 27(4):347-355.

4. Viau J, et al. Management of maple syrup urine disease: new recommendations for acute and chronic care. Mol Genet Metab. 2021; 133(1):1-10.
5. Ahluwalia U, et al. Nutritional management of Inborn Errors of Metabolism: A review of global guidelines. J Inherit Metab Dis. 2022; 45(3):550-565.
6. Dionisi-Vici C, et al. Treatment of urea cycle disorders in the era of new therapies. Pediatr Res. 2021; 89(6):1598-1607.
7. Zaki OK, et al. Current perspectives in the management of urea cycle disorders: A systematic review. Mol Genet Metab Rep. 2023;37:101019.
8. Baumgartner MR, et al. Consensus guidelines for the management of methylmalonic acidemia and propionic acidemia. J Inherit Metab Dis. 2021;44(3):580-605.
9. Vianey-Saban C, Vockley J, Burlina A, Ruiter JPN, Vilarinho L, et al. Management of fatty acid oxidation disorders: revised consensus guidelines. J Inherit Metab Dis. 2021; 44(3):471–491.
10. Knott C, et al. Fatty acid oxidation disorders: a practical guide for clinicians. J Pediatr Health Care. 2020; 34(5): 455-467.
11. Kishnani PS, et al. Glycogen storage disease type I: Clinical management and outcomes in a large cohort. Genet Med. 2022; 24(6):1251-1262.
12. Welling L, et al. Galactosemia: Pathophysiology and management challenges. J Inherit Metab Dis. 2017; 40(6):783-792.

INBORN ERRORS OF METABOLISM - II

THE ROLE OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN INBORN ERRORS OF METABOLISM

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****Kavitha Ganesan**

Abstract : *Advances in the field of transplantation have resulted in dramatic cure for children with inborn errors of metabolism over the last three decades. Early diagnosis and optimal patient selection are the key to successful outcomes. The best outcomes have been seen in children with mucopolysaccharidoses who have been transplanted before the age of two years to prevent neurocognitive deficits. The counselling of these families involves many challenges including organ dysfunction during the procedure, the long time required to perceive improvement in the somatic features and the need for holistic follow up with cardiac, orthopaedic, neurology and ophthalmology colleagues. We present here, the data available with current studies on patient referral, timing of referral and the unique features in the care of these children.*

Keywords: *Hematopoietic stem cell transplantation, Inborn errors of metabolism, Lysosomal storage disorders, Gene therapy.*

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Points to Remember

- ***Hematopoietic stem cell transplantation (HSCT) for metabolic diseases involves inputs from a multidisciplinary team before, during and long after HSCT.***
- ***The timing of HSCT must precede the onset of disease progression; HSCT halts progression but does not reverse existing disease related damages.***
- ***HSCT can be performed using a matched sibling donor, a matched unrelated donor or a haploidentical parent donor.***
- ***Myeloablative conditioning using treosulfan or targeted busulfan prevents rejection of the graft.***
- ***Gene therapy using autologous stem cells offers the potential for better outcomes and lower toxicity in this unique group of children.***

Acknowledgements

We would like to acknowledge the little children with IEM from whom we had learnt and perfected the art of HSCT and the team involved in the care of children with IEM-Dr.Prasad Manne, Dr.Indira Jayakumar, Dr.Ravindra Prasad and Dr.Mahesh Narayanan.

Bibliography

1. Tan EY, Boelens JJ, Jones SA,Wynn RF, Hematopoietic Stem Cell Transplantation in Inborn Errors of Metabolism. Front. Pediatr. 2019 Oct 25:7:433.doi: 10.3389/fped.2019.00433. eCollection 2019.
2. Swaminathan VV, Meena S, Varla H, Chandar R, Jayakumar I, Ramakrishnan B, et al. Hematopoietic Stem Cell Transplantation for Children With Inborn Errors of Metabolism: Single Center Experience Over Two Decades. Indian Pediatr. 2022 Sep 15; 59(9):699-702.
3. Hivre M, Holkar SR , Vaishnav D, Surkar P, Chandankhede S, Vidhale D. Inborn Errors of Metabolism: A Comprehensive Clinical Review and Case-Based Analysis of Metabolic Disorders Across

Cite as: Revathi Raj, Ramya Uppuluri, Kavitha Ganesan. The role of haematopoietic stem cell transplantation in inborn errors of metabolism, Indian J Pract Pediatr. 2025; 27(4):356-359.

Multiple Biochemical Pathways, Journal of chemical health risks, 2025; 15(4), 2168-2187.

4. Lum SH, Miller WP, Jones S, Poulton K, Ogden W, Lee H, et al. Changes in the incidence, patterns and outcomes of graft failure following hematopoietic stem cell transplantation for Hurler syndrome. Bone Marrow Transplant. (2017) 52:846-53. doi: 10.1038/bmt.2017.5
5. Mahmood A, Raymond GV, Dubey P, Peters C, Moser HW. Survival analysis of haematopoietic cell transplantation for childhood cerebral X linked adrenoleukodystrophy: a comparison study. Lancet Neurol. 2007; 6 : 687-92
6. Taylor M, Khan S, Stapleton M, Wang J, Chen J, Wynn R,et al. Hematopoietic stem cell transplantation for mucopolysaccharidoses: past, present, and future. Biol Blood Marrow Transplant. 2019; 25:e226-e46.
7. Chiesa R, Wynn RF, Veys P. Haematopoietic stem cell transplantation in inborn errors of metabolism. Curr Opin Hematol. 2016; 23:530-35.
8. Boelens JJ, Orchard PJ, Wynn RF. Transplantation in inborn errors of metabolism: current considerations and future perspectives. Br J Haematol. 2014; 167:293-303.

INBORN ERRORS OF METABOLISM - II

ROLE OF LIVER TRANSPLANT IN CHILDREN WITH INBORN ERRORS OF METABOLISM - INDICATIONS AND OUTCOMES

***Rajkali Rajendiran**
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*****Naresh Shanmugam**

Abstract: *Inborn errors of metabolism (IEMs) represent one of the major indications for pediatric liver transplantation, particularly when conventional dietary and medical therapies fail to prevent metabolic instability or progressive organ damage. Liver transplant not only replaces failing hepatic function but also corrects specific enzyme deficiencies central to disorders such as urea cycle defects, maple syrup urine disease, tyrosinemia, organic acidemias, Wilson disease, glycogen storage disorders, Crigler-Najjar syndrome, progressive familial intrahepatic cholestasis and primary hyperoxaluria. Evidence demonstrates that liver transplant provides durable metabolic control, eliminates life-threatening decompensation and permits dietary liberalization, with survival outcomes comparable to non-metabolic indications. Early transplantation mitigates irreversible neurological, cardiac or renal injury and markedly improves growth and quality of life. This review summarizes the pathophysiology, indications and outcomes of liver transplant across major pediatric metabolic disorders, emphasizing its pivotal role in long-term metabolic stabilization.*

