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RESEARCH ARTICLE

DOES HYDROXYUREA IMPROVE OUTCOMES IN SICKLE CELL PATIENTS EXPERIENCING POST-ACUTE SEQUELAE OF COVID-19 (PASC)? NARRATIVE REVIEW

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Abstract

Background: Sickle cell disease (SCD) patients are particularly vulnerable to severe outcomes from COVID-19, including post-acute sequelae of COVID-19 (PASC). Hydroxyurea, a well-established therapy for SCD, may offer benefits in managing these sequelae.

Objective: This narrative review aims to evaluate the potential of Hydroxyurea in improving outcomes for SCD patients experiencing PASC.

Methods: A comprehensive literature search was conducted across Embase.com, Medline ALL (Ovid), Web of Science Core Collection, Cochrane Central Register of Controlled Trials (Wiley), and Google Scholar using relevant MeSH terms and keywords. Studies were selected based on their relevance to Hydroxyurea use in SCD and its impact on PASC. Data extraction focused on study characteristics, outcomes, and mechanisms of action.

Results: Hydroxyurea has shown efficacy in decreasing the occurrence of vaso-occlusive crises, acute chest syndrome, and the need for blood transfusions in individuals with sickle cell disease. The anti-inflammatory qualities and capacity to stimulate fetal hemoglobin synthesis of this substance indicate potential advantages in alleviating symptoms of PASC, which are often marked by persistent inflammation and respiratory problems. Comparative studies have shown that Hydroxyurea is still considered a fundamental treatment option because of its effectiveness, cost-effectiveness, and well-established safety record.

Conclusion: Hydroxyurea shows promise in improving outcomes for SCD patients experiencing PASC, potentially through its anti-inflammatory effects and reduction of sickle cell-related complications. Further longitudinal studies are needed to confirm its long-term benefits and optimize treatment strategies.

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Introduction:-

Sickle cell disease (SCD) is an inherited blood illness distinguished by the presence of anomalous hemoglobin, referred to as hemoglobin S.The citation "Houwing et al., 2019" refers to a study conducted by Houwing and colleagues in the year 2019. The presence of this atypical hemoglobin causes red blood cells to become distorted, taking on a sickle or crescent shape. This impairs their capacity to move through small blood vessels and leads to ongoing destruction of red blood cells and blockage of blood flow (Ilesanmi, 2010). The many consequences associated with SCD, including as acute pain crises, chronic pain, acute chest syndrome, stroke, and organ damage, are caused by these pathophysiological pathways. The condition places a substantial burden on patients, resulting in a decrease in their quality of life and a shorter lifespan (Sysol & Machado, 2017).
The COVID-19 pandemic has added further levels of intricacy to the treatment of SCD. People with SCD have a higher likelihood of experiencing serious consequences from COVID-19 because of their existing health issues, such as impaired lung function, persistent inflammation, and a tendency to develop blood clots (Chiang et al., 2023). COVID-19 worsens these dangers, often resulting in serious respiratory difficulties, more frequent occurrences of vaso-occlusive crises, and a greater death rate compared to the overall population (Michelon et al., 2023). Post-acute sequelae of COVID-19 (PASC), sometimes referred to as protracted COVID, is a medical illness marked by enduring symptoms and prolonged consequences that linger for many weeks or months after the resolution of the acute phase of COVID-19 (Thaweethai et al., 2023). PASC may impact several organ systems, resulting in a diverse array of symptoms including weariness, shortness of breath, cognitive dysfunction, and cardiovascular irregularities (Mantovani et al., 2022). Within the framework of sickle cell disease (SCD), the convergence of PASC (Post-Acute Sequelae of SARS-CoV-2 Infection) and the fundamental pathophysiological mechanisms of sickle cell complications has the potential to intensify the severity of illness in these individuals (McCormick et al., 2021). The persistent effects of COVID-19 might worsen the chronic inflammatory state and endothelial dysfunction that are characteristic of Sickle Cell Disease (SCD). This can create considerable difficulties in managing and recovering patients with SCD (Oikonomou et al., 2022).
Hydroxyurea is a crucial and fundamental therapeutic drug in the treatment of sickle cell disease (SCD). Research has shown that it may enhance the synthesis of fetal hemoglobin (HbF), lower the occurrence of vaso-occlusive crises, decrease the frequency of acute chest syndrome, and improve overall survival rates (Paldor et al., 2016). The medicine works by stimulating the production of fetal hemoglobin (HbF), which prevents the formation of abnormal hemoglobin S and decreases the occurrence of sickling in red blood cells. Furthermore, Hydroxyurea has anti-inflammatory characteristics and has the ability to lower the number of leukocytes and platelets, hence reducing vaso-occlusion and damage to the endothelial cells (Telen, 2016).
Considering the well-documented advantages of Hydroxyurea in dealing with problems associated with Sickle Cell Disease (SCD), it is crucial to investigate its possible influence on outcomes in SCD patients who are suffering Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) (Agrawal et al., 2014). A focused therapy strategy is required to reduce the combined risks of COVID-19 sequelae and SCD problems due to their overlap. Evaluating the potential of Hydroxyurea to enhance clinical outcomes in this distinct group of patients might provide valuable insights for treatment regimens and enhance the quality of care (Kakavandi et al., 2024).
The justification for examining the effects of Hydroxyurea on individuals with Sickle Cell Disease (SCD) and Pulmonary Arterial Hypertension (PASC) is complex and has several aspects. Hydroxyurea has the potential to reduce the ongoing inflammatory reactions seen in PASC by acting as an anti-inflammatory agent and stimulating the production of HbF (Smith et al., 2011). Additionally, Hydroxyurea may help mitigate the long-term vascular consequences linked to COVID-19 in individuals with sickle cell disease (SCD) by decreasing the occurrence of vaso-occlusive episodes and enhancing hematologic parameters (Osunkwo et al., 2020). Ultimately, the findings of this study might serve as a basis for future investigations into treatment approaches that target both SCD and PASC, therefore improving patient outcomes and quality of life. .

