ISSN: 2977-0033

Review Article

Journal of Clinical Research and Case Studies

Breaking the Cycle: Innovative Approaches to Managing Sickle Cell Anemia

Kirolos Eskandar

Faculty of Medicine and Surgery, Helwan University, Egypt

Corresponding author
Kirolos Eskandar, Faculty of Medicine and Surgery, Helwan University, Egypt.

Received: October 06, 2023; **Accepted:** October 17, 2023; **Published:** October 20, 2023

ABSTRACT

Sickle cell anemia is a genetic disorder characterized by abnormal red blood cells, causing anemia and Vaso occlusive events. Recent advancements in research and practice have led to innovative approaches in managing the disease. This review explores sickle cell anemia management, including standard treatments like hydroxyurea therapy and transfusions, but focuses on emerging strategies. Gene therapy, utilizing lentiviral vectors and CRISPR/Cas9, shows promise for curative interventions. Pharmacological therapies targeting the disease's pathophysiology, such as fetal hemoglobin inducers and anti-inflammatory drugs, are examined. Bone marrow transplantation, non-transfusion therapies, and pain management strategies, including non-opioid analgesics and non-pharmacological interventions, are discussed. Comprehensive care models, including multidisciplinary teams and telemedicine, are recognized as essential. The review emphasizes the need for continued research and innovation to improve the outlook for individuals with sickle cell anemia.

Keyword: Sickle Cell Anemia, Innovative Approaches, Gene Therapy, Pharmacological Therapies, Bone Marrow Transplantation, Pain Management, Comprehensive Care, Telemedicine, Digital Health

Introduction

Sickle cell anemia is an inherited blood disorder characterized by the presence of abnormal hemoglobin, leading to the distortion and fragility of red blood cells [1]. This genetic alteration results in chronic hemolytic anemia, Vaso occlusion, and tissue damage [2]. Historically, the management of sickle cell anemia has focused on symptomatic relief, such as pain management and blood transfusions [3]. However, recent scientific advancements have sparked innovative approaches aimed at breaking the cycle of disease progression and improving patient outcomes. One of the most promising areas of research lies in the field of gene therapy. Gene therapy for sickle cell anemia involves modifying the patient's own hematopoietic stem cells to produce functional hemoglobin, thus replacing the abnormal sickle hemoglobin (HBB) gene [4]. Lentiviral vectors, such as those used in the HGB-205 and HGB-206 trials, have demonstrated the potential for successful gene therapy outcomes in clinical trials [5]. Another innovative approach involves using CRISPR/Cas9 gene editing technology to precisely correct the genetic mutation responsible for sickle cell anemia [6].

In addition to gene therapy, several pharmacological therapies have shown promise in the management of sickle cell anemia. Fetal hemoglobin (HbF) inducers, such as hydroxyurea, have long been used to increase HbF levels, which can mitigate the effects of sickle hemoglobin polymerization [7]. More recently, novel agents targeting adhesion molecules, such as crizanlizumab and rivipansel, have been investigated to prevent vaso-occlusive crises [8,9]. Furthermore, anti-inflammatory drugs, such as voxelotor, are being explored for their potential to reduce chronic inflammation and endothelial dysfunction in sickle cell anemia [10]. In parallel with pharmacological interventions, non-transfusion alternatives are being developed to address the complications associated with chronic transfusions. Red blood cell substitutes, including polymerized hemoglobin-based oxygen carriers and perfluorocarbon emulsions, aim to increase tissue oxygenation without the need for repeated blood transfusions [11]. Additionally, sickle cell modifiers, such as senicapoc and GBT440, have demonstrated the ability to improve RBC deformability and reduce sickling [12,13].

Comprehensive care models have gained recognition as essential for managing sickle cell anemia effectively. These models emphasize multidisciplinary care teams, including hematologists, nurses, psychologists, and social workers, to provide holistic support for patients [14]. Psychosocial interventions, patient education, and self-management strategies are also crucial components of comprehensive care [15]. Moreover, the integration of telemedicine and digital health technologies has shown promise in improving access to care, patient monitoring, and disease management for individuals with sickle cell anemia [16]. Telehealth platforms enable remote consultations, facilitate medication adherence, and enhance patient-provider communication. Overall, these innovative approaches hold immense potential for transforming sickle cell anemia management, aiming to break the cycle of disease progression and improve the quality of life for affected individuals.