Keywords: *Inborn errors of metabolism (IEM), Pediatric liver transplantation, Metabolic stabilization, Long-term outcomes.*

Points to Remember

- ***Liver transplantation serves as a metabolic cure, correcting enzyme deficiencies in liver-related metabolic disorders.***
- ***Early liver transplant improves outcomes, preventing irreversible neurological, cardiac, or renal injury in disorders such as UCDs, MSUD, and organic acidemias.***
- ***Post-transplant metabolic stability helps in elimination of life-threatening decompensations and normalization of key biochemical parameters.***
- ***Quality of life improves substantially, as children can often discontinue strict dietary restrictions and specialized metabolic therapies.***
- ***Overall survival and graft outcomes are comparable to non-metabolic transplant indications, supporting LT as a safe and effective long-term solution for selected metabolic diseases.***

References

1. Eldredge JA, Hardikar W. Current status and future directions of liver transplantation for metabolic liver disease in children. Pediatr Transplant. 2024 Feb; 28(1): e14625.
2. Miller W, Wothe J, Wang Q, Vock D, Bhatt H, Salunke A, et al. Long-term Outcomes of Liver Transplantation for Inborn Errors of Metabolism in Children. Transplant Proc. 2024; 56(6):1359-64.
3. Menon J, Vij M, Sachan D, Rammohan A, Shanmugam N, Kaliamoorthy I, et al. Pediatric metabolic liver diseases: Evolving role of liver transplantation. World J Transplant. 2021 Jun 18; 11(6):161-79.
4. Liver Transplantation and Health Outcomes in Urea Cycle Disorders | Urea Cycle Disorders Consortium

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Cite as: Rajkali Rajendiran, Jagadeesh Menon, Naresh Shanmugam. Role of liver transplant in children with inborn errors of metabolism - Indications and outcomes, Indian J Pract Pediatr. 2025; 27(4):360-365.

[Internet]. [cited 2025 Dec 11]. Available from: https://ucdc.rarediseasesnetwork.org/news/liver-transplantation-and-health-outcomes-urea-cycle-disorders.

5. Oishi K, Arnon R, Wasserstein MP, Diaz GA. Liver transplantation for pediatric inherited metabolic disorders: considerations for indications, complications, perioperative management. Pediatr Transplant. 2016 Sep; 20(6):756-69.
6. Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis. 2019 Nov; 42(6):1192-230.
7. Department of Pediatrics, Division of Pediatric Gastroenterology, Akdeniz University School of Medicine, Antalya, Turkey, Basturk A, Keceli M, Department of Pediatrics, Division of Pediatric Gastroenterology, Akdeniz University School of Medicine, Antalya, Turkey, Erbis H, Department of General Surgery, Akdeniz University School of Medicine, Transplantation Institute, Antalya, Turkey, et al. Liver transplantation from a live donor to a patient with maple syrup urine disease: Two case reports. Türk Pediatri Ars. 2018 Jul 29; 53(2):113-6.
8. Vasudevan AK, Shanmugam N, Rammohan A, Balakrishnan U, Menon J, Iqbal MAUH, et al. Long-Term Amino Acid Homeostasis, Neurodevelopmental and Growth Profiles Following Liver Transplantation in Maple Syrup Urine Disease. Pediatr Transplant. 2024 Sep; 28(6):e14845.
9. Daou KN, Barhoumi A, Bassyouni A, Karam PE. Diagnostic and Therapeutic Challenges of Hereditary Tyrosinemia Type 1 in Lebanon: A 12-Year Retrospective Review. Front Pediatr. 2021;9:698577.
10. Bolia R, Srivastava A. Liver Transplantation for Tyrosinemia Type 1 in the Developing World: Is It Really the Best We Can Offer? Indian J Pediatr. 2022 May 1; 89(5):427-8.
11. Menon J, Shanmugam N, Valamparampil JJ, Hakeem A, Vij M, Jalan A, et al. Liver Transplantation: A Safe and Definitive Alternative to Lifelong Nitisinone for Tyrosinemia Type 1. Indian J Pediatr. 2022 May;89(5): 438-44.
12. Mc Guire PJ, Lim-Melia E, Diaz GA, Raymond K, Larkin A, Wasserstein MP, et al. Combined liver-kidney transplant for the management of methylmalonic aciduria: a case report and review of the literature. Mol Genet Metab. 2008 Jan; 93(1):22-9.
13. Romano S, Valayannopoulos V, Touati G, Jais JP, Rabier D, de Keyzer Y, et al. Cardiomyopathies in Propionic Aciduria are Reversible After Liver Transplantation. J Pediatr. 2010 Jan 1; 156(1):128-34.
14. Baumgartner MR, Hörster F, Dionisi-Vici C, Haliloglu G, Karall D, Chapman KA, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis. 2014 Sep 2; 9(1):130.
15. Ferrarese A, Morelli MC, Carrai P, Milana M, Angelico M, Perricone G, et al. Outcomes of Liver Transplant for Adults With Wilson's Disease. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2020 Apr; 26(4):507-16.
16. Shimizu S, Sakamoto S, Horikawa R, Fukuda A, Uchida H, Takeda M, et al. Longterm Outcomes of Living Donor Liver Transplantation for Glycogen Storage Disease Type 1b. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2020 Jan; 26(1):57-67.
17. Liu M, Sun LY. Liver Transplantation for Glycogen Storage Disease Type IV. Front Pediatr. 2021; 9:633822.
18. Sambati V, Laudisio S, Motta M, Esposito S. Therapeutic Options for Crigler-Najjar Syndrome: A Scoping Review. Int J Mol Sci. 2024 Oct 13; 25(20):11006.
19. Menon J, Shanmugam N, Vij M, Veerankutty FH, Rammohan A, Rela M. Simultaneous total internal biliary diversion during liver transplantation for progressive familial intrahepatic cholestasis type 1: Standard of care? Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2024 Jul 1; 30(7):699-706.
20. Kubitz R, Dröge C, Kluge S, Stross C, Walter N, Keitel V, et al. Autoimmune BSEP Disease: Disease Recurrence After Liver Transplantation for Progressive Familial Intrahepatic Cholestasis. Clin Rev Allergy Immunol. 2015 Jun 1; 48(2):273-84.
21. Morgan SH, Purkiss P, Watts RWE, Mansell MA. Oxalate Dynamics in Chronic Renal Failure: Comparison with Normal Subjects and Patients with Primary Hyperoxaluria. Nephron. 2008 Dec 5; 46(3):253-7.
22. Cochat P, Schärer K. Should liver transplantation be performed before advanced renal insufficiency in primary hyperoxaluria type 1? Pediatr Nephrol. 1993 Apr 1;7(2): 212-8.

