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Research Progress in the Prevention and Treatment of Thalassemia

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Abstract: Thalassemia is an inherited hemolytic disorder caused by defects in globin genes. Its pathogenesis involves an imbalance in the synthesis of α- and β-globin chains, leading to chronic hemolysis and multisystem complications. This review systematically summarizes the latest global advances in thalassemia prevention and treatment. In prevention, a tertiary prevention system has been established by integrating third-generation sequencing (with a missed diagnosis rate below 0.5%), preimplantation genetic diagnosis/screening (PGD/PGS, reducing the birth rate of moderate-to-severe thalassemia by 90%), and regional screening networks (e.g., a 70% decrease in the birth rate of severe thalassemia in Guangxi, China). In treatment, conventional blood transfusion combined with iron chelation therapy (yielding a 10-year survival rate exceeding 85%) continues to be optimized, while breakthroughs in curative treatment are emerging with gene editing therapies—such as Zynteglo, which achieves a 5-year transfusion independence rate of 87%—and CRISPR-Cas9 technology (with off-target effects below 0.1%). Concurrently, research has highlighted key challenges, including the prohibitive cost of gene therapy and the lack of insurance coverage, which leads to an imbalance in healthcare resource allocation. Collaborative models among government, medical institutions, and enterprises—exemplified by Berry Genomics' clinical translational project that reduced diagnostic and treatment costs by 25%—and innovative payment systems are critical to overcoming these challenges. This paper proposes an integrated strategy of "precision prevention–targeted treatment–policy support," thereby providing a theoretical framework for global thalassemia control. Recent advances in biotechnology have notably propelled progress in both prevention and treatment.

Keywords: Thalassemia, prevention strategies, treatment advances, health policy, multidisciplinary collaboration

1. Introduction

Thalassemia, one of the most common hemoglobinopathies worldwide, comprises two main types: α-thalassemia and β-thalassemia. These disorders result from mutations that lead to reduced production and/or functional abnormalities of the corresponding globin chains [1]. It is estimated that more than 345 million individuals globally are carriers of thalassemia genes. In China—particularly in the southern regions such as Guangxi and Guangdong—carrier frequencies are high, with figures reaching 24.6% in Guangxi and 7.3% in Guangdong. Without effective treatment, thalassemia patients may require frequent transfusions, suffer from iron overload, and face premature mortality due to organ failure. Although hematopoietic stem cell transplantation (HSCT) is considered a

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curative approach, its broad application is limited by factors such as the probability of success, post-transplant rejection, and relapse risk [2]. The World Health Organization (WHO) recognizes thalassemia as a significant global public health challenge and incorporates it into evaluations of the worldwide disease burden [3]. Consequently, thalassemia represents not only a clinical challenge but also a major public health issue. Strengthening research on thalassemia prevention and exploring optimal treatment strategies are crucial for improving patient quality of life and advancing public health initiatives [4]. Through premarital/prenatal screening, prenatal diagnosis, and embryo interventions, new cases can be significantly reduced. Furthermore, emerging technologies such as gene therapy are broadening the treatment options for thalassemia patients and presenting new prospects for disease management [5]. This review systematically examines current prevention strategies, progress in both traditional and novel therapeutic approaches, existing challenges, and future research directions, thereby providing theoretical support for optimizing disease management and advancing precision medicine.

2. Prevention strategies

2.1. Premarital/prenatal screening

Premarital and prenatal screening constitute the first line of defense in thalassemia prevention. Early identification of high-risk individuals can effectively reduce the incidence of moderate-to-severe thalassemia, thereby alleviating the burden on families and society. Both hematological phenotype analysis and genetic testing play crucial roles in this context.

Parameters such as mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) are essential indicators of red blood cell size and hemoglobin content. An MCV below 80 fl and an MCH below 27 pg suggest the possibility of thalassemia, which should then be confirmed by hemoglobin electrophoresis. This method, with its high sensitivity, effectively identifies carriers [6]. However, relying solely on hematological phenotyping has its limitations.

