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Review Article

Management of Inborn Errors of Metabolism: Current Strategies and Future Directions

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Abstract

Inborn errors of metabolism (IEMs) are a diverse collection of single-gene abnormalities that interfere with metabolic pathways and can lead to multisystem disease throughout an individual's life. Management strategies have transitioned from primarily supportive care and dietary modification to disease-modifying interventions, encompassing enzyme replacement therapy (ERT), substrate reduction, pharmacological chaperones, organ and haematopoietic transplantation, cystostatic/cofactor therapies, and rapidly advancing genetic therapies, including gene addition, haematopoietic stem cell gene therapy, and genome editing. The extension of newborn screening, the development of better diagnostic tools (such tandem mass spectrometry and next-generation sequencing), and a better understanding of how diseases progress have all made it possible to start treatment earlier and give patients more personalised care. There are still problems, such as different levels of effectiveness in different organ systems (particularly the CNS), high treatment costs, restricted access around the world, and ethical and regulatory challenges for new treatments. Future directions encompass targeted gene correction, enhanced safety and efficacy of gene delivery technologies, optimised intervention timing (pre-/neonatal), improved blood-brain barrier (BBB) delivery, and worldwide implementation strategies to assure equity.

Key words: metabolism; management; strategies; directives

Introduction

Inborn errors of metabolism (IEMs) encompass a heterogeneous and growing category of genetic illnesses marked by deficiencies in biochemical pathways due to mutations in genes that encode enzymes, transporters, cofactors, or other functional proteins critical for proper metabolic functions. Sir Archibald Garrod first came up with the idea of IEMs in 1908. He called them "chemical individuality," which stressed how metabolic differences are passed down from one generation to the next and how they affect health [1]. In the last thirty years, improvements in biochemical screening, molecular diagnoses, and therapies have changed many IEMs from deadly disorders in newborns to chronic diseases that may be treated. However, the diversity of presentation, the limited effectiveness of numerous systemic therapy for neurological disorders, and concerns over cost and accessibility persist as clinical and policy obstacles.[1] IEMs are usually passed down in an autosomal recessive pattern, but X-linked and mitochondrial inheritance patterns are becoming more common [2]. In all, they are not uncommon; although each illness may have a low prevalence, together they represent a substantial burden of morbidity and mortality, with an estimated incidence of 1 in 800 to 1 in 2500 live births, contingent upon the population examined [3]. The clinical range of inborn errors of metabolism (IEMs) is extensive, encompassing acute neonatal metabolic crises, chronic multisystem involvement, neurodevelopmental impairment, organ failure, and progressive degenerative illness. Pathophysiologically, IEMs frequently arise from one of three primary mechanisms: (1) the buildup of harmful substrates or metabolites near the enzyme block, (2) a lack of necessary products for normal bodily function, or (3) a breakdown of energy generation routes [4]. These pathways highlight the fundamental fact that a solitary enzyme deficiency can result in significant metabolic dysregulation. Numerous inborn errors of metabolism (IEMs), including amino acid metabolism disorders (e.g., phenylketonuria), organic acidemias, urea cycle disorders, and fatty acid oxidation defects, may manifest as life-threatening metabolic decompensation during the neonatal or infantile stages, frequently induced by catabolic stress, infection, or dietary protein overload [5]. Tandem mass spectrometry (MS/MS), genome sequencing, and expanded newborn screening programs have all made a big difference in how IEMs are

diagnosed. Early diagnosis by newborn screening has for the prompt implementation of potentially life-saving therapies, including dietary modification, pharmaceutical cofactor therapy, substrate reduction therapy, and, in certain instances, organ transplantation [6]. Nonetheless, numerous inborn errors of metabolism (IEMs) continue to be underdiagnosed owing to vague clinical manifestations and restricted access to specialised testing in resource-limited environments. The use of next-generation sequencing (NGS), metabolomics, and systems biology in the last several years has changed the way we classify IEMs, showing us new illnesses and giving new names to old ones. Additionally, novel therapies—such as gene therapy, mRNA-based interventions, and enzyme replacement therapy—are revolutionising the therapeutic landscape, presenting innovative strategies for altering disease development and enhancing long-term outcomes [7,8].

In general, IEMs provide an important link between genetics, biochemistry, clinical medicine, and public health. It is important to know how they work, how they show up in patients, how to diagnose them, and how therapies are changing so that doctors can act quickly, get better results for their patients, and keep making progress in precision medicine.

Methods (summary of the search)

This review compiles current high-quality evaluations, guideline statements, and foundational reports (2020–2025) concerning newborn screening, diagnostics, established and novel medicines, transplantation, gene and cell therapies, and the health systems dimensions of IEM care. Key sources encompassed comprehensive IEM overviews, specialised studies on enzyme replacement and chaperone therapies, gene therapy and haematopoietic stem cell gene therapy reports, and contemporary policy/implementation documents regarding the extension of newborn screening. (There are citations throughout for selected sources, and a list of them at the end.)