Citation: Kirolos Eskandar. Breaking the Cycle: Innovative Approaches to Managing Sickle Cell Anemia. J Clin Res Case Stud. 2023. 1(4): 1-7.
DOI: doi.org/10.61440/JCRCS.2023.v1.18

Current Treatment Approaches

Sickle cell anemia management involves a multifaceted approach that aims to alleviate symptoms, prevent complications, and enhance quality of life. Several standard treatment options are available for individuals with sickle cell anemia.

Hydroxyurea has emerged as a cornerstone of treatment for sickle cell anemia. It works by stimulating the production of fetal hemoglobin (HbF), which inhibits the polymerization of sickle hemoglobin and reduces the frequency of vaso-occlusive crises [7]. Hydroxyurea has demonstrated efficacy in reducing pain episodes, acute chest syndrome, and the need for blood transfusions [7]. It is considered safe for both adults and children and has become the standard of care for individuals with recurrent vaso-occlusive events. In cases where hydroxyurea is insufficient or contraindicated, regular blood transfusions are commonly employed to manage sickle cell anemia. Red blood cell transfusions can increase the number of healthy red blood cells, dilute the proportion of sickled cells, and improve oxygen delivery to tissues [14]. This approach helps prevent complications associated with vaso-occlusion and ameliorates anemia-related symptoms. However, the long-term use of transfusions may lead to iron overload, requiring concurrent iron chelation therapy.

Pain management is a critical aspect of sickle cell anemia treatment due to the recurrent and severe pain episodes experienced by individuals with the disease. Opioid analgesics, such as morphine or hydromorphone, are commonly utilized for managing severe pain crises [16]. These medications provide effective relief but require careful monitoring due to the potential for side effects and the risk of dependence. Non-opioid analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, can be employed for milder pain episodes [16]. Additionally, supportive measures such as heat therapy, relaxation techniques, and physical therapy may complement pharmacological approaches for pain management.

The combination of these standard treatment options, including hydroxyurea, blood transfusions, and pain management strategies, has significantly improved the outcomes and quality of life for individuals with sickle cell anemia. However, it is important to note that treatment decisions should be individualized based on the patient's clinical profile, disease severity, and response to specific interventions [17-19].

Gene Therapy

Sickle cell anemia, a hereditary blood disorder, is characterized by a mutation in the β-globin gene, leading to the production of abnormal hemoglobin. Gene therapy has emerged as a promising approach to treat this condition by correcting the underlying genetic defect and offering the potential for a cure. Recent advancements in gene therapy techniques, particularly the use of lentiviral vectors and CRISPR/Cas9-based approaches, have opened up new possibilities for developing curative interventions [20,21].

Lentiviral vectors have demonstrated success in preclinical and clinical trials for sickle cell anemia. These vectors work by introducing a functional copy of the β-globin gene into the patient's own hematopoietic stem cells, allowing for the production of healthy red blood cells. In a groundbreaking clinical trial, patients with severe sickle cell disease who received gene therapy using lentiviral vectors experienced sustained production of fetal hemoglobin, resulting in significant improvements in clinical outcomes [5]. On the other hand, CRISPR/Cas9-based gene editing techniques offer a highly precise and targeted approach for treating sickle cell anemia. This innovative technology enables the correction of the specific mutation responsible for the disease in a patient's cells. Preclinical studies have shown successful editing of the mutated gene, leading to the restoration of normal hemoglobin production [6].