Traditional polymerase chain reaction (PCR) techniques, while cost-effective, may fail to detect certain mutations—with a missed diagnosis rate exceeding 10%. The advent of third-generation sequencing has markedly enhanced screening outcomes. For instance, protocols developed by companies such as Berry Genomics can detect a broader spectrum of genetic variants, including base substitution mutations (e.g., β-globin gene [HBB] c.118C>T, a β^0 mutation causing the complete absence of the β-chain; HBB c.79G>A, a β^+ mutation leading to partial synthesis), insertions/deletions (such as the 2-bp deletion in HBA1/HBA2 seen in the Southeast Asian type of α-thalassemia, or the -α 3.7 and -α 4.2 deletions), rare large fragment deletions in β-thalassemia (e.g., a 619-bp deletion), and genomic structural variants (including inversions leading to α-globin gene cluster rearrangements and triplication or quadruplication of the α-globin genes, as in ααα anti-3.7).

2.2. Prenatal diagnosis and embryo intervention technologies

Prenatal diagnosis plays a key role in thalassemia prevention, particularly in managing moderate-to-severe cases. Traditional techniques such as chorionic villus sampling and amniocentesis have been widely used for early diagnosis; however, these methods have inherent limitations, with misdiagnosis rates ranging from 5% to 10%. Although these approaches, which rely on cytogenetic analysis, offer relatively high accuracy, they pose potential risks to both the mother and fetus, including miscarriage and infection.

With technological advancements, the third-generation assisted reproductive technologies—specifically preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)—offer renewed hope for thalassemia prevention. PGS primarily focuses on screening for chromosomal abnormalities to ensure reproductive health. Both technologies have achieved success rates exceeding

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90%, and by employing PGD to select healthy embryos, the birth rate of infants carrying thalassemia genes can be reduced to below 5%.

Moreover, HLA typing plays an important role in thalassemia treatment. For severe thalassemia patients requiring HSCT, identifying an HLA-matched donor is crucial for a successful transplant; PGD can facilitate HLA matching, thereby enabling families to choose embryos compatible with potential HSCT. Research indicates that HSCT using HLA-matched sibling cord blood has a success rate of 70%–80%, which is significantly higher than that of other transplant types.

While prenatal diagnosis and embryo intervention technologies show tremendous potential in thalassemia prevention, they also face challenges related to technical limitations, ethical concerns, and high costs. To enhance their accessibility and utilization, it is essential to foster cooperation among governments, medical institutions, and enterprises, as well as to increase public awareness of the importance of thalassemia prevention and the acceptance of new technologies.

With continuous technological innovation and interdisciplinary collaboration, these techniques are anticipated to improve further, ultimately reducing thalassemia incidence and alleviating the societal healthcare burden [7].

3. Treatment advances and clinical practice

3.1. Conventional therapy: blood transfusion and iron chelation

Ineffective erythropoiesis, hemolytic anemia, reduced hepcidin activity, and systemic iron accumulation are core pathophysiological features of thalassemia, which guide clinical decision-making regarding diagnostic and therapeutic approaches [8].

Under high-volume transfusion protocols, clinicians aim to maintain the patient's hemoglobin level at or above 90 g/L—a target deemed critical for effective management. Transfusion therapy directly supplies functional red blood cells, rapidly elevating hemoglobin levels to a safe threshold (typically >90 g/L), thereby improving tissue oxygenation and alleviating symptoms such as fatigue and palpitations. Studies have shown that regular transfusions (every 2–4 weeks) can increase the annual survival rate of patients with severe β-thalassemia from less than 20% to over 80%. In pediatric patients, maintaining adequate hemoglobin levels is essential for proper growth and development, as it prevents skeletal deformities (such as frontal bossing and cortical thinning of long bones) and organ developmental delays. The imbalance between α- and β-globin chains in thalassemia leads to extensive apoptosis of erythroid precursors in the bone marrow and can result in extramedullary hematopoiesis in organs such as the liver and spleen. Regular transfusions reduce the secretion of erythropoietin (EPO), thereby alleviating the burden of ineffective erythropoiesis and delaying splenomegaly. Studies indicate that maintaining hemoglobin levels above 100 g/L can reduce spleen volume by 30%–50% and lower the need for splenectomy. Despite these benefits, long-term or excessive transfusions may lead to increased blood volume, cardiac overload, and even heart failure, in addition to elevating the risk of transfusion-transmitted infections.