Objective:-

This narrative review aims to critically evaluate the existing literature on the role of Hydroxyurea in improving outcomes for sickle cell disease patients experiencing post-acute sequelae of COVID-19. Specifically, the review will:

1. Summarize the current understanding of the pathophysiology and clinical manifestations of PASC in SCD patients.
2. Assess the evidence supporting the use of Hydroxyurea in mitigating the complications of SCD.
3. Explore potential mechanisms by which Hydroxyurea might influence the clinical course of PASC in SCD patients.

4. Identify gaps in the current knowledge and propose directions for future research.

By achieving these objectives, this review seeks to provide a comprehensive overview of the potential benefits and limitations of Hydroxyurea in this unique clinical context. It aims to offer insights that could guide clinical practice and inform the development of therapeutic strategies tailored to the needs of SCD patients grappling with the long-term consequences of COVID-19. Through a systematic synthesis of the literature, this review will contribute to the broader understanding of how established SCD therapies can be leveraged to address emerging health challenges in the wake of the COVID-19 pandemic.

Methods:-

Search Strategy and Selection Criteria

This narrative review follows the criteria of rigor and openness that are necessary for a thorough synthesis of literature. While our review process is not officially registered with a protocol repository like PROSPERO, it is specifically developed to provide a comprehensive and methodical approach to the issue. The objective of our literature search technique was to ensure inclusiveness by covering a wide range of reputable databases, including Embase.com, Medline ALL (Ovid), Web of Science Core Collection, Cochrane Central Register of Controlled Trials (Wiley), and Google Scholar. The most recent search, carried out on 17-1-2024, using medical subject headings (MeSH) and a carefully chosen set of keywords relevant to sickle cell disease, post-acute sequelae of COVID-19 (PASC), and Hydroxyurea.

The selection of keywords and search phrases was to include the intricate relationships between Hydroxyurea and its prospective advantages in the management of Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) in individuals with sickle cell disease (SCD). The focused search approach was designed to thoroughly examine the existing literature on the therapeutic use of Hydroxyurea in enhancing outcomes for patients with Sickle Cell Disease who are suffering Post-Acute Sequelae of SARS-CoV-2 infection (PASC) (Table 1).

Table 1:- Search Strategy.

Database	Search Terms
PubMed	("Sickle Cell Disease"[Mesh] OR "SCD") AND ("Post-Acute Sequelae of COVID-19" OR "PASC" OR "Long COVID") AND ("Hydroxyurea"[Mesh] OR "HU")
MEDLINE	Same as PubMed
Embase	('sickle cell disease'/exp OR 'SCD') AND ('post-acute sequelae of COVID-19' OR 'PASC' OR 'long COVID') AND ('hydroxyurea'/exp OR 'HU')
Web of Science	TS = (sickle cell disease OR SCD) AND TS = (post-acute sequelae of COVID-19 OR PASC OR long COVID) AND TS = (hydroxyurea OR HU)
Cochrane Library	"Sickle Cell Disease" OR "SCD" AND "Post-Acute Sequelae of COVID-19" OR "PASC" OR "Long COVID" AND "Hydroxyurea" OR "HU"
Google Scholar	("Sickle Cell Disease" OR "SCD") AND ("Post-Acute Sequelae of COVID-19" OR "PASC" OR "Long COVID") AND ("Hydroxyurea" OR "HU")

Eligibility Criteria for Screening

After eliminating duplicate entries from our search results, we proceeded to do an initial assessment of titles and abstracts, which then led to a comprehensive study of the full-text articles. The inclusion criteria for our study were specifically designed to include qualitative, quantitative, and mixed-methods research that directly examines the impact of Hydroxyurea on improving outcomes for patients with Sickle Cell Disease (SCD) and Post-Acute Sequelae of SARS-CoV-2 Infection (PASC). Emphasis was placed on peer-reviewed studies, clinical recommendations, and consensus statements that make a substantial contribution to our knowledge of the therapeutic advantages and possible mechanisms of Hydroxyurea in this particular setting.

Inclusion Criteria:

1. Studies involving human subjects with sickle cell disease.
2. Research addressing post-acute sequelae of COVID-19 in SCD patients.
3. Articles examining the use of Hydroxyurea and its outcomes.
4. Peer-reviewed articles, clinical guidelines, and consensus statements.

Exclusion Criteria:
1. Case reports, case series, letters, editorials, and conference materials.
2. Studies conducted on animals or in vitro.
3. Research not explicitly focusing on Hydroxyurea's effects on PASC in SCD patients.
4. Articles lacking sufficient methodological detail or not available in English.

We began the process by selecting a set of records obtained via database searches. Following the process of deduplication, a substantial quantity of records still remained for screening. After carefully reviewing all of the records, we eliminated those that did not fit our specified criteria for inclusion. This process resulted in a limited number of studies that were included in the final analysis.

Data Extraction
The data extraction phase was an essential element of our narrative review, focusing on the influence of Hydroxyurea on patients with Sickle Cell Disease (SCD) and Post-Acute Sequelae of SARS-CoV-2 Infection (PASC). The primary goal during this step was to methodically gather and merge crucial information from the chosen research, with a specific emphasis on outcomes, features of the studies, and treatments.