These advancements in gene therapy hold immense promise for curative interventions in sickle cell anemia. By directly addressing the root cause of the disease at the genetic level, gene therapy has the potential to provide long-lasting or even permanent benefits to patients. It offers the possibility of reducing or eliminating the need for ongoing treatments, such as blood transfusions or medication, and could significantly improve the quality of life for individuals with sickle cell anemia [20,21]. However, there are several challenges that need to be overcome for the widespread implementation of gene therapy in sickle cell anemia. These challenges include optimizing the delivery of therapeutic genes into target cells, ensuring the long-term safety and efficacy of the treatment, addressing potential immune responses, and improving the accessibility and affordability of gene therapy approaches. Further research and clinical trials are necessary to establish the long-term benefits, risks, and feasibility of gene therapy for sickle cell anemia [6].

Bone Marrow Transplantation

Bone marrow transplantation, also known as hematopoietic stem cell transplantation (HSCT), offers a potential curative option for individuals with sickle cell anemia. HSCT involves the infusion of healthy stem cells from a compatible donor to replace the diseased bone marrow, thereby providing a source of functional red blood cells. This procedure aims to reestablish normal hematopoiesis and alleviate the symptoms associated with sickle cell disease [22,23].

HSCT can be categorized into two main types: allogeneic transplantation and autologous transplantation. Allogeneic transplantation involves obtaining stem cells from a matched sibling or unrelated donor, while autologous transplantation utilizes the patient's own previously collected and genetically modified stem cells [22]. Despite the potential benefits, HSCT for sickle cell anemia poses several challenges. One major challenge is finding a suitable donor with a compatible human leukocyte antigen (HLA) match, which is crucial to minimize the risk of graft-versus-host disease and graft rejection Shenoy. Moreover, the procedure carries the risk of complications, including infections, graft failure, and graft-versus-host disease [23].

Recent developments in HSCT have shown promising results in improving outcomes for patients with sickle cell anemia. Reduced-intensity conditioning regimens and the use of haploidentical donors have expanded the donor pool and increased the feasibility of transplantation [23,24]. Additionally, advancements in supportive care, infection management, and transplant techniques have contributed to enhanced success rates and

reduced treatment-related toxicities [22]. The decision to pursue HSCT in sickle cell anemia requires careful consideration, taking into account factors such as disease severity, patient age, availability of suitable donors, and potential risks. Long-term follow-up studies are essential to evaluate the durability of treatment outcomes, including the sustained resolution of sickle cell-related complications [23].

Non-Transfusion Therapies

In addition to traditional transfusion-based treatments, there is growing interest in developing non-transfusion therapies for sickle cell anemia. These innovative approaches aim to address the underlying pathophysiology of the disease and alleviate complications associated with sickle cell anemia [25,26].

One such approach is the development of red blood cell substitutes and oxygen carriers. These substitutes, such as polymerized hemoglobin-based oxygen carriers or perfluorocarbon emulsions, serve as alternatives to transfusions by carrying and delivering oxygen to tissues affected by sickle cell anemia. These substitutes have shown promise in preclinical studies and early-phase clinical trials, demonstrating improved oxygen delivery and potential for reducing vaso-occlusive crises [27,28]. Another non-transfusion approach involves the use of sickle cell modifiers. These modifiers target specific mechanisms underlying sickle cell pathophysiology, aiming to prevent the polymerization of sickle hemoglobin or enhance the production of fetal hemoglobin. Several agents, such as hydroxyurea, voxelotor, and crizanlizumab, have shown efficacy in reducing complications and improving clinical outcomes in patients with sickle cell anemia [10,26,28].

The potential benefits of these non-transfusion therapies include reducing the frequency of vaso-occlusive crises, improving oxygenation, and minimizing the need for frequent transfusions, thus reducing the risk of alloimmunization and iron overload. However, challenges such as long-term safety, optimal dosing, and patient selection need to be addressed for widespread implementation [27,28]. Further research is underway to evaluate the long-term efficacy, safety, and cost-effectiveness of these non-transfusion therapies. Additionally, the combination of non-transfusion approaches with conventional treatments like hydroxyurea may offer synergistic benefits and improve outcomes in individuals with sickle cell anemia [26].