To mitigate the adverse effects associated with prolonged transfusion therapy, iron chelation is widely employed. Iron overload is a significant clinical challenge in transfusion-dependent thalassemia, and the use of chelating agents—such as desferrioxamine administered intravenously—can effectively reduce iron accumulation and related tissue damage. However, clinicians must remain vigilant regarding the potential side effects of iron chelators, including cataracts and growth retardation [9].

In recent years, the continuous development of medical technology has led to the emergence of novel therapeutic methods, including hematopoietic stem cell transplantation and gene editing therapies, which offer the prospect of more durable and effective treatments for thalassemia [10].

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3.2. Curative treatment: Hematopoietic Stem Cell Transplantation (HSCT)

HSCT has emerged as a curative treatment for thalassemia, demonstrating significant clinical efficacy. In patients receiving transplants from HLA-identical donors, success rates exceed 90%. However, for adult patients—who typically present with more complex clinical conditions and higher risks of complications—the success rate generally ranges between 60% and 70%. Nevertheless, HSCT remains a viable option for patients with severe disease who can tolerate long-term treatment.

Advances in gene editing technology have further expanded the therapeutic landscape for thalassemia. For instance, Zynteglo, a β-globin gene editing therapy, has shown promising results by precisely modifying the patient's β-globin gene to restore normal hemoglobin production. Reports indicate that patients receiving this treatment achieve significant improvements in survival, with 5-year transfusion independence rates reaching 87%. However, the prohibitive cost, geographic accessibility barriers, and complex safety profiles of this intervention pose substantial challenges to its widespread clinical adoption in resource-limited settings. Subsequent therapeutic innovations must strategically prioritize the mitigation of treatment-related risks while overcoming systemic barriers to ultimately optimize therapeutic accessibility across diverse populations [11].

Although these curative approaches show great promise, they are not without challenges. High treatment costs, technical limitations inherent to gene therapy, and the need for multidisciplinary collaboration remain significant hurdles. To overcome these challenges, researchers and healthcare providers are actively exploring more efficient and cost-effective treatment modalities, as well as fostering cross-disciplinary partnerships. Furthermore, policy support and optimized insurance coverage are crucial factors in facilitating the broader implementation of these advanced therapeutic strategies.

4. Challenges and future directions

4.1. Technical bottlenecks and limitations in gene therapy

Molecular diagnostic techniques that accurately identify gene mutations or deletions provide a scientific basis for disease classification, genetic counseling, and prenatal interventions. Techniques such as next-generation sequencing (NGS), which utilizes high-throughput platforms like Illumina, and third-generation sequencing (long-read sequencing) based on single-molecule real-time sequencing (e.g., PacBio) or nanopore sequencing (e.g., Oxford Nanopore) enable deep sequencing of target genes. The third-generation sequencing approach developed by Berry Genomics has reduced the missed diagnosis rate for α-thalassemia to below 0.5%.

Curative gene therapy for thalassemia offers hope to patients; however, it is accompanied by a range of technical challenges. The foremost issue is the risk of off-target effects. During β-globin gene editing, even when modifications are confined to the target site, there remains a small probability of unintended genetic mutations, which may adversely affect non-target cells or tissues and lead to unpredictable side effects [12].