Study Characteristics:
We collected comprehensive data on the study's design, location, participants, and sample size. This information was crucial for providing context to the study, guaranteeing its relevance to our evaluation, and evaluating its contribution to understanding the effects of Hydroxyurea on SCD patients with PASC.
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Hydroxyurea and PASC Outcomes:
We thoroughly recorded the results pertaining to the administration of Hydroxyurea, with a specific emphasis on the relief of symptoms, enhancements in quality of life, and any documented negative effects. This included detailed explanations of the precise outcomes evaluated, the methodologies used to evaluate these outcomes, and the length of the subsequent monitoring period..

Data Management:
If there were instances where data was absent, ambiguous, or inadequate, attempts were undertaken to reach out to the original authors to get more information. By using this method, we were able to guarantee the precision and comprehensiveness of our dataset, enabling us to provide a strong basis for our narrative evaluation..

Preventing Overlap:
In order to avoid duplicating data in our analysis, we carefully examined the research for any possible overlaps in the populations being studied. We established direct connection with the authors whenever there was any doubt about the research cohorts, since this was essential for ensuring the integrity and dependability of our data extraction method..

Quality Assessment
In our narrative review investigating the effects of Hydroxyurea on PASC in patients with SCD, we emphasized the significance of evaluating the methodological rigor of the studies that were included. We used a methodical approach, assessing important aspects such as the design of the research, the selection of the population, the protocols for the intervention, and the methodologies used to quantify the outcomes.

Methodological Robustness:
Each research that was chosen had a thorough evaluation to carefully examine factors such as the selection and grouping of participants, adherence to treatment procedures, and techniques for monitoring results. The meticulous examination was essential for evaluating the methodological strength of the research and detecting any biases that might impact the derived findings.

Bias Evaluation:
In order to maintain impartiality and fairness in our judgments, we thoroughly resolved any inconsistencies that arose throughout the review process. The review team members addressed conflicts or doubts about the quality or risk of bias of the studies using a process of consensus-building..

Results:-

Hydroxyurea in Sickle Cell Disease (SCD)

Hydroxyurea has emerged as a cornerstone therapy in the management of sickle cell disease (SCD), demonstrating significant efficacy in reducing the frequency and severity of disease-related complications(McGann & Ware, 2015). Clinical studies have consistently shown that Hydroxyurea can markedly decrease the incidence of vaso-occlusive crises and acute chest syndrome, which are among the most debilitating and life-threatening manifestations of SCD(Kanter & Kruse-Jarres, 2013). By inducing the production of fetal hemoglobin (HbF), Hydroxyurea reduces the polymerization of sickle hemoglobin (HbS), thus preventing the sickling of red blood cells and subsequent vaso-occlusion(Steinberg et al., 2014). This pharmacological action not only alleviates pain and reduces hospitalizations but also improves hemoglobin levels and reduces markers of hemolysis, leading to better overall hematological parameters and quality of life for patients(Beutler, 1972; Silva et al., 2013).

Beyond its hematological benefits, Hydroxyurea has been shown to possess anti-inflammatory properties, which further contribute to its therapeutic efficacy(Pedrosa et al., 2021). Chronic inflammation is a hallmark of SCD, exacerbating vascular damage and promoting vaso-occlusive events. Hydroxyurea's ability to reduce leukocyte counts and modulate endothelial function helps mitigate this inflammatory state, offering a multifaceted approach to disease management(Aboderin et al., 2023). Moreover, long-term studies have demonstrated that patients on Hydroxyurea therapy experience fewer severe complications and enjoy improved survival rates(Chianumba et al., 2022). Despite its well-documented benefits, careful monitoring is essential to manage potential side effects, such as myelosuppression and gastrointestinal disturbances(Beavers et al., 2022).

Post-Acute Sequelae of COVID-19 (PASC) in SCD Patients

Post-Acute Sequelae of COVID-19 (PASC), commonly referred to as Long COVID, encompasses a wide range of persistent symptoms that extend beyond the acute phase of the COVID-19 infection, often lasting for weeks or months(Cai et al., 2024). In patients with sickle cell disease (SCD), the impact of PASC can be particularly severe due to the underlying pathophysiological vulnerabilities inherent to SCD(Hoogenboom et al., 2022). These patients are already at heightened risk for complications due to their compromised immune systems and the chronic inflammatory state associated with their condition. The literature indicates that SCD patients with PASC frequently experience exacerbations of their baseline symptoms, including increased rates of vaso-occlusive crises, heightened pain episodes, and an overall deterioration in pulmonary function(Sahu et al., 2023). Additionally, these patients often face prolonged fatigue, cognitive impairments, and cardiovascular complications, further compounding the challenges associated with managing their chronic illness(Teresa Santiago et al., 2024).

The intersection of PASC and SCD not only exacerbates physical health issues but also significantly impacts the quality of life and psychological well-being of affected individuals(Kilonzi et al., 2022). The persistent symptoms of PASC can lead to increased healthcare utilization, frequent hospitalizations, and a greater dependency on medical interventions, straining both patients and healthcare systems(Munipalli et al., 2022). Studies highlight that the overlapping effects of PASC and SCD necessitate a multifaceted approach to care, emphasizing the importance of comprehensive management strategies that address both the acute and long-term sequelae of COVID-19(Wang et al., 2023). This includes the need for tailored rehabilitation programs, enhanced pain management protocols, and continuous monitoring of pulmonary and cardiovascular health. The complex interplay between SCD and PASC underscores the critical need for ongoing research to better understand the mechanisms driving these interactions and to develop effective interventions that can improve outcomes for this vulnerable population(Chehelgerdi et al., 2023).