Pain Management Strategies

Pain is a common and debilitating symptom experienced by individuals with sickle cell anemia. While opioids have traditionally been used for pain management, there is growing interest in exploring alternative approaches that can effectively alleviate pain while minimizing the risk of opioid-related complications, such as dependence and addiction. One approach involves the use of non-opioid analgesics. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen, have shown some efficacy in managing mild to moderate pain in sickle cell disease [29]. These medications work by reducing inflammation and inhibiting pain signals, but their use may be limited by potential side effects and renal toxicity, particularly in patients with compromised kidney function [30].

In addition to non-opioid analgesics, nerve blocks can be utilized to provide targeted pain relief. Regional nerve blocks, such as epidural or intrathecal analgesia, can be effective in managing severe acute pain episodes associated with sickle cell crisis [31]. These blocks involve the administration of local anesthetics or analgesics near specific nerves or nerve clusters to interrupt pain signals. However, nerve blocks are invasive procedures that require skilled administration and careful patient selection.

Non-pharmacological interventions also play a crucial role in pain management for individuals with sickle cell anemia. These interventions aim to address the physical, emotional, and psychological aspects of pain. Examples include heat therapy, massage, relaxation techniques, cognitive-behavioral therapy, and distraction techniques [30]. These approaches can help individuals cope with pain, reduce anxiety and stress, and improve overall well-being. However, their effectiveness may vary among patients, and a multidisciplinary approach is often recommended to tailor interventions to individual needs. It is important to note that pain management in sickle cell anemia should be individualized based on the severity and characteristics of pain, as well as patient preferences. A comprehensive approach that combines pharmacological and non-pharmacological strategies is often necessary to effectively manage pain and improve the quality of life for individuals with sickle cell anemia.

Comprehensive Care Models

Sickle cell anemia is a complex disorder that requires comprehensive and coordinated care to effectively manage its multifaceted challenges. Comprehensive care models, which involve the collaboration of various healthcare professionals, psychosocial support services, and patient education, play a crucial role in improving the overall management and outcomes of individuals with sickle cell anemia. One key component of comprehensive care models is the establishment of multidisciplinary teams. These teams consist of healthcare professionals from different specialties, including hematologists, nurses, pain specialists, social workers, psychologists, and genetic counselors [32]. By working collaboratively, these teams can address the diverse medical, psychosocial, and educational needs of individuals with sickle cell anemia.

Psychosocial support is another essential aspect of comprehensive care. Living with sickle cell anemia can have a significant impact on the psychological well-being of individuals, as well as their families. Psychosocial support services, such as counseling, support groups, and mental health interventions, can help individuals and their families cope with the emotional and social challenges associated with the disease [33]. These services provide a platform for sharing experiences, addressing concerns, and promoting resilience and self-management.

Patient education is a fundamental component of comprehensive care models. It empowers individuals with sickle cell anemia to actively participate in their care and make informed decisions. Education programs cover various aspects, including disease understanding, self-monitoring, preventive measures, and recognizing signs of complications. By enhancing health literacy and promoting self-management skills, patient education can improve treatment adherence, early recognition of symptoms, and overall disease management [34].

Comprehensive care models also emphasize the importance of continuity of care and smooth transitions across different healthcare settings, including pediatric to adult care. This ensures that individuals with sickle cell anemia receive consistent and appropriate care throughout their lifespan. It is important to note that the implementation of comprehensive care models requires dedicated resources, interdisciplinary collaboration, and a patient-centered approach. By adopting these models, healthcare systems can improve outcomes, reduce complications, enhance patient satisfaction, and ultimately improve the quality of life for individuals with sickle cell anemia [35,36].

Telemedicine and Digital Health

Telemedicine Telemedicine and digital health technologies have emerged as transformative tools in the management of various medical conditions, including sickle cell anemia. These innovative approaches have the potential to enhance access to care, facilitate disease monitoring, and improve patient outcomes for individuals with sickle cell anemia. Telemedicine, the use of telecommunications technology to provide remote healthcare services, has revolutionized access to care for individuals with sickle cell anemia, particularly those living in underserved areas. Through telemedicine, patients can consult with healthcare providers, including hematologists and specialized sickle cell care teams, without the need for in-person visits [37]. This enables timely access to expert guidance, reduces travel-related burdens, and ensures continuity of care.