Considerations in epidemiology and natural history

IEMs are not uncommon; estimates differ by geography and screening parameters, but together they contribute significantly to paediatric morbidity. Natural histories are specific to each condition, and prompt diagnosis is frequently the primary factor influencing outcome, as irreparable organ damage, especially neurological, can manifest early. Comprehensive registries and treatabolome initiatives have elucidated which inborn errors of metabolism (IEMs) are suitable for disease-modifying medication, emphasising the necessity for early detection and longitudinal natural history investigations to guide treatment timing and outcomes.[9]

Newborn screening and diagnostic advancements

Tests in the lab and at the molecular level

Expanded metabolic panels utilising tandem mass spectrometry (MS/MS), in conjunction with tailored metabolite assays and next-generation sequencing (NGS), have significantly enhanced diagnostic yield and reduced the time to diagnosis. Combining biochemical phenotyping with quick NGS (including quick exome/genome) is becoming the norm at tertiary centres for newborns and babies who are very sick and are thought to have IEM. These technologies are very important because many treatments need to be done quickly. [10]

Expansion of newborn screening (NBS)

The use of MS/MS and reflex genomic methods to expand NBS makes it possible to find treatable IEMs early and make pre-symptomatic therapies that enhance outcomes for many illnesses. Cost-effectiveness assessments and feasibility studies advocate for the extensive implementation of MS/MS-based NBS in numerous countries; nonetheless, execution necessitates workforce training, supplementary infrastructure, and the evaluation of false positives and variants of dubious relevance. [11] Management strategies that have been in place for a long time

i. Dietary and cofactor treatments

Dietary therapy is still the most important part of treatment for many IEMs, such as phenylketonuria (PKU), maple syrup urine disease (MSUD), urea cycle abnormalities, and organic acidemias. When done early, changing the amounts of macronutrients, cutting out harmful substrates, and giving missing downstream nutrients (such specialised amino-acid formulations) stop the buildup and allow normal development. Supplementing cofactors, like pyridoxine for certain types of homocystinuria or PLP-sensitive diseases, or tetrahydrobiopterin for specific PKU variants, works when a genetic or biochemical test shows that the person is responsive. These methods are low-tech, but they need to be followed consistently and with help from people from different fields, like nutritionists and metabolic nurses. [8]

ii. Enzyme replacement treatment (ERT)

ERT, which is the systemic infusion of a recombinant enzyme, was a big change for several lysosomal storage disorders (LSDs), like Gaucher disease, Pompe disease, and various mucopolysaccharidoses. ERT enhances visceral, haematologic, and, in certain instances, cardiac manifestations while decreasing morbidity and mortality. However, ERT exhibits restricted penetration of the blood–brain barrier (BBB), resulting in limited efficacy for neurological manifestations unless administered intrathecally or through alternative methods. Long-term immunogenicity, infusion load, and high costs are significant constraints. Recent evaluations summarise how clinical experience is changing and how formulation and delivery are getting better. [12]

iii. Substrate reduction therapy (SRT)

SRT lowers the production of the hazardous substrate that comes before the faulty enzyme. In some cases, it can be taken by mouth instead of or in addition to ERT. For instance, eliglustat, an oral glucosylceramide synthase inhibitor, is a well-known SRT for Gaucher disease type 1 that has been shown to work well and be safe in many patients, including new findings on children. Patients who cannot or do not want to get regular intravenous ERT may benefit from SRT. [13]

iv. Small compounds and pharmacological chaperones

Pharmacological chaperones, which are tiny compounds that stabilise enzymes that have been misfolded and restore their activity, have become important in medicine. Migalastat is the most well-known example for amenable mutations in Fabry disease. It is an oral, tailored treatment that works well in individuals with certain genotypes. Reviews and consensus statements delineate selection criteria, monitoring processes, and outcomes. Other small compounds, such as nitisinone for hereditary tyrosinaemia type I and pyridoxine for responsive homocystinuria, are well-known pieces of the therapeutic toolbox. [14]

v. Transplantation of organs (liver, kidney)

Liver transplantation (LT) can offer a definitive metabolic enzyme source for specific hepatic inborn errors of metabolism (e.g., some urea cycle abnormalities, Wilson disease, selected organic acidemias). LT addresses systemic metabolic deficiencies when the liver is the principal location of enzyme expression, although it entails operational risks and necessitates

lifelong immunosuppression. More and more evidence shows that LT is the best treatment for some patients, and its role is changing as transplantation and perioperative care improve. [15]

1v. Haematopoietic stem cell transplantation (HSCT) Allogeneic HSCT provides a source of donor cells that release functioning enzyme, cross-correcting numerous lysosomal and peroxisomal illnesses (e.g., certain mucopolysaccharidoses, adrenoleukodystrophy). HSCT is most effective when conducted early—before irreparable neurologic damage—and when donors and conditioning regimens are optimised. Better outcomes have resulted from better ways to choose donors, lower-toxicity conditioning, and better supportive care. [16]