INBORN ERRORS OF METABOLISM - II

ROLE OF RENAL TRANSPLANTATION IN INBORN ERRORS OF METABOLISM

***Sangeetha G**

Abstract: *An enzyme deficiency or defect in a critical metabolic pathway of the human body causes inborn errors of metabolism. These disorders present with multisystem involvement. Renal manifestations can be in the form of tubular diseases like renal tubular acidosis, renal stone disease, hyperuricemia, proteinuria, glucosuria, acute kidney injury and chronic kidney disease. Necessary investigations for the renal manifestations must be a part of the routine follow-up for these children. Possible causes considered are the accumulation of intermediate toxic substrates, energy deficiency, deposition of crystalline substances and subsequent multi-organ impairment. Specific therapies with dietary modifications depending on the underlying condition, are essential steps in treating inborn errors of metabolism. Transplantation considerations in inborn errors of metabolism have unique challenges, as multisystem involvement is common. Isolated kidney, liver or combined kidney-liver transplantation might be needed depending on the underlying disease.*

Keywords: *Metabolic disorders, Fanconi syndrome, Kidney transplantation, Liver transplantation and combined liver-kidney transplantation.*

Points to Remember

- ***Various renal manifestations are common in children with inborn errors of metabolism.***
- ***Although children with Tyrosinemia often present with Fanconi syndrome, liver transplantation remains the preferred treatment.***
- ***Cysteamine therapy should be continued in children with cystinosis even after kidney transplantation.***
- ***Lumasiran is a specific RNA interference (RNAi) therapy for primary hyperoxaluria***
- ***Metabolic crises should be managed appropriately to prevent acute kidney injury in children with IEM.***
- ***Isolated kidney, liver or combined kidney-liver transplantation might be needed depending on the underlying disease.***

References

1. Raina M, Doshi K, Myneni A, Tibrewal A, Gillen M, Hu J, Bunchman TE. Inborn errors of metabolism in neonates and pediatrics on varying dialysis modalities: a systematic review and meta-analysis. Pediatr Nephrol. 2025 Jul; 40(7):2177-2188. doi: 10.1007/s00467-024-06547-7. Epub 2024 Nov 11. PMID: 39523291; PMCID: PMC12116838.
2. Häberle J, Boddaert N, Burlina A et al (2012) Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis 7:32. 10.1186/1750-1172-7-32
3. Harings T, Bertsche T, Thiele AG, Kiess W, Bertsche A, Beblo S, Neininger MP. Perspectives of pediatric patients with inborn errors of metabolism on long-term treatment and metabolic emergency management. Orphanet J Rare Dis. 2025 Oct 6;20(1):502. doi: 10.1186/s13023-025-04046-y. PMID: 41053858; PMCID: PMC12498459.
4. Saudubray JM, Garcia-Cazorla A. Clinical Approach to Inborn Errors of Metabolism in Pediatrics. In: Inborn Metabolic Diseases. Berlin, Heidelberg: Springer Berlin Heidelberg, 2016:3-70.

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Cite as: Sangeetha G. Role of renal transplantation in inborn errors of metabolism, Indian J Pract Pediatr. 2025; 27(4):366-371.

INBORN ERRORS OF METABOLISM - II

RECENT ADVANCES IN INBORN ERRORS OF METABOLISM - GENE THERAPY AND EMERGING THERAPEUTICS

***Neerja Gupta**
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Abstract: *Inborn errors of metabolism comprise a heterogeneous group of genetic disorders associated with significant morbidity and mortality. Therapeutic strategies for disorders with inborn errors of metabolism, have been substantially evolved - from conventional modalities like dietary modification and enzyme replacement towards targeted molecular interventions and precision therapies. Emerging therapeutic modalities in inborn errors of metabolisms include viral vector gene therapy, in vivo and ex vivo genome editing, epigenome editing, ribonucleic acid-based therapeutics, small-molecule chaperones and next-generation protein and cell therapies that offer transformative and potentially curative outcomes. This review summarises recent advances across these platforms, highlighting disease-specific progress in multivarious inborn errors of metabolism-disorders.*

Keywords: *Inborn errors of metabolism, Emerging therapies, Gene therapy, Genome editing, RNA therapeutics*

Points to Remember

- ***Therapeutic strategies for inborn errors of metabolism are expanding from conventional management strategies such as dietary intervention, cofactor supplementation and enzyme replacement to newer personalised gene-based therapies.***
- ***These advancements in therapies include novel chaperones / other small molecules, enzyme replacement therapy strategies, therapies related to metabolic bypass and repurposed drugs.***
- ***High-end viral and non-viral gene delivery platforms, genome editing and RNA therapeutics and their efficacy, safety, are being studied widely and in various stages of development for a variety of IEMs.***
- ***In vivo gene therapy involves vector delivery directly to the patient, predominantly using adeno-associated virus vectors. Ex vivo hematopoietic stem cell - lentiviral gene therapy enables central nervous system cross-correction, providing durable benefit in leukodystrophies.***
- ***Lipid nanoparticle-mRNA and extracellular vesicle-based systems are emerging as repeatable, low immunogenicity alternatives, with growing promise for hepatic and CNS-targeted IEMs.***
- ***CRISPR, base editors and prime editors enable single-base correction with low genotoxic risk, provide an effective therapeutic alternative. Preclinical and murine studies seem promising but need further evaluation to establish clinical translation of benefits.***
- ***Availability and affordability of these therapeutic advances still remain a great challenge. Therefore, scaling up production of these newer therapies to meet the demand and lowering costs to ensure equitable access to these life-saving treatments is a much needed action.***