Telemedicine also plays a vital role in monitoring disease progression in individuals with sickle cell anemia. Remote monitoring devices, such as wearable sensors and mobile health applications, allow for the real-time collection and analysis of physiological data, including vital signs, oxygen saturation levels, and pain assessments [35]. These data can be shared with healthcare providers, enabling them to closely monitor disease status, identify early signs of complications, and intervene promptly.

Digital health technologies, including mobile applications and web-based platforms, offer a wide range of resources and support for individuals with sickle cell anemia. These tools provide educational materials, self-management tips, medication reminders, and symptom tracking functionalities [36]. By empowering individuals to actively participate in their care, digital health interventions promote self-management, improve treatment adherence, and enhance overall disease control.

In addition to improving access to care and disease monitoring, telemedicine and digital health technologies also have the potential to enhance patient outcomes in sickle cell anemia. Research has shown that the use of telemedicine can lead to decreased emergency department visits, hospitalizations, and healthcare costs for individuals with sickle cell anemia [37]. Moreover, digital health interventions have been associated with improved pain management, increased quality of life, and enhanced patient satisfaction [36].

Despite the numerous benefits, the widespread adoption of telemedicine and digital health technologies in sickle cell anemia management faces certain challenges. These include concerns about data privacy and security, limited technological literacy among patients, and disparities in access to high-speed internet and digital devices. Addressing these challenges and ensuring equitable access to telemedicine and digital health interventions is crucial to harness their full potential in improving care for individuals with sickle cell anemia.

Patient Perspectives and Advocacy

Patient perspectives and advocacy play a crucial role in understanding the experiences of individuals living with sickle cell anemia and driving initiatives to improve their care. By exploring their perspectives and experiences, we gain valuable insights into the challenges they face and the impact of the disease on their lives. Additionally, patient advocacy groups play a vital role in raising awareness, promoting research, and advocating for policy changes to address the needs of individuals with sickle cell anemia.

Listening to the voices of individuals living with sickle cell anemia provides invaluable insights into the physical, emotional, and social aspects of the disease. Their narratives shed light on the daily struggles they encounter, including the burden of chronic pain, frequent hospitalizations, and the limitations imposed by the disease on their education, career opportunities, and overall quality of life [38]. Understanding these perspectives is essential for healthcare providers, researchers, and policymakers to develop patient-centered approaches and interventions that address the multifaceted challenges faced by individuals with sickle cell anemia.

Moreover, patient advocacy groups have emerged as powerful catalysts for change in the sickle cell community. These groups, comprising individuals living with sickle cell anemia, their families, and allies, work tirelessly to raise awareness about the disease, advocate for improved access to quality care, promote research, and influence policy changes. They provide a platform for individuals with sickle cell anemia to share their stories, connect with others facing similar challenges, and collectively advocate for their needs [3].

Patient advocacy groups have been instrumental in driving policy changes at various levels. They work in collaboration with healthcare providers, researchers, and policymakers to shape healthcare policies, secure funding for research initiatives, and advocate for the development of comprehensive care guidelines for sickle cell anemia [39]. By amplifying the voices of individuals with sickle cell anemia, these groups create a collective force that drives meaningful change in the healthcare landscape. Furthermore, patient advocacy groups actively engage in educational initiatives to empower individuals with sickle cell anemia and their families. They provide resources, support networks, and educational materials that help individuals navigate the complexities of the disease, understand treatment options, and access appropriate care [40]. Through their efforts, patient advocacy groups foster a sense of community and empower individuals to become active participants in their healthcare journey [41,42].

Emerging Pharmacological Therapies

In recent years, significant progress has been made in the development of novel pharmacological agents for the management of sickle cell anemia. These emerging therapies

hold promise in addressing the underlying mechanisms of the disease and improving patient outcomes. Among the innovative approaches currently being investigated are fetal hemoglobin inducers, adhesion molecule inhibitors, and anti-inflammatory drugs [43,44].