New and changing ways of doing things

1. Gene addition treatment (AAV, lentiviral vectors)

Gene therapy strategies for IEMs are swiftly advancing. Adeno-associated virus (AAV) vectors facilitate in vivo gene addition to target tissues (e.g., liver, muscle, CNS) and have led to authorised products for non-IEM monogenic illnesses; likewise, AAV and lentiviral methodologies are currently undergoing trials for IEMs. Local CNS-directed and systemic gene treatments that restore inadequate enzyme function are examples of successes. However, limitations include vector immunogenicity, durability of expression, payload size constraints, and varying CNS penetration. Regulatory approvals for IEM gene treatments have started to come in. For instance, gene therapy for aromatic L-amino acid decarboxylase (AADC) deficiency was granted in late 2024. This shows that the therapies are clinically possible and that there are regulatory pathways. [17]

2. Gene therapy for haematopoietic stem cells (HSC-GT)

HSC-GT employs autologous haematopoietic stem cells ex vivo transduced, often with lentiviral vectors, to produce functional enzymes, subsequently returned after conditioning. This combines the benefits of HSCT's cross-correction with a lower risk of graft-versus-host disease. HSC-GT has demonstrated potential in many neurometabolic illnesses, achieving sustained systemic and central nervous system enzyme activity in preliminary trials, and is a focal point of translational research. [18]

3. Editing the genome and base/prime editing

Genome editing (CRISPR/Cas-based technologies), base editors, and prime editors provide the capability for accurate rectification of harmful variations. Preclinical studies provide proof-of-concept for rectifying metabolic gene abnormalities both in vivo and ex vivo; clinical translation is being approached with caution because to potential on-target and off-target dangers, delivery difficulties, and ethical implications. Subsequent clinical trials will ascertain the safety and longevity of human IEMs. [19] [19]

4. mRNA treatment and new ways to give it

mRNA therapies provide temporary enzyme expression without integrating into the genome. Early translational research and clinical trials are investigating mRNA for hepatic and systemic rectification of metabolic deficiencies; lipid nanoparticles and other carrier technologies are essential for targeted administration and immunogenicity control. Researchers are also looking into nanotechnology to make it easier for drugs to get through the BBB and target certain tissues. [12] Problems with putting things into practice in the clinic In many modalities (dietary, enzyme replacement therapy, haematopoietic stem cell transplantation, gene therapy), earlier intervention—preferably pre-symptomatic—results in enhanced neurological and developmental outcomes for numerous inborn errors of metabolism (IEMs). To get the most out of it, newborn screening and quick diagnostic processes are quite important. But time needs to be weighed against the hazards of high-intensity treatments and the unknowns about how well variants work. [11][16]

Assessing outcomes and natural history data

To test new treatments and help regulators make judgements, we need clear clinical objectives, patient-reported outcomes, biomarkers, and research of how diseases progress naturally. The "treatabolome" method gathers information on treatable genes and phenotypes to help choose therapies and plan trials. [9]

CNS delivery and neurological disorders

The BBB restricts the effectiveness of numerous systemic treatments for neurological symptoms. Research is being done on intrathecal/intracerebral enzyme delivery, BBB-penetrant small compounds, CNS-directed gene therapy, and HSC-GT, which allows enzyme-secreting microglia to grow in the body. Each of these has its own safety and effectiveness issues. [18][12] Safety, immunogenicity, and long-term surveillance Immunologic responses to recombinant enzymes or viral vectors (pre-existing antibodies to AAV serotypes) can limit efficiency; immune modulation methods and monitoring are crucial. Long-term monitoring is essential for assessing late effects, response durability, and the possibility for insertional mutagenesis in integrating vectors. [12][26] Cost, access, and health policy The enormous cost of modern therapies (ERT, gene therapies) makes it hard to keep them going and fair. Policy solutions (value-based pricing, outcomes-based contracts, national rare illness funds, manufacturing scale-up) and local production techniques are being investigated, yet many patients throughout the world still can't get medications that could change their lives [27]. Real-world stories highlight ethical obligations for fair access and prioritisation of treatable illnesses under limited public health funds.[28].

Conclusion

The treatment of IEMs has entered a new phase. Established modalities—dietary therapy, cofactor supplementation, ERT, SRT, HSCT, and transplantation—continue to be essential and have enhanced outcomes for numerous illnesses. At the same time, faster progress in gene and cell therapies, genome editing, and delivery technologies promises long-lasting or even curative options for IEMs that could not be treated before. To reach this potential, we need to keep focussing on early diagnosis (more newborn screening and quick molecular testing), carefully planned clinical trials based on natural history studies, ways to get over CNS delivery problems, and strong policy frameworks to make sure everyone has equal access. Multidisciplinary care teams and global cooperation will be necessary to turn scientific progress into better results for patients around the world.

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