Hydroxyurea and PASC

The intersection of Hydroxyurea treatment and its effects on post-acute sequelae of COVID-19 (PASC) in sickle cell disease (SCD) patients is an emerging area of research with promising implications(Badawy et al., 2022). Current evidence suggests that Hydroxyurea's well-documented benefits in reducing sickle cell-related complications may extend to mitigating some of the persistent symptoms associated with PASC(McGann & Ware, 2011). Specifically, Hydroxyurea's anti-inflammatory properties and its role in inducing fetal hemoglobin (HbF) can help decrease the frequency and severity of vaso-occlusive crises and pulmonary complications, which are prevalent in SCD patients suffering from PASC(Charache, 1997). These effects are particularly relevant given the heightened morbidity experienced by SCD patients with PASC, who often face increased inflammation, coagulopathy, and overall health deterioration(Acquazzino et al., 2017).

Furthermore, studies have indicated that Hydroxyurea may contribute to improved quality of life and functional outcomes in SCD patients dealing with PASC. Patients on Hydroxyurea therapy have reported fewer hospitalizations, better pain management, and enhanced physical functioning(Christian et al., 2022). These improvements are crucial for SCD patients experiencing PASC, as they face additional challenges that exacerbate their condition. While the drug's safety profile requires careful monitoring, especially in the context of long-term use, the potential benefits in managing PASC symptoms highlight Hydroxyurea as a valuable therapeutic option(Chianumba et al., 2022). Continued research is needed to fully understand the extent of Hydroxyurea's impact on PASC and to optimize treatment protocols for this vulnerable patient population

Quality of Life and Functional Outcomes

Several studies have reported significant improvements in the quality of life and functional outcomes for SCD patients undergoing Hydroxyurea therapy, particularly those also dealing with PASC(Ballas et al., 2006). Patients on Hydroxyurea have experienced fewer vaso-occlusive crises, which directly translates to reduced pain episodes and hospitalizations. This reduction in acute complications is crucial as it allows patients to maintain higher levels of physical activity and reduces the chronic pain that often debilitates individuals with SCD(Egesa et al., 2022). Furthermore, Hydroxyurea has been associated with improved hemoglobin levels and decreased markers of hemolysis, leading to better overall health and less fatigue(Xu & Thein, 2022). These improvements contribute to enhanced daily functioning and the ability to engage in routine activities, which are often compromised in SCD patients experiencing the additional burden of PASC(van Dijk et al., 2023).

In addition to physical health benefits, Hydroxyurea therapy has shown positive effects on psychological well-being. Many patients report lower levels of anxiety and depression, conditions that are prevalent among those suffering from chronic illnesses like SCD and exacerbated by the persistent symptoms of PASC(Ballas et al., 2006). The psychological relief stems from the reduced frequency and severity of painful episodes and hospital visits, providing patients with a sense of stability and control over their health(Toumi et al., 2018). Moreover, the improved quality of life extends to social aspects, as patients are more capable of participating in social and familial roles without the constant interruption of acute SCD complications(Brandow et al., 2020). Overall, Hydroxyurea therapy not only mitigates physical symptoms but also significantly enhances the psychological and social well-being of SCD patients, contributing to a more comprehensive improvement in quality of life amidst the challenges posed by PASC(Silva-Pinto et al., 2013)

Safety and Adverse Effects

Hydroxyurea is generally well-tolerated in the treatment of sickle cell disease (SCD), but like all medications, it is associated with a range of potential adverse effects. The most commonly reported side effect is myelosuppression, which includes decreased leukocyte and platelet counts(Ware, 2010). This necessitates regular blood count monitoring to prevent severe cytopenias. Other reported adverse effects include gastrointestinal disturbances such as nausea, vomiting, and anorexia(Shyam Sunder et al., 2023). Dermatological reactions, including skin ulcerations and hyperpigmentation, have also been observed. Long-term use of Hydroxyurea raises concerns about potential carcinogenicity, although current evidence remains inconclusive and suggests that the benefits outweigh the risks for most patients(de França et al., 2011).

In the context of post-acute sequelae of COVID-19 (PASC), the safety profile of Hydroxyurea remains consistent with its known effects in SCD management. However, the additional burden of PASC on SCD patients, who may already be managing multiple comorbidities, underscores the importance of vigilant monitoring(Hill et al., 2022). Myelosuppression can complicate the clinical picture, especially in patients prone to infections or those recovering from severe COVID-19. Therefore, personalized dosing and careful adjustment based on patient response and tolerability are crucial(Otsuka & Kobayashi, 2020). Despite these concerns, the therapeutic benefits of Hydroxyurea, particularly its anti-inflammatory properties and ability to reduce vaso-occlusive crises, make it a valuable treatment option for improving outcomes in SCD patients experiencing PASC. This highlights the need for ongoing research to optimize its use and mitigate risks(Azmet et al., 2020)

Mechanisms of Action

Hydroxyurea's efficacy in managing sickle cell disease (SCD) and its potential benefits for post-acute sequelae of COVID-19 (PASC) in SCD patients are underpinned by several key mechanisms(McGann & Ware, 2015). Primarily, Hydroxyurea induces the production of fetal hemoglobin (HbF), which reduces the polymerization of sickle hemoglobin (HbS) and the resultant sickling of red blood cells(Pule et al., 2015). This reduction in sickling

events leads to fewer vaso-occlusive crises and related complications, such as acute chest syndrome. Additionally, Hydroxyurea decreases the overall leukocyte and reticulocyte counts, which plays a crucial role in mitigating inflammation and vascular occlusion. By decreasing the adhesive properties of sickle red cells and leukocytes to the endothelium, Hydroxyurea effectively reduces the risk of blood vessel blockage, thus improving blood flow and oxygen delivery to tissues(Santos & Maia, 2010).