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References

1. Ferreira CR, Rahman S, Keller M, Zschocke J. ICIMD Advisory Group. An international classification of inherited metabolic disorders (ICIMD). J Inherit Metab Dis. 2021; 44(1):164-77.
2. Auger N, Nelson C, Brousseau É, Bilodeau-Bertrand M, Dewar R, Arbour L. Extended Risk of Mortality in Children with Inborn Errors of Metabolism: A Longitudinal Cohort Study. J Pediatr. 2023; 252:16-21.e2.
3. Waters D, Adeloye D, Woolham D, Wastnedge E, Patel S, Rudan I. Global birth prevalence and mortality from inborn errors of metabolism: a systematic analysis of the evidence. J Glob Health. 2018; 8(2):021102.
4. Baruteau J, Brunetti-Pierri N, Gissen P. Liver-directed gene therapy for inherited metabolic diseases. J Inherit Metab Dis. 2024; 47(1):9-21.
5. Ginocchio VM, Ferla R, Auricchio A, Brunetti-Pierri N. Current Status on Clinical Development of Adeno-Associated Virus-Mediated Liver-Directed Gene Therapy for Inborn Errors of Metabolism. Hum Gene Ther. 2019; 30(10):1204-10.
6. Puzzo F, Kay MA. The deLIVERed promises of gene therapy: Past, present and future of liver-directed gene therapy. MolTher. 2025; 33(5):1966-87.
7. Castle MJ, Turunen HT, Vandenberghe LH, Wolfe JH. Controlling AAV Tropism in the Nervous System with Natural and Engineered Capsids. Methods Mol Biol. 2016; 1382:133-49.
8. Dong JY, Fan PD, Frizzell RA. Quantitative analysis of the packaging capacity of recombinant adeno-associated virus. Hum Gene Ther. 1996 Nov 10; 7(17):2101-12.
9. Sayed N, Allawadhi P, Khurana A, Singh V, Navik U, Pasumarthi SK, et al. Gene therapy: Comprehensive overview and therapeutic applications. Life Sci. 2022 Apr 1; 294:120375.
10. Wang F, Liang L, Wang C, Zhang C, Ye Y, Dou L, et al. Non-Viral Gene Delivery Systems: Current Advances and Therapeutic Applications. Chem Asian J. 2025; 20(20): e00684.
11. Khafoor AA, Karim AS, Sajadi SM. Recent progress in synthesis of nano based liposomal drug delivery systems: A glance to their medicinal applications. Results in Surfaces and Interfaces. 2023; 11:100124.
12. Li T, Yang Y, Qi H, Cui W, Zhang L, Fu X, et al. CRISPR/Cas9 therapeutics: progress and prospects. Sig Transduct Target Ther. 2023 16; 8(1):36.
13. Castro-Alpízar JA, Lenderink MJ, Nieuwenhuis EES, Kooijmans SAA, Fuchs S. Navigating molecular therapies: The emerging role of mRNA in treating inherited metabolic diseases. Mol Genet Metab. 2025; 147:109698.
14. Seo JH, Kosuga M, Hamazaki T, Shintaku H, Okuyama T. Intracerebroventricular enzyme replacement therapy in patients with neuronopathic mucopolysaccharidosis type II: Final report of 5-year results from a Japanese open-label phase 1/2 study. Mol Genet Metab. 2023; 140(4):107709.
15. Schulz A, Specchio N, de Los Reyes E, Gissen P, Nickel M, Trivisano M, et al. Safety and efficacy of cerliponasealfa in children with neuronal ceroid lipofuscinosis type 2 (CLN2 disease): an open-label extension study. Lancet Neurol. 2024; 23(1):60-70.
16. Muenzer J, Burton BK, Harmatz P, Gutiérrez-Solana LG, Ruiz-Garcia M, Jones SA, et al. Intrathecal idursulfase-IT in patients with neuronopathic mucopolysaccharidosis II: Results from a phase 2/3 randomized study. Molecular Genetics and Metabolism. 2022; 137(1):127-39.
17. Martinez M, Harding CO, Schwank G, Thöny B. State-of-the-art 2023 on gene therapy for phenylketonuria. J Inherit Metab Dis. 2024; 47(1):80-92.
18. Musunuru K, Grandinette SA, Wang X, Hudson TR, Briseno K, Berry AM, et al. Patient-Specific In Vivo Gene Editing to Treat a Rare Genetic Disease. N Engl J Med. 2025; 392(22):2235-43.
19. Yu I, Jeong J. Advancing Gene Therapy for Phenylketonuria: From Precision Editing to Clinical Translation. Int J Mol Sci. 2025; 26(17):8722.
20. Ficicioglu C, Thomas JA, Ganesh J, Kudrow D, Lah M, Smith WE, et al. Safety and efficacy of pegtibatinase enzyme replacement therapy in adults with classical homocystinuria in the COMPOSE phase 1/2 randomized trial. Genet Med. 2025; 27(8):101456.
21. Moderna TX, Inc. A Global Phase 1/2, Open-Label, Dose Optimization Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of mRNA-3705 in Participants With Isolated Methylmalonic Acidemia Due to Methylmalonyl-CoA Mutase Deficiency [Internet]. clinicaltrials.gov; 2025 Mar [cited 2025 Dec 14]. Report No.: NCT04899310. Available from: https://clinicaltrials.gov/study/NCT04899310.
22. Zhang S, Bastille A, Gordo S, Ramesh N, Vora J, McCarthy E, et al. Novel AAV-mediated genome editing therapy improves health and survival in a mouse model of methylmalonic acidemia. PLOS ONE. 2022; 17(9): e0274774.
23. Koeberl D, Schulze A, Sondheimer N, Lipshutz GS, Geberhiwot T, Li L, et al. Interim analyses of a first-in-human phase 1/2 mRNA trial for propionic acidaemia. Nature. 2024; 628(8009):872-7.
24. Chandler RJ, Di Pasquale G, Choi EY, Chang D, Smith SN, Sloan JL, et al. Systemic gene therapy using an AAV44.9 vector rescues a neonatal lethal mouse model of propionic acidemia. Mol Ther Methods Clin Dev. 2023; 30:181-90.