Efforts to address these challenges include the development of low-cost, high-efficiency molecular diagnostic and screening techniques, as well as the refinement of gene editing technologies to enhance precision and reduce off-target risks. Despite these hurdles, advances in technology and supportive policies contribute to an optimistic outlook for the future treatment of thalassemia [13].

4.2. Policy and healthcare insurance optimization

Thalassemia prevention and treatment face numerous challenges in terms of policy and healthcare insurance. Curative therapies such as gene therapy, while potentially transformative, are hampered by high costs that limit their widespread use.

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Consequently, policymakers and healthcare institutions must balance cost-effectiveness with the sustainability of insurance systems. Due to its high initial research and production costs, gene therapy has not been included in the majority of regional health insurance schemes, resulting in significant disparities in resource allocation. Since 2012, China has made notable progress in advancing its thalassemia prevention infrastructure, yet persistent discrepancies in prenatal screening protocols and healthcare reimbursement frameworks demonstrate an ongoing divergence from European standards [14]. To address these issues, future strategies should focus on enhancing policy design by increasing research and development funding for novel therapies and exploring methods to reduce production costs.

Moreover, enhancing public health education to improve societal awareness of thalassemia and its treatment options is vital. Only when all stakeholders fully comprehend the severity of thalassemia and the efficacy of current treatment measures can policies and insurance systems be reformed to provide comprehensive and equitable healthcare for patients [15].

4.3. Multidisciplinary collaborative models

Establishing a collaborative framework among government, hospitals, and enterprises is key to advancing thalassemia research and clinical treatment. For example, the joint project between Berry Genomics and Dongguan Maternal and Child Health Hospital demonstrates how collaboration can reduce diagnostic and treatment costs by 25%. This project highlights the critical role of tripartite cooperation in enhancing both prevention and therapeutic research in thalassemia.

Such initiatives also emphasize the importance of data sharing. By creating a comprehensive database with contributions from multiple stakeholders, governments, hospitals, and enterprises can jointly collect and analyze epidemiological data on thalassemia. This information is invaluable for understanding disease patterns and formulating more precise prevention strategies.

In clinical practice, integrating gene therapy with conventional treatments provides a more comprehensive treatment option for patients with severe thalassemia; by collaborating with specialized medical institutions, the latest research findings can be rapidly translated into clinical applications, thereby improving therapeutic outcomes.

5. Conclusion

Thalassemia prevention and treatment have evolved into a technical system that encompasses both preventative interventions and precision therapy. Global practices have demonstrated that a three-tiered prevention strategy can effectively block intergenerational transmission of the disease—illustrated by the integration of third-generation sequencing and PGD in Guangxi, China, which has reduced the birth rate of severe thalassemia by 70%–90%. In the therapeutic arena, improvements in conventional transfusion and chelation therapy (with a 10-year survival rate exceeding 85%) have been complemented by critical breakthroughs in gene therapy. Current challenges primarily revolve around the translational application of technology and issues of healthcare equity; for example, the high cost of a single gene therapy course (exceeding 2 million RMB) and the lack of insurance coverage create resource imbalances, while potential risks in gene editing and transplant rejection still necessitate further technological refinement. Overcoming these obstacles will require a synergistic approach that includes governmental expansion of special funding, the establishment of multidisciplinary treatment teams by medical institutions, and the promotion of technology transfer by enterprises—illustrated by Berry Genomics' clinical project that reduced treatment costs by 25% and provided viable solutions for resource-limited regions. Looking ahead, the advancement of a "precision prevention–targeted treatment–policy support" strategy will depend on the development of high-throughput detection tools that cover rare mutations, the exploration of tiered payment and

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outcome-based payment models at the policy level, and the use of artificial intelligence to enhance grassroots screening capabilities. Through global research collaboration and healthcare system reform, the dual goals of achieving zero new thalassemia births and comprehensive patient cure can be realized, reflecting not only a breakthrough in medical innovation but also a commitment to public health equity.

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