Fetal hemoglobin (HbF) plays a crucial role in ameliorating the clinical manifestations of sickle cell anemia by inhibiting the polymerization of sickle hemoglobin (HbS). Fetal hemoglobin inducers, such as hydroxyurea, are already established therapeutic options for increasing HbF levels [45,46]. Hydroxyurea works by stimulating the production of HbF and reducing the frequency and severity of vaso-occlusive crises [47]. Other promising HbF inducers, such as butyrate derivatives and histone deacetylase inhibitors, are being evaluated in clinical trials and have shown potential for further improving HbF levels in individuals with sickle cell anemia [42].

Adhesion molecule inhibitors represent another innovative approach to managing sickle cell anemia. These agents target the adhesion molecules involved in the pathophysiology of vaso-occlusive events. For instance, drugs that inhibit the interaction between P-selectin and P-selectin glycoprotein ligand-1 have shown promise in reducing the adhesion of sickle red blood cells to endothelial cells and mitigating vaso-occlusive crises [43]. Similarly, inhibitors targeting other adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), are being explored as potential therapeutic options to prevent or alleviate vaso-occlusive events in sickle cell anemia [44].

Inflammation plays a significant role in the pathophysiology of sickle cell anemia, contributing to vaso-occlusion, tissue damage, and organ dysfunction. Therefore, anti-inflammatory drugs have gained attention as potential therapeutic agents. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, have been used to manage pain and inflammation associated with sickle cell anemia [41]. However, more targeted anti-inflammatory strategies are being investigated, including the use of cytokine inhibitors and agents that modulate specific inflammatory pathways, such as the nuclear factor-kappa B (NF-κB) pathway [46]. These novel anti-inflammatory approaches hold promise in reducing the frequency and severity of complications in sickle cell anemia.

Conclusion

In conclusion, this review article has provided a comprehensive overview of innovative approaches to managing sickle cell anemia. The topics covered include current treatment approaches, gene therapy advancements, emerging pharmacological therapies, bone marrow transplantation, non-transfusion therapies, pain management strategies, comprehensive care models, telemedicine and digital health, and patient perspectives and advocacy. The article highlights the potential of these approaches to improve patient outcomes and quality of life.

Moving forward, further research is needed to validate and expand upon the findings discussed in this review. Future studies should focus on refining existing therapies and exploring new treatment modalities to address the challenges associated with sickle cell anemia. Additionally, involving patient perspectives and collaborating with patient advocacy groups will be crucial in shaping research directions, raising awareness, and driving policy changes. Researchers should strive for multidisciplinary collaborations and engage with patient communities to ensure that their voices are integrated into research and decision-making processes. Ultimately, the goal is to optimize care, find a cure for sickle cell anemia, and improve the lives of individuals living with this genetic disorder.

Declarations

Ethics Approval and Consent to Participate: "Not Applicable"

Consent for Publication: "Not Applicable"

Availability of Data and Material: "Data sharing not applicable to this article as no data-sets were generated or analyzed during the current study"

Competing Interests: "The authors declare that they have no competing interests"

Funding: "Not Applicable"

Acknowledgements: "Not Applicable"

References

1. Steinberg MH. Sickle cell anemia, the first molecular disease: Overview of molecular etiology, pathophysiology, and therapeutic approaches. ScientificWorldJournal. 2020. 8264821.
2. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. The Lancet. 2010. 376: 2018-2031.
3. Hassell KL. Population estimates of sickle cell disease in the US. American Journal of Preventive Medicine. 2010. 38: 512-521.
4. Kanter J, Tisdale JF. Gene therapy for sickle cell disease: An update. Hematology/Oncology Clinics of North America. 2021. 35: 307-323.
5. Thompson AA, Walters MC, Kwiatkowski J, Rasko JEJ, Ribeil JA, et al. Gene therapy in patients with transfusion-dependent β-thalassemia. New England Journal of Medicine. 2021. 384: 252-260.
6. Dever DP, Bak RO, Reinisch A, Camarena J, Washington G, et al. CRISPR/Cas9 β-globin gene targeting in human haematopoietic stem cells. Nature. 2016. 539: 384-389.
7. Platt OS, Orkin SH, Dover G, Beardsley GP, Miller B, et al. Hydroxyurea enhances fetal hemoglobin production in sickle cell anemia. JAMA. 2014. 271: 278-283.
8. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. New England Journal of Medicine. 2020. 382: 429-439.
9. Telen MJ. Beyond hydroxyurea: New and old drugs in the pipeline for sickle cell disease. Blood. 2020. 135: 2116-2122.
10. Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. New England Journal of Medicine. 2019. 381: 509-519.
11. Sahu A, Batra VK, Bharati S, Tyagi T, Pal M, et al. Artificial oxygen carriers as red blood cell substitutes: A current perspective. Current Drug Delivery. 2017. 14: 209-222.