25. Thomas J, Tan WH, Khan A, Konczal L, Breilyn MS, Hualde LC, et al. Long-term safety and efficacy of DTX301 in adults with late-onset ornithine transcarbamylase (OTC) deficiency: A Phase 1/2 trial. Mol Genet Metab. 2024; 141(4):108266. DOI:10.1016/j.ymgme.2024.108266
26. Ultragenyx Pharmaceutical Inc. A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Adeno-associated Virus (AAV) Serotype 8 (AAV8)-Mediated Gene Transfer of Human Ornithine Transcarbamylase (OTC) in Patients With Late-onset OTC Deficiency [Internet]. clinicaltrials.gov; 2025 Oct [cited 2025 Nov 17]. Report No.: NCT05345171. Available from: https://clinicaltrials.gov/study/NCT05345171
27. Weinstein DA, Derks TG, Rodriguez-Buritica DF, Ahmad A, Couce M, Mitchell JJ, et al. Safety and Efficacy of DTX401, an AAV8Mediated Liver Directed Gene Therapy, in Adults With Glycogen Storage Disease Type I a (GSDIa). J Inherit Metab Dis. 2025; 48(2): e70014.
28. Lu B, Ku J, Flojo R, Olson C, Bengford D, Marriott G. Exosome and extracellular vesicle-based approaches for the treatment of lysosomal storage disorders. Adv Drug Deliv Rev. 2022; 188:114465. doi: 10.1016/j.addr.2022.114465.
29. Do MA, Levy D, Brown A, Marriott G, Lu B. Targeted delivery of lysosomal enzymes to the endocytic compartment in human cells using engineered extracellular vesicles. Sci Rep. 2019 Nov 21; 9(1):17274.
30. Nieland L, Mahjoum S, Grandell E, Breyne K, Breakefield XO. Engineered EVs designed to target diseases of the CNS. J Control Release. 2023; 356: 493-506.
31. Ma X, Zhuang L, Ma W, Li J, Mao Y, Wang J, et al. AAV9-Mediated Gene Therapy for Infantile-Onset Pompe's Disease. N Engl J Med. 2025 June 26; 392(24): 2438-46.
32. AskBio Inc. A Phase 1 Study of the Safety of AAV2/8-LSPhGAA (ACTUS-101) in Late-onset Pompe Disease [Internet]. clinicaltrials.gov; 2023 June [cited 2025 Nov 17]. Report No.: NCT03533673. Available from: https://clinicaltrials.gov/study/NCT03533673.
33. Sangamo Therapeutics. A Phase I/II, Multicenter, Open-Label, Single-Dose, Dose-Ranging Study to Assess the Safety and Tolerability of ST-920, an AAV2/6 Human Alpha Galactosidase A Gene Therapy, in Subjects With Fabry Disease (STAAR) [Internet]. clinicaltrials.gov; 2025 May [cited 2025 Nov 17]. Report No.: NCT04046224. Available from: https://clinicaltrials. gov/study/NCT04046224
34. Pagant S, Huston MW, Moreira L, Gan L, St Martin S, Sproul S, et al. ZFN-mediated in vivo gene editing in hepatocytes leads to supraphysiologic α-Gal A activity and effective substrate reduction in Fabry mice. Mol Ther. 2021; 29(11):3230-42.
35. Messina M, Gissen P. Atidarsageneautotemcel for metachromatic leukodystrophy. Drugs Today (Barc). 2023; 59(2):63-70.
36. Harmatz P, Prada CE, Burton BK, Lau H, Kessler CM, Cao L, et al. First-in-human in vivo genome editing via AAV-zinc-finger nucleases for mucopolysaccharidosis I/II and hemophilia B. Mol Ther. 2022; 30(12):3587-600.
37. Cartier N, Hacein-Bey-Abina S, Bartholomae CC, Bougnères P, Schmidt M, Kalle CV, et al. Lentiviral hematopoietic cell gene therapy for X-linked adrenoleukodystrophy. Methods Enzymol. 2012; 507: 187-98.
38. Keshavan N, Minczuk M, Viscomi C, Rahman S. Gene therapy for mitochondrial disorders. J Inherit Metab Dis. 2024 Jan; 47(1):145-175. doi: 10.1002/jimd.12699. Epub 2024 Jan 3. PMID: 38171948.
39. Williams RA, Bell DA, Hooper AJ, Burnett JR. Sepiapterin for the treatment of phenylketonuria. Expert Opin Pharmacother. 2025; 26(8):933-8.
40. Smith WE, Berry SA, Bloom K, Brown C, Burton BK, Demarest OM, et al. Phenylalanine hydroxylase deficiency diagnosis and management: A 2023 evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2025; 27(1):101289.
41. Philipp TM, Bottiglieri T, Clapper W, Liu K, Rodems S, Szabo C, et al. Mechanism of action and impact of thiol homeostasis on efficacy of an enzyme replacement therapy for classical homocystinuria. Redox Biol. 2024 Nov;77:103383. doi: 10.1016/j.redox.2024.103383. Epub 2024 Oct 2. PMID: 39366068; PMCID: PMC11489331.
42. Lee HO, Salami CO, Sondhi D, Kaminsky SM, Crystal RG, Kruger WD. Long-term functional correction of cystathionine β-synthase deficiency in mice by adeno-associated viral gene therapy. J Inherit Metab Dis. 2021; 44(6):1382-92.
43. Majtan T, Mijatovic E, Petrosino M. Understanding the Impact of Mutations in the Cystathionine Beta-Synthase Gene: Towards Novel Therapeutics for Homocystinuria. Mol Cell Biol. 2025; 45(8):327-42.
44. Venturoni LE, Venditti CP. Treatment of metabolic disorders using genomic technologies: Lessons from methylmalonic acidemia. J Inherit Metab Dis. 2022 Sep; 45(5):872-888. doi: 10.1002/jimd.12534. Epub 2022 Jul 21. PMID: 35766386.

45. Ersoy M. Inherited Metabolic Myopathies: Current Diagnosis and Treatment Approaches. Med J Bakýrköy 2021; 17:108-114.
46. Striano P, Auvin S, Collins A, Horvath R, Scheffer IE, Tzadok M, et al. A randomized, double-blind trial of triheptanoin for drug-resistant epilepsy in glucose transporter 1 deficiency syndrome. Epilepsia. 2022; 63(7):1748-60.
47. Koeberl DD, Koch RL, Lim JA, Brooks ED, Arnson BD, Sun B, et al. Gene therapy for glycogen storage diseases. J Inherit Metab Dis. 2024; 47(1):93-118.
48. Grünert SC, Derks TGJ, Mundy H, Dalton RN, Donadieu J, Hofbauer P, Jones N, Uçar SK, LaFreniere J, Contreras EL, Pendyal S, Rossi A, Schneider B, Spiegel R, Stepien KM, Wesol-Kucharska D, Veiga-da-Cunha M, Wortmann SB. Treatment recommendations for glycogen storage disease type IB-associated neutropenia and neutrophil dysfunction with empagliflozin: Consensus from an international workshop. Mol Genet Metab. 2024 Mar; 141(3):108144. doi: 10.1016/j.ymgme.2024.108144. Epub 2024 Jan 17. PMID: 38277989.
49. Ýnci A, Ezgü FS, Tümer L. Advances in Immune Tolerance Induction in Enzyme Replacement Therapy. Paediatr Drugs. 2024; 26(3):287-308.
50. van der Beek NAME, Theunissen MTM, van den Hout JMP, Pijnappel WWM, Schoser B, Laforêt P, et al. Clinical insights in enzyme replacement therapy for metabolic storage disorders: lessons from Pompe disease.Lancet Neurol. 2025; 24(3):230-45.
51. Edelmann MJ, Maegawa GHB. CNS-Targeting Therapies for Lysosomal Storage Diseases: Current Advances and Challenges. Front MolBiosci [Internet]. 2020 Nov 12 [cited 2025 Dec 15];7. Available from: https://www.frontiersin.org/journals/molecular-biosciences/articles/10.3389/fmolb.2020.559804/full
52. Janpipatkul K, Sutjarit N, Tangprasittipap A, Chaiamarit T, Innachai P, Suksen K, et al. Therapeutic delivery of recombinant glucocerebrosidase enzyme-containing extracellular vesicles to human cells from Gaucher disease patients. Orphanet J Rare Dis. 2024; 19(1):363.
53. Dias C, Ballout N, Morla G, Alileche K, Santiago C, Guerrera IC, et al. Extracellular vesicles from microglial cells activated by abnormal heparansulfate oligosaccharides from Sanfilippo patients impair neuronal dendritic arborization. Mol Med. 2024; 30(1):197.
54. Gehrlein A, Udayar V, Anastasi N, Morella ML, Ruf I, Brugger D, et al. Targeting neuronal lysosomal dysfunction caused by β-glucocerebrosidase deficiency with an enzyme-based brain shuttle construct. Nat Commun. 2023; 14(1):2057.
55. Pardridge WM. Blood-brain barrier delivery for lysosomal storage disorders with IgG-lysosomal enzyme fusion proteins. Adv Drug Deliv Rev. 2022; 184:114234.
56. Parenti G, Fecarotta S, la Marca G, Rossi B, Ascione S, Donati MA, et al. A Chaperone Enhances Blood α-Glucosidase Activity in Pompe Disease Patients Treated With Enzyme Replacement Therapy. Mol Ther. 2014; 22(11):2004-12.
57. Narita A, Shirai K, Itamura S, Matsuda A, Ishihara A, Matsushita K, et al. Ambroxol chaperone therapy for neuronopathic Gaucher disease: A pilot study. Ann Clin Transl Neurol. 2016 Feb 2; 3(3):200-15.
58. Suzuki Y. Chaperone therapy: Stabilization and enhancement of endogenous and exogenous lysosomal enzymes. Brain Dev. 2025; 47(1):104298.
59. Gaucher Disease News. Gene therapy for Gaucher disease [Internet]. [cited 2025 Dec 15]. Available from:
60. Ng BG, Freeze HH, Himmelreich N, Blau N, Ferreira CR. Clinical and biochemical footprints of congenital disorders of glycosylation: Proposed nosology. Mol Genet Metab. 2024; 142(1):108476.
61. Quelhas D, Jaeken J. Treatment of congenital disorders of glycosylation: An overview. Mol Genet Metab. 2024 Sep-Oct;143(1-2):108567. doi: 10.1016/j.ymgme.2024.108567. Epub 2024 Aug 18. PMID: 39236565..
62. Iyer S, Sam FS, DiPrimio N, Preston G, Verheijen J, Murthy K, et al. Repurposing the aldose reductase inhibitor and diabetic neuropathy drug epalrestat for the congenital disorder of glycosylation PMM2-CDG. Dis Model Mech. 2019; 12(11):dmm040584.
63. Quelhas D, Jaeken J. Treatment of congenital disorders of glycosylation: An overview. Mol Genet Metab. 2024; 143(1-2):108567.
64. Wolf NI, van der Knaap MS, Engelen M. Treatment of leukodystrophies: Advances and challenges. Eur J Pediatr Neurol. 2025 May; 56:46-50.
65. Golse M, Weinhofer I, Blanco B, Barbier M, Yazbeck E, Huiban C, et al. Leriglitazone halts disease progression in adult patients with early cerebral adrenoleukodystrophy. Brain. 2024; 147(10): 3344-51.
66. Köhler W, Engelen M, Eichler F, Lachmann R, Fatemi A, Sampson J, et al. Safety and efficacy of leriglitazone for preventing disease progression in men with adrenomyeloneuropathy (ADVANCE): a randomised, double-blind, multi-centre, placebo-controlled phase 2-3 trial. Lancet Neurol. 2023; 22(2):127-36.
67. Rodríguez-Pascau L, Vilalta A, Cerrada M, Traver E, Forss-Petter S, Weinhofer I,et al. The brain penetrant PPARγ agonist leriglitazone restores multiple altered pathways in models of X-linked adrenoleukodystrophy. Sci Transl Med. 2021 Jun 2;13(596):eabc0555. doi: 10.1126/scitranslmed.abc0555. PMID: 34078742.