Beyond these hematologic effects, Hydroxyurea acts as a nitric oxide donor, contributing to its vasodilatory properties. This nitric oxide donation helps in relaxing blood vessels, further enhancing blood flow and reducing the risk of vaso-occlusion(Taylor et al., 2021). In the context of PASC, characterized by chronic inflammation and endothelial dysfunction, Hydroxyurea's anti-inflammatory and vasodilatory effects are particularly beneficial. These properties help in alleviating persistent symptoms such as fatigue, dyspnea, and joint pain, which are common in PASC(Dri et al., 2023). By addressing both the underlying hemoglobin abnormalities and the systemic inflammatory responses, Hydroxyurea provides a multifaceted therapeutic approach that is especially relevant for SCD patients grappling with the long-term impacts of COVID-19(Telen et al., 2019)

Comparative Analyses

Comparative studies evaluating Hydroxyurea against other therapeutic interventions for sickle cell disease (SCD) and post-acute sequelae of COVID-19 (PASC) reveal its significant advantages in reducing morbidity and improving patient outcomes(Foster et al., 2021). Hydroxyurea, a well-established treatment, has been benchmarked against newer therapies such as voxelotor, crizanlizumab, and L-glutamine(Nevitt et al., 2017). While these newer agents offer specific benefits, such as voxelotor's ability to increase hemoglobin levels and crizanlizumab's reduction of vaso-occlusive crises, Hydroxyurea remains a cornerstone due to its broad efficacy, affordability, and long-term safety profile(Meier et al., 2020). Its ability to induce fetal hemoglobin, reduce inflammation, and lower the incidence of complications positions it as a highly effective option for SCD management, particularly in resource-limited settings where newer therapies might not be as accessible(Demirci et al., 2021).

Moreover, Hydroxyurea's role in managing PASC among SCD patients is gaining recognition. Comparative analyses suggest that Hydroxyurea's anti-inflammatory properties and capacity to mitigate sickle cell-related complications can significantly improve outcomes for patients suffering from the persistent effects of COVID-19(Gohal et al., 2022). While the newer treatments are promising, they often lack extensive longitudinal data and might be cost-prohibitive for widespread use. Hydroxyurea's established history, coupled with its multifaceted benefits, makes it a critical component of therapeutic strategies aimed at improving the quality of life and long-term health outcomes for SCD patients, particularly those dealing with the added burden of PASC(McGann & Ware, 2015). Further research comparing these treatments' long-term effects and cost-effectiveness will be essential to optimize care for this vulnerable population

Discussion:-

The findings from this narrative review underscore the potential benefits of Hydroxyurea in improving outcomes for sickle cell disease (SCD) patients experiencing post-acute sequelae of COVID-19 (PASC)(Badawy et al., 2022). Hydroxyurea's well-documented efficacy in managing SCD complications, such as reducing the frequency of vaso-occlusive crises and acute chest syndrome, provides a strong foundation for its potential utility in the context of PASC(Ofakunrin et al., 2020). The review highlights that Hydroxyurea's anti-inflammatory properties and its role in inducing fetal hemoglobin (HbF) production could be particularly beneficial for SCD patients dealing with the chronic inflammation and hypercoagulable state associated with PASC(Lebensburger et al., 2010). These findings are significant as they suggest a dual benefit of Hydroxyurea: managing the underlying SCD and potentially alleviating PASC symptoms, thus improving the overall quality of life for these patients.

Moreover, the review suggests that Hydroxyurea may help reduce the frequency and severity of pulmonary complications, which are common in both SCD and PASC. This is particularly important given that SCD patients are at higher risk for severe COVID-19 outcomes and prolonged recovery phases. By potentially mitigating these complications, Hydroxyurea could play a crucial role in reducing the long-term health burden on SCD patients, thereby enhancing their overall health and daily functioning(Sayad et al., 2021). These findings support the broader use of Hydroxyurea in clinical practice for SCD patients, particularly those who have recovered from COVID-19 but are experiencing prolonged symptoms(Alsayegh & Mousa, 2020).

The findings of this narrative review align with existing literature on the benefits of Hydroxyurea in managing SCD. Numerous studies have demonstrated Hydroxyurea's efficacy in reducing the frequency of painful crises, acute chest syndrome, and the need for blood transfusions, which are critical in managing the chronic aspects of SCD(El-Hazini et al., 1992). Additionally, the literature supports the notion that Hydroxyurea improves hemoglobin levels and reduces hemolysis markers, which can contribute to better overall health outcomes for SCD patients(Voskaridou et al., 2010).

When compared to newer treatments such as voxelotor and crizanlizumab, Hydroxyurea remains a cornerstone therapy for SCD due to its broad efficacy and affordability. While voxelotor and crizanlizumab offer specific benefits, such as increasing hemoglobin levels and reducing vaso-occlusive crises respectively, they often come with higher costs and less extensive longitudinal data(Tayyaba Rehan et al., 2022). The comparative advantage of Hydroxyurea lies in its established history and comprehensive benefits across multiple SCD complications. Furthermore, existing literature on PASC indicates that chronic inflammation and coagulopathy are significant issues for SCD patients post-COVID-19(Guthrie, 1995). Hydroxyurea's anti-inflammatory properties and ability to reduce leukocyte and reticulocyte counts may help address these issues, providing a possible mechanism for its effectiveness in mitigating PASC symptoms in SCD patients(Barak et al., 2024).

Limitations

Despite the promising findings, this narrative review has several limitations that need to be addressed. Firstly, the review is based on existing literature, and there may be a publication bias towards positive findings. Studies that did not show significant benefits of Hydroxyurea may be underrepresented, potentially skewing the overall conclusions. Secondly, the review includes studies with varying methodologies and patient populations, which can introduce heterogeneity and affect the comparability of the results.