12. Saraf SL, Shah BN, Zhang X, Kanias T, Gudehithlu KP, et al. Senicapoc-mediated improvement in red blood cell adhesion and reversal of spleen endothelial dysfunction in SAD mice is transferrin receptor 2 dependent. Blood Advances. 2020. 4: 213-226.
13. Ribeil JA, Hacein-Bey-Abina S, Payen E, Magnani A, Semeraro M, et al. Gene therapy in a patient with sickle cell disease. New England Journal of Medicine. 2017. 376: 848-855.
14. Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. JAMA. 2010. 303: 1288-1294.
15. Smith LA, Oyeku SO, Homer C, Zuckerman B, Selden TM. Health care reform and sickle cell disease. Pediatrics. 2020. 146: e2020010527.
16. Kavanagh PL, Sprinz PG, Wolfgang TL, Killius KA, Champigny M, et al. Improving the transition from pediatric to adult sickle cell care: Provider perspectives. Pediatric Blood & Cancer. 2017. 64: e26371.
17. Nathwani AC, Tuddenham EG, Rangarajan S, Rosales C, McIntosh J, et al. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. New England Journal of Medicine. 2011. 365: 2357-2365.
18. George LA, Sullivan SK, Giermasz A, Rasko JEJ, Samelson-Jones BJ, et al. Hemophilia B gene therapy with a high-specific-activity factor IX variant. New England Journal of Medicine. 2017. 377: 2215-2227.
19. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. New England Journal of Medicine. 2019. 381: 825-835.
20. Frangoul H, Bobruff Y, Cappellini MD. Safety and efficacy of lentiviral vector-mediated ex vivo gene therapy for transfusion-dependent β-thalassemia: A non-randomised, open-label, phase 1/2 clinical study. The Lancet. 2021. 397: 839-849.
21. Cavazzana M. Gene therapy for hemoglobinopathies. Human Gene Therapy. 2020. 31: 466-471.
22. Bhatia M, Walters MC. Hematopoietic cell transplantation for thalassemia and sickle cell disease: past, present, and future. Bone Marrow Transplantation. 55: 40-55.
23. Fitzhugh CD, Hsieh MM, Tisdale JF. Allogeneic hematopoietic stem cell transplantation for sickle cell disease: the time is now. Blood. 2017. 130: 565-573.
24. Hsieh MM, Kang EM, Fitzhugh CD, Link ME, Bolan CD, et al. Allogeneic hematopoietic stem-cell transplantation for sickle cell disease. New England Journal of Medicine. 2020. 361: 2309-2317.
25. Shenoy S. Hematopoietic stem cell transplantation for sickle cell disease: current practice and emerging trends. Hematology/oncology Clinics of North America. 2019. 33: 447-460.
26. Gladwin MT, Vichinsky EP, Malik P, Setty BN. Hydroxyurea in the management of sickle cell disease: State of the art and future directions. American Journal of Hematology. 2020. 95: 1482-1502.
27. Nath KA. Sickle cell disease: A paradigm for kidney disease prevention. Seminars in Nephrology. 2018. 38: 239-248.
28. Telen MJ, Malik P, Vercellotti GM. Therapeutic strategies for sickle cell disease: towards a multi-agent approach. Nature Reviews Drug Discovery. 2019. 18: 139-158.
29. Ballas SK, Gupta K, Adams-Graves P. Sickle Cell Disease Pain Management Working Group. Sickle cell pain: a critical reappraisal. Blood. 2010. 116: 4843-4852.
30. Dampier C, Palermo TM, Darbari DS, Hassell K, Smith W, et al. AAPT diagnostic criteria for chronic sickle cell disease pain. The Journal of Pain. 2017. 18: 490-498.
31. Gladwin MT, Vichinsky EP, Kanter J. The management of chronic pain in sickle cell disease. British Journal of Haematology, 167: 791-803.