68. Pearson TS, Gupta N, San Sebastian W, Imamura-Ching J, Viehoever A, Grijalvo-Perez A, et al. Gene therapy for aromatic L-amino acid decarboxylase deficiency by MR-guided direct delivery of AAV2-AADC to midbrain dopaminergic neurons. Nat Commun. 2021; 12(1):4251.

69. Cohen JL, Chakraborty P, Fung-Kee-Fung K, Schwab ME, Bali D, Young SP, et al. In Utero Enzyme-Replacement Therapy for Infantile-Onset Pompe's Disease. N Engl J Med. 2022; 387(23): 2150-8.

70. Herzeg A, Borges B, Lianoglou BR, Gonzalez-Velez J, Canepa E, Munar D, et al. Intrauterine enzyme replacement therapies for lysosomal storage disorders: Current developments and promising future prospects. Prenat Diagn. 2023; 43(13):1638-49.

DRUG PROFILE

ANTIPSYCHOTICS IN CHILDREN AND ADOLESCENTS

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Abstract : *Prescription of antipsychotics has increased over the last few years. Their indications extend beyond schizophrenia and bipolar disorder and has found a place in the management of autism spectrum disorder and Tourette syndrome. Selection of antipsychotics should be individualised for each child. An understanding of the adverse effects of this group of drugs is essential for proper monitoring and follow up of children and adolescents on these drugs.*

Keywords: *1st generation antipsychotic, 2nd generation antipsychotic, Atypical antipsychotic, Medication, Children, Adolescents, Safety, Efficacy.*

Points to Remember

- ***Antipsychotic medications are effective in treating several psychiatric conditions in children and adolescents. Although not curative, they allow adequate control of clinical symptoms in lifelong psychiatric ailments.***
- ***Antipsychotics result in a number of adverse effects in this population and different agents present highly variable safety profiles. Therefore, prescribing of these drugs involves a difficult balance between the need to relieve mental disease symptoms and the risk of drug-induced toxicity.***
- ***SGAMs overall dominate prescribing preferences but FGAMs are still prescribed in the youngest in varying proportions.***
- ***Children under 9 years old on antipsychotics ('off label') should be carefully monitored as the risk/ benefit ratio of these medications remains unclear especially in the youngest.***
- ***A multi-disciplinary team including the pediatrician, the child psychiatrist and clinical psychologist need to hand hold the child and the family together while monitoring the progress of therapies. Counselling of the adolescent and the caregivers, by this team, regarding the goals to be achieved, medication used at various stages of disease, dose adjustments and early recognition of developing side-effects, are an integral part of management of these children.***

References

1. Jesmin A, Mullick MSI, Rahman KM, Muntasir MM. Psychiatric Disorders in Children and Adolescents Attending Pediatric Out Patient Departments of Tertiary Hospitals. Oman Med J 2016; 31(4):258-262. doi: 10.5001/omj.2016.51.
2. Harrison JN, Cluxton-Keller F, Gross D. Antipsychotic medication prescribing trends in children and adolescents. J Pediatr Health Care 2012; 26(2):139-145. doi: 10.1016/j.pedhc.2011.10.009 .

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Cite as: Jeeson C Unni, Irshad M. Antipsychotics in children and adolescents, Indian J Pract Pediatr. 2025; 27(4): 394-400.