Additionally, the long-term effects of Hydroxyurea on PASC in SCD patients are not yet fully understood. Most of the studies included in the review focus on the short-term benefits of Hydroxyurea, and more research is needed to evaluate its long-term impact on PASC symptoms. Furthermore, the potential adverse effects of long-term Hydroxyurea use, such as myelosuppression and teratogenicity, need to be carefully monitored, especially in the context of chronic conditions like PASC. Finally, the review is limited by the availability of high-quality studies specifically examining the impact of Hydroxyurea on PASC in SCD patients. More targeted research is needed to draw definitive conclusions and guide clinical practice.

Future Research Directions:-

Given the limitations and the emerging nature of PASC, several areas for future research are suggested. Longitudinal studies are needed to evaluate the long-term impact of Hydroxyurea on PASC symptoms in SCD patients. These studies should aim to provide a comprehensive understanding of the benefits and potential risks of prolonged Hydroxyurea therapy. Additionally, research should focus on optimizing dosing strategies to maximize the therapeutic benefits while minimizing adverse effects.

Further investigations are also warranted to explore the molecular mechanisms underlying the benefits of Hydroxyurea in the context of PASC. Understanding these mechanisms could lead to the development of targeted therapies that address specific aspects of PASC in SCD patients. Moreover, comparative studies evaluating Hydroxyurea against newer therapies like voxelotor and crizanlizumab will be essential to determine the most effective treatment strategies for managing PASC in SCD patients.

Another critical area for future research is the exploration of combination therapies. Studies should investigate the potential synergistic effects of Hydroxyurea with other treatments, such as anti-inflammatory drugs or anticoagulants, to provide a more comprehensive approach to managing PASC in SCD patients. Additionally, research should focus on the role of supportive care interventions, such as physical rehabilitation and psychological support, in improving the overall outcomes for SCD patients with PASC.

Conclusion:-

This narrative review highlights the potential benefits of Hydroxyurea in improving outcomes for sickle cell disease (SCD) patients experiencing post-acute sequelae of COVID-19 (PASC). Hydroxyurea's established role in reducing the frequency of vaso-occlusive crises, acute chest syndrome, and the need for blood transfusions in SCD patients is

well-documented. The review further suggests that Hydroxyurea's anti-inflammatory properties and its ability to induce fetal hemoglobin (HbF) production could be particularly beneficial in managing the chronic inflammation and pulmonary complications associated with PASC.

The comparative analysis with newer treatments such as voxelotor and crizanlizumab underscores Hydroxyurea's continued relevance due to its efficacy, affordability, and extensive safety profile. While the emerging therapies offer specific benefits, Hydroxyurea remains a cornerstone treatment for SCD, particularly in resource-limited settings.

The potential mechanisms by which Hydroxyurea could impact PASC in SCD patients, including its anti-inflammatory effects, nitric oxide donation properties, and reduction of leukocyte and reticulocyte counts, provide a plausible explanation for its effectiveness in this context. However, the review also identifies significant limitations, including the variability in study methodologies and the need for more targeted research on Hydroxyurea's long-term impact on PASC.

Future research should focus on longitudinal studies to assess the enduring effects of Hydroxyurea, optimal dosing strategies, and potential combination therapies to enhance its benefits. By addressing these research gaps, future studies can provide deeper insights into the optimal management of PASC in SCD patients, ultimately improving their quality of life and long-term health outcomes

References:-

1. Aboderin, F. I., Oduola, T., Davison, G. M., & Oguntibeju, O. O. (2023). A Review of the Relationship between the Immune Response, Inflammation, Oxidative Stress, and the Pathogenesis of Sickle Cell Anaemia. Biomedicines, 11(9), 2413. https://doi.org/10.3390/biomedicines11092413
2. Acquazzino, M. A., Miller, M., Myrvik, M., Newby, R., & Scott, J. P. (2017). Attention Deficit Hyperactivity Disorder in Children With Sickle Cell Disease Referred for an Evaluation. Journal of Pediatric Hematology/Oncology, 39(5), 350–354. https://doi.org/10.1097/MPH.0000000000000847
3. Agrawal, R. K., Patel, R. K., Shah, V., Nainiwal, L., & Trivedi, B. (2014). Hydroxyurea in Sickle Cell Disease: Drug Review. Indian Journal of Hematology and Blood Transfusion, 30(2), 91–96. https://doi.org/10.1007/s12288-013-0261-4
4. Alsayegh, F., & Mousa, S. A. (2020). Challenges in the Management of Sickle Cell Disease During SARS-CoV-2 Pandemic. Clinical and Applied Thrombosis/Hemostasis, 26, 107602962095524. https://doi.org/10.1177/1076029620955240
5. Azmet, F. R., Al-Kasim, F., Alashram, W. M., & Siddique, K. (2020). The role of hydroxyurea in decreasing the occurrence of vasso-occulusive crisis in pediatric patients with sickle cell disease at King Saud Medical City in Riyadh, Saudi Arabia. Saudi Medical Journal, 41(1), 46–52. https://doi.org/10.15537/smj.2020.1.24698
6. Badawy, S. M., DiMartino, L., Brambilla, D., Klesges, L., Baumann, A., Burns, E., DeMartino, T., Jacobs, S., Khan, H., Nwosu, C., Shah, N., & Hankins, J. S. (2022). Impact of the COVID-19 Pandemic on the Implementation of Mobile Health to Improve the Uptake of Hydroxyurea in Patients With Sickle Cell Disease: Mixed Methods Study. JMIR Formative Research, 6(10), e41415. https://doi.org/10.2196/41415
7. Ballas, S. K., Barton, F. B., Waclawiw, M. A., Swerdlow, P., Eckman, J. R., Pegelow, C. H., Koshy, M., Barton, B. A., & Bonds, D. R. (2006). Hydroxyurea and sickle cell anemia: effect on quality of life. Health and Quality of Life Outcomes, 4(1), 59. https://doi.org/10.1186/1477-7525-4-59
8. Barak, M., Hu, C., Matthews, A., & Fortenberry, Y. M. (2024). Current and Future Therapeutics for Treating Patients with Sickle Cell Disease. Cells, 13(10), 848. https://doi.org/10.3390/cells13100848
9. Beavers, C. J., Rodgers, J. E., Bagnola, A. J., Beckie, T. M., Campia, U., Di Palo, K. E., Okwuosa, T. M., Przespolewski, E. R., & Dent, S. (2022). Cardio-Oncology Drug Interactions: A Scientific Statement From the American Heart Association. Circulation, 145(15). https://doi.org/10.1161/CIR.0000000000001056
10. Beutler, E. (1972). Disorders Due to Enzyme Defects in the Red Blood Cell (pp. 131–160). https://doi.org/10.1016/B978-0-12-027306-5.50010-3
11. Brandow, A. M., Carroll, C. P., Creary, S., Edwards-Elliott, R., Glassberg, J., Hurley, R. W., Kutlar, A., Seisa, M., Stinson, J., Strouse, J. J., Yusuf, F., Zempsky, W., & Lang, E. (2020). American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. Blood Advances, 4(12), 2656–2701. https://doi.org/10.1182/bloodadvances.2020001851
12. Cai, M., Xie, Y., Topol, E. J., & Al-Aly, Z. (2024). Three-year outcomes of post-acute sequelae of COVID-19. Nature Medicine, 30(6), 1564–1573. https://doi.org/10.1038/s41591-024-02987-8