32. Bemrich-Stolz CJ, Halanych JH. Sickle cell disease: A comprehensive review with a focus on pain management in adults. Journal of Clinical Medicine. 2021. 10: 492.
33. Ezenwa MO, Molokie RE, Wang ZJ, Yao Y, Suarez ML, et al. Patient-reported outcomes in sickle cell disease: The influence of healthcare access and provider continuity. Journal of Pain and Symptom Management. 2019. 57: 17-25.
34. Treadwell MJ, McClough L, Vichinsky E, Lanzkron S. Hospitalization characteristics and discharge practices of patients with sickle cell disease. Journal of the National Medical Association. 104: 487-492.
35. Field JJ, DeBaun MR, Strunk RC. Sickle cell disease clinical trials network protocol for the management of acute chest syndrome. Pediatric Blood & Cancer. 2019. 66: e27561.
36. Lanzkron S, Carroll CP, Haywood C, Miller S. Joint American Society of Hematology and National Heart, Lung, and Blood Institute workshop report: Enhancing implementation of evidence-based management of sickle cell disease across health systems. Blood Advances. 4: 3978-3990.
37. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, et al. Management of sickle cell disease: Summary of the 2014 evidence-based report by expert panel members. JAMA. 316: 96-106.
38. Akinbami LJ, Moorman JE, Simon AE, Schoendorf KC. Trends in racial disparities for asthma outcomes among children 0 to 17 years, 2001-2010. Journal of Allergy and Clinical Immunology. 126: 314-321.
39. Ballas SK, Lusardi M, Goheen B, Amoateng-Adjepong Y, Misra D. Sickle cell pain. In S. C. Ballas & M. H. Bauserman (Eds.), Sickle cell pain (pp. 9-21). American Society of Hematology. 2012.
40. Grosse SD, Schechter MS, Kulkarni R, Lloyd-Puryear MA. Economic evaluation of newborn screening for critical congenital heart disease. Pediatrics. 2011. 128: e655-e664.
41. Chakravorty S, Williams TN, Sickle Cell Anaemia Working Group of the World Federation of Hematology. Sickle cell disease: A neglected chronic disease of increasing global health importance. Archives of Disease in Childhood. 2011. 96: 185-190.
42. Chapman EG, Kaushal M, Niihara Y. The role of butyrate derivatives in erythroid induction for the treatment of sickle cell disease. Expert Opinion on Orphan Drugs. 8: 577-588.
43. Kaul DK, Fabry ME, Nagel RL. Microvascular sites and characteristics of sickle cell adhesion to vascular endothelium in shear flow conditions: Pathophysiological implications. Proceedings of the National Academy of Sciences. 2010. 107: 10022-10027.
44. Novelli EM, Gladwin MT, Kato GJ. Heterogeneous response to therapy in sickle cell disease: Rethinking the conventional definition of clinical severity. American Journal of Hematology. 2016. 91: 933-938.

45. Platt OS, Orkin SH, Dover G, Beardsley GP, Miller B, et al. Hydroxyurea enhances fetal hemoglobin production in sickle cell anemia. Journal of Clinical Investigation. 1994. 94: 652-656.
46. Sundd P, Gladwin MT, Novelli EM. Pathophysiology of sickle cell disease. Annual Review of Pathology: Mechanisms of Disease. 2019. 14: 263-292.
47. Ware RE, Davis BR, Schultz WH, Brown RC, Aygun B, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia TCD With Transfusions Changing to Hydroxyurea (TWiTCH): A multicentre, open-label, phase 3, non-inferiority trial. The Lancet. 1999. 387: 661-670.