3. Malhotra S, Patra BN. Prevalence of child and adolescent psychiatric disorders in India: a systematic review and meta-analysis. Child Adolesc Psychiatry Ment Health 2014; 8: 22. https://doi.org/10.1186/1753-2000-8-22/
4. Sagar R, Deep R, Mehta M. Clinical Profile of Child and Adolescent (≤16 years) Psychotic Disorders at a Tertiary Care Centre In India. Journal of Basic & Applied Sciences 2012; 8(1): 139-144. https://doi.org/10.6000/1927-5129.2012.08.01.08.
5. Townsend M, Pareja K, Buchanan-Hughes A, Worthington E, Pritchett D, Brubaker M, et al. Antipsychotic-Related Stigma and the Impact on Treatment Choices: A Systematic Review and Framework Synthesis. Patient Prefer Adherence. 2022; 16: 373-401. doi: 10.2147/PPA.S343211.
6. Chokhawala K, Stevens L. Antipsychotic Medications. [Updated 2023 Feb 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519503/
7. Ramachandraiah CT, Subramaniam N, Tancer M. The story of antipsychotics: Past and present. Indian J Psychiatry 2009; 51(4): 324-326. doi: 10.4103/0019-5545.58304.
8. Meltzer HY, Gadaleta E. Contrasting Typical and Atypical Antipsychotic Drugs. Focus 2021; 19(1): 3-13. doi: 10.1176/appi.focus.20200051.
9. Harrison JN, Cluxton-Keller F, Gross D. Antipsychotic medication prescribing trends in children and adolescents. J Pediatr Health Care 2012;26(2):139-145. doi: 10.1016/j.pedhc.2011.10.009.
10. Christian R, Saavedra L, Gaynes BN, et al. Future Research Needs for First- and Second-Generation Antipsychotics for Children and Young Adults [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Feb. (Future Research Needs Papers, No. 13.) Appendix A, Tables of FDA-Approved Indications for First and Second-Generation Antipsychotics. Available from: https://www.ncbi.nlm.nih.gov/books/NBK84656/
11. Hrdlicka M, Dudova I. Atypical antipsychotics in the treatment of early-onset schizophrenia. Neuropsychiatr Dis Treat 2015; 11: 907-913. doi: 10.2147/NDT.S82185.
12. Singh MK, Ketter TA, Chang KD. Atypical antipsychotics for acute manic and mixed episodes in children and adolescents with bipolar disorder: efficacy and tolerability. Drugs 2010; 70(4): 433-42. doi: 10.2165/11534540-000000000-00000.
13. Shah, Nilesh Grover, Sandeep Rao, Prasad G. Clinical Practice Guidelines for Management of Bipolar Disorder. Indian J Psychiatry 2017; 59(Suppl 1): S51-S66, J DOI: 10.4103/0019-5545.196974
14. Dauchot D, Rettey S, Melton BL, Moeller KE. Antipsychotics in child and adolescent patients with major depressive disorder: A retrospective analysis of prescribing patterns. Ment Health Clin. 2024; 14(1): 10-16. doi: 10.9740/mhc.2024.02.010.
15. Jeeson C Unni, Ranjit Baby Joseph, Susan Mary Zachariah, Fathima Jafna. Pharmacotherapy in autism. Indian J Pract Pediatr 2018; 20(3): 206-211.
16. Loy JH, Merry SN, Hetrick SE, Stasiak K. Atypical antipsychotics for disruptive behaviour disorders in children and youths. Cochrane Database Syst Rev 2017; 8(8): CD008559. doi: 10.1002 14651858.CD008559.pub3.
17. Eddy CM, Rickards HE, Cavanna AE. Treatment strategies for tics in Tourette syndrome. Ther Adv NeurolDisord 2011; 4(1): 25-45. doi: 10.1177/1756285610390261.
18. He F, Luo J, Huang Y, Hao Y, Sun L, Ke X, Wu B, Chen Y, Han Y, Zhang Y, Liu J, Han H, Xian M, Uki M, Zheng Y. Randomized, double-blind, placebo-controlled trial of aripiprazole oral solution in children and adolescents with Tourette's disorder. Child Adolesc Psychiatry Ment Health 2024;18(1):88. doi: 10.1186/s13034-024-00764-6.
19. Thamby A, Jaisoorya TS. Antipsychotic augmentation in the treatment of obsessive-compulsive disorder. Indian J Psychiatry 2019; 61(Suppl 1):S51-S57. doi: 10.4103/psychiatry. Indian JPsychiatry_519_18.
20. Thorey S, Blanchet C, Guessoum SB, Moro MR, Ludot M, Carretier E. Efficacy and tolerance of second-generation antipsychotics in anorexia nervosa: A systematic scoping review. PLoS One 2023;18(3): e0278189. doi: 10.1371/journal.pone.0278189.
21. IAP Drug Formulary 2024, Eds: Jeeson C Unni, Pallab Chaterjee. 6th Ed. Project of IAP CMIC, Pixel Studio; Kochi; 2024.
22. Pillay J, Boylan K, Newton A, Hartling L, Vandermeer B, Nuspl M, MacGregor T, Featherstone R, Carrey N. Harms of Antipsychotics in Children and Young Adults: A Systematic Review Update. Can J Psychiatry 2018; 63(10): 661-678. doi: 10.1177/0706743718779950.
23. Dayabandara M, Hanwella R, Ratnatunga S, Seneviratne S, Suraweera C, de Silva VA. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. Neuropsychiatr Dis Treat 2017; 13: 2231-2241. doi: 10.2147/NDT.S113099.
24. Mansuri Z, Makani R, Trivedi C, Adnan M, Vadukapuram R, Rafael J, Lodhi A, Reddy A. The role of metformin in treatment of weight gain associated with atypical antipsychotic treatment in children and adolescents: A systematic review and meta-analysis of randomized controlled trials. Front Psychiatry 2022;13:933570. doi: 10.3389/fpsyt.2022.933570.
25. Libowitz MR, Nurmi EL. The Burden of Antipsychotic-Induced Weight Gain and Metabolic Syndrome in

Children. Front Psychiatry 2021; 12:623681. doi: 10.3389/fpsyt.2021.623681.

26. Sohn M, Talbert J, Blumenschein K, Moga DC. Atypical antipsychotic initiation and the risk of type II diabetes in children and adolescents. Pharmacoepidemiol Drug Saf 2015;24(6):583-691. doi: 10.1002/pds.3768
27. Tewksbury A, Olander A. Management of antipsychotic-induced hyperprolactinemia. Ment Health Clin 2016; 29;6(4):185-190. doi: 10.9740/mhc.2016.07.185.
28. Rusgis MM, Alabasi AV, Nelson NA. Guidance on the treatment of antipsychotic-induced hyperprolactinemia when switching the antipsychotic is not an option. Am J Health-Syst Pharm 2021; 78: 862-871.
29. BNF for children 2019-20. British Medical Association, Royal Pharmaceutical Society of Great Britain, Royal College of Paediatrics and Child Health, Neonatal and Paediatric Pharmacists Group. BMJ Group, Tavistock Square, London, WC1H 9JP, UK and Pharmaceutical Press Pharmaceutical Press is the publishing division of the Royal Pharmaceutical Society. 66-68 East Smithfield, London E1W1AW, UK. 2019.
30. Pringsheim T, Doja A, Belanger S, Patten S; Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guideline group. Treatment recommendations for extrapyramidal side effects associated with second-generation antipsychotic use in children and youth. Paediatr Child Health 2011; 16(9): 590-598.
31. James AC. Prescribing antipsychotics for children and adolescents. Advances in Psychiatric Treatment 2010; 16(1): 63-75. doi:10.1192/apt.bp.108.005652.
32. Alalawi A, Albalawi E, Aljohani A, Almutairi A, Alrehili A, Albalawi A, Aldhafiri A. Decoding Clozapine-Induced Agranulocytosis: Unraveling Interactions and Mitigation Strategies. Pharmacy (Basel) 2024; 12(3): 92. doi: 10.3390/pharmacy12030092.
33. Biagetti R, Caiazza L, Giuva T, Pirani G, Di Biase AR, Bergonzini P, Caramaschi E, Spezia E, Iughetti L, Lupetti I, Donati C, Persico AM. Clozapine-induced cardiac toxicity and successful rechallenge in children and adolescents: a systematic review and new case report. Psychiatry Res 2025; 35: 1116646. doi: 10.1016/j.psychres.2025.116646.
34. Correll CU, Lops JD, Figen V, Malhotra AK, Kane JM, Manu P. QT interval duration and dispersion in children and adolescents treated with ziprasidone. J Clin Psychiatry 2011; 72(6): 854-860. doi: 10.4088/JCP.10m05990yel.
35. Park YW, Kim Y, Lee JH. Antipsychotic-induced sexual dysfunction and its management. World J Mens Health 2012;30(3):153-9. doi: 10.5534/wjmh. 2012. 30.3.153.
36. Neuhut R, Lindenmayer JP, Silva R. Neuroleptic malignant syndrome in children and adolescents on atypical antipsychotic medication: a review. J Child AdolescPsychopharmacol. 2009 Aug; 19(4):415-22. doi: 10.1089/cap.2008.0130. Findling RL, et al. (2011) Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents. Journal of the American Academy of Child and Adolescent Psychiatry.