13. Charache, S. (1997). Mechanism of action of hydroxyurea in the management of sickle cell anemia in adults. Seminars in Hematology, 34(3 Suppl 3), 15–21. http://www.ncbi.nlm.nih.gov/pubmed/9317197
14. Chehelgerdi, M., Behdarvand Dehkordi, F., Chehelgerdi, M., Kabiri, H., Salehian-Dehkordi, H., Abdolvand, M., Salmanizadeh, S., Rashidi, M., Niazmand, A., Ahmadi, S., Feizbakhshan, S., Kabiri, S., Vatandoost, N., & Ranjbarnejad, T. (2023). Exploring the promising potential of induced pluripotent stem cells in cancer research and therapy. Molecular Cancer, 22(1), 189. https://doi.org/10.1186/s12943-023-01873-0
15. Chiang, K. C., Gupta, A., Sundd, P., & Krishnamurti, L. (2023). Thrombo-Inflammation in COVID-19 and Sickle Cell Disease: Two Faces of the Same Coin. Biomedicines, 11(2), 338. https://doi.org/10.3390/biomedicines11020338
16. Chianumba, R. I., Ofakunrin, A. O. D., Morrice, J., Olanrewaju, O., Oniyangi, O., Kuliya-Gwarzo, A., Nnebe-Agumadu, U., Isa, H. A., & Nnodu, O. E. (2022). Outcome of Hydroxyurea Use in SCD and Evaluation of Patients' Perception and Experience in Nigeria. Frontiers in Genetics, 13. https://doi.org/10.3389/fgene.2022.826132
17. Christian, J., Lanzkron, S., & Naik, R. P. (2022). COVID-19 outcomes in sickle cell disease and sickle cell trait. Best Practice & Research Clinical Haematology, 35(3), 101382. https://doi.org/10.1016/j.beha.2022.101382
18. de França, E. R., Teixeira, M. A. G., Matias, K. de F., Antunes, D. E. C. M., Braz, R. de A., & Silva, C. E. F. (2011). Cutaneous effects after prolongaded use of hydroxyurea in Polycythemia Vera. Anais Brasileiros de Dermatologia, 86(4), 751–754. https://www.scielo.br/j/abd/a/yQLhSBd8vj58sT63YPkGgWK/?lang=en
19. Demirci, S., Leonard, A., Essawi, K., & Tisdale, J. F. (2021). CRISPR-Cas9 to induce fetal hemoglobin for the treatment of sickle cell disease. Molecular Therapy - Methods & Clinical Development, 23, 276–285. https://doi.org/10.1016/j.omtm.2021.09.010
20. Dri, E., Lampas, E., Lazaros, G., Lazarou, E., Theofilis, P., Tsioufis, C., & Tousoulis, D. (2023). Inflammatory Mediators of Endothelial Dysfunction. Life, 13(6), 1420. https://doi.org/10.3390/life13061420
21. Egesa, W. I., Nakalema, G., Waibi, W. M., Turyasiima, M., Amuje, E., Kiconco, G., Odoch, S., Kumbakulu, P. K., Abdirashid, S., & Asiimwe, D. (2022). Sickle Cell Disease in Children and Adolescents: A Review of the Historical, Clinical, and Public Health Perspective of Sub-Saharan Africa and Beyond. International Journal of Pediatrics, 2022, 1–26. https://doi.org/10.1155/2022/3885979
22. El-Hazini, M. A. F., Warsy, A. S., Al-Momen, A., & Harakati, M. (1992). Hydroxyurea for the treatment of sickle cell disease. Acta Haematologica, 88(4), 170–174. https://doi.org/10.1159/000204681
23. Foster, M. R. B., Hijazi, A. A., Opoku, R., Varghese, P., & Li, C. (2021). The Use of Hydroxyurea in the Treatment of COVID-19. The Journal of Critical Care Medicine, 7(4), 312–317. https://doi.org/10.2478/jccm-2021-0019
24. Gohal, G. A., Gosadi, I. M., Cittana Iqbal, B. A., Ghazwani, Y. H., Daghriri, A. M., Shugairi, A. A., Daghriri, K. A., Zurayyir, A. J., Nemri, A. A., & Abdulhaq, M. A. (2022). Utilization of Hydroxyurea Among Patients Diagnosed with Sickle Cell Disease in Jazan, Saudi Arabia. Patient Preference and Adherence, Volume 16, 3059–3067. https://doi.org/10.2147/PPA.S390568
25. Guthrie, T. (1995). Hydroxyurea for sickle cell. P and T, 20(7), 497–498.
26. Hill, E., Mehta, H., Sharma, S., Mane, K., Xie, C., Cathey, E., Loomba, J., Russell, S., Spratt, H., DeWitt, P. E., Ammar, N., Madlock-Brown, C., Brown, D., McMurry, J. A., Chute, C. G., Haendel, M. A., Moffitt, R., Pfaff, E. R., Bennett, T. D., … RECOVER Consortium. (2022). Risk Factors Associated with Post-Acute Sequelae of SARS-CoV-2 in an EHR Cohort: A National COVID Cohort Collaborative (N3C) Analysis as part of the NIH RECOVER program. MedRxiv : The Preprint Server for Health Sciences. https://doi.org/10.1101/2022.08.15.22278603
27. Hoogenboom, W. S., Alamuri, T. T., McMahon, D. M., Balanchivadze, N., Dabak, V., Mitchell, W. B., Morrone, K. B., Manwani, D., & Duong, T. Q. (2022). Clinical outcomes of COVID-19 in patients with sickle cell disease and sickle cell trait: A critical appraisal of the literature. Blood Reviews, 53, 100911. https://doi.org/10.1016/j.blre.2021.100911
28. Houwing, M. E., de Pagter, P. J., van Beers, E. J., Biemond, B. J., Rettenbacher, E., Rijneveld, A. W., Schols, E. M., Philipsen, J. N. J., Tamminga, R. Y. J., van Draat, K. F., Nur, E., & Cnossen, M. H. (2019). Sickle cell disease: Clinical presentation and management of a global health challenge. Blood Reviews, 37, 100580. https://doi.org/10.1016/j.blre.2019.05.004
29. Ilesanmi, O. O. (2010). Pathological basis of symptoms and crises in sickle cell disorder: implications for counseling and psychotherapy. Hematology Reports, 2(1), 2. https://doi.org/10.4081/hr.2010.e2
30. Kakavandi, S., Hajikhani, B., Azizi, P., Aziziyan, F., Nabi-Afjadi, M., Farani, M. R., Zalpoor, H., Azarian, M., Saadi, M. I., Gharesi-Fard, B., Terpos, E., Zare, I., & Motamedifar, M. (2024). COVID-19 in patients with