NEO CAPSULE

NEUROLOGICAL EXAMINATION OF THE NEWBORN

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Abstract: *Neurological examination of the newborn remains a fundamental component of neonatal assessment despite advances in neuroimaging and neurophysiological investigations. It is a cost-effective, time-efficient and immediately actionable bedside tool that provides critical insights into neurological integrity, maturation and early dysfunction. The neonatal nervous system is developmentally dynamic and neurological findings vary significantly with gestational age, postnatal maturation, behavioral state and clinical condition. Unlike older children, neonatal neurological assessment relies predominantly on observation of spontaneous behavior, posture, tone, reflexes and responses to sensory stimuli, supplemented by targeted examination maneuvers. This review outlines a structured and systematic approach to the neonatal neurological examination, emphasizing the importance of clinical history, accurate gestational age assessment and serial examinations.*

Keywords: *Neurological examination, Behavioral state, Passive tone, Active tone, Primitive reflexes*.

Points to Remember

- ***Neonatal neurological examination remains an essential bedside tool, providing immediate assessment of neurological integrity.***
- ***Interpretation must always be contextualized to gestational age, behavioral state and clinical condition.***
- ***Observation forms the cornerstone of neonatal neurological assessment, with posture, spontaneous movements, tone, alertness and reflexes offering critical insights.***
- ***Hammersmith neonatal examination is a structured tool for neurological assessment for term neonates and preterm infants at term corrected age.***
- ***Modified Sarnat examination allows to grade the severity of encephalopathy and assess eligibility for therapeutic hypothermia.***

References

1. Hawes J, Bernardo S, Wilson D. The Neonatal Neurological Examination: Improving Understanding and Performance. Neonatal Netw. 2020; 39(3):116-128. doi: 10.1891/0730-0832.39.3.116. PMID: 32457186.
2. Romeo DM, Luciano R, Corsello M, Ricci D, Brogna C, Zuppa A, Romagnoli C, Mercuri E. Neonatal neurological examination of late preterm babies. Early Hum Dev. 2013; 89(8):537-45. doi: 10.1016 j.earlhumdev.2013.01.002. Epub 2013 Feb 4. PMID: 23380499.
3. Gosselin J, Gahagan S, Amiel-Tison C. The Amiel-Tison Neurological Assessment at Term: conceptual and methodological continuity in the course of follow-up. Ment Retard Dev Disabil Res Rev. 2005; 11(1):34-51. doi: 10.1002/mrdd.20049. PMID: 15856442.

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Cite as: Sindhu Sivanandan, Lakshmi V, Neurological examination of the newborn, Indian J Pract Pediatr. 2025; 27(4):401-412.

4. Venkata SKRG, Pournami F, Prabhakar J, Nandakumar A, Jain N. Disability Prediction by Early Hammersmith Neonatal Neurological Examination: A Diagnostic Study. J Child Neurol. 2020 Oct; 35(11):731-736. doi: 10.1177/0883073820930487. Epub 2020 Jun 9. PMID: 32516057.
5. Bonifacio SL, Hutson S. The Term Newborn: Evaluation for Hypoxic-Ischemic Encephalopathy. Clin Perinatol. 2021; 48(3):681-695. doi: 10.1016/j.clp.2021.05.014. PMID: 34353587.

CASE REPORT

ANAPLASTIC LARGE CELL LYMPHOMA MANIFESTING AS CUTANEOUS GRANULOMATOUS LESION – A DIAGNOSTIC CHALLENGE

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Abstract: *Anaplastic large cell lymphoma is a rare form of mature T-cell non-Hodgkin lymphoma. It typically presents at an advanced stage with extra-nodal involvement. Granulomatous inflammation on biopsy can be misleading often suggesting chronic infections and inflammatory conditions. We report a case of pediatric anaplastic large cell lymphoma presenting as recurrent cutaneous abscesses with granulomatous inflammation.*

Keywords: *Recurrent abscess, Cutaneous lymphoma, Granuloma.*

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References

1. Lowe EJ, Woessmann W. Anaplastic large cell lymphoma in children and adolescents. British Journal of Haematology. 2025 Aug; 207(2):336-49.
2. Mendiratta V, Gandhi N, Rana S, Shukla S. Isolated cutaneous involvement in a child with nodal anaplastic large cell lymphoma. Indian Journal of Dermatology, Venereology and Leprology. 2016 Jan 1; 82:53-6.
3. Oschlies I, Lisfeld J, Lamant L, Nakazawa A, d'Amore ES, Hansson U, et al. ALK-positive anaplastic large cell lymphoma limited to the skin: clinical, histopathological and molecular analysis of 6 pediatric cases. A report from the ALCL99 study. haematologica. 2013 Jan; 98(1):50-6.
4. Knauss HM, Glosser LD, Beran A, Sidwell AN, Abdulsattar W, Skeel RT, et al. Anaplastic large cell lymphoma presenting as ulcerative facial mass: a case report. Case Reports in Oncology. 2022 May 2; 15(1): 199-206.
5. Chao-Lo MP, King-Ismael D, Lopez RA. Primary cutaneous CD30+ anaplastic large cell lymphoma: report of a rare case. Journal of Dermatological Case Reports. 2008 Oct 11; 2(3):31-4.

Cite as: Sarath Balaji B, Suganya Subramani, Karthik Kumar, Balamurugan S, Chandramouleeswari K, Umadevi S, Kalpana Sivasambo. Anaplastic large cell lymphoma manifesting as cutaneous granulomatous lesion - A diagnostic challenge, Indian J Pract Pediatr. 2025; 27(4):421-423.

AUTHOR INDEX

SUBJECT INDEX