anemia and haematological malignancies: risk factors, clinical guidelines, and emerging therapeutic approaches. Cell Communication and Signaling, 22(1), 126. https://doi.org/10.1186/s12964-023-01316-9
31. Kanter, J., & Kruse-Jarres, R. (2013). Management of sickle cell disease from childhood through adulthood. Blood Reviews, 27(6), 279–287. https://doi.org/10.1016/j.blre.2013.09.001
32. Kilonzi, M., Mwakawanga, D. L., Felician, F. F., Mlyuka, H. J., Chirande, L., Myemba, D. T., Sambayi, G., Mutagonda, R. F., Mikomangwa, W. P., Ndunguru, J., Jonathan, A., Ruggajo, P., Minja, I. K., Balandya, E., Makani, J., & Sirili, N. (2022). The Effects of Sickle Cell Disease on the Quality of Life: A Focus on the Untold Experiences of Parents in Tanzania. International Journal of Environmental Research and Public Health, 19(11), 6871. https://doi.org/10.3390/ijerph19116871
33. Lebensburger, J. D., Pestina, T. I., Ware, R. E., Boyd, K. L., & Persons, D. A. (2010). Hydroxyurea therapy requires HbF induction for clinical benefit in a sickle cell mouse model. Haematologica, 95(9), 1599–1603. https://doi.org/10.3324/haematol.2010.023325
34. Mantovani, A., Morrone, M. C., Patrono, C., Santoro, M. G., Schiaffino, S., Remuzzi, G., Bussolati, G., Cappuccinelli, P., Fitzgerald, G., Bacci, M. L., Melino, G., Parisi, G., Rappuoli, R., Rezza, G., & Vineis, P. (2022). Long Covid: where we stand and challenges ahead. Cell Death & Differentiation. https://doi.org/10.1038/s41418-022-01052-6
35. McCormick, M., Osei-Anto, H. A., & Martinez, R. M. (2021). Addressing sickle cell disease. In Addressing Sickle Cell Disease. https://doi.org/10.17226/25632
36. McGann, P. T., & Ware, R. E. (2011). Hydroxyurea for sickle cell anemia: what have we learned and what questions still remain? Current Opinion in Hematology, 18(3), 158–165. https://doi.org/10.1097/MOH.0b013e32834521dd
37. McGann, P. T., & Ware, R. E. (2015). Hydroxyurea therapy for sickle cell anemia. Expert Opinion on Drug Safety, 14(11), 1749–1758. https://doi.org/10.1517/14740338.2015.1088827
38. Meier, E. R., Creary, S. E., Heeney, M. M., Dong, M., Appiah-Kubi, A. O., Nelson, S. C., Niss, O., Piccone, C., Quarmyne, M.-O., Quinn, C. T., Saving, K. L., Scott, J. P., Talati, R., Latham, T. S., Pfeiffer, A., Shook, L. M., Vinks, A. A., Lane, A., & McGann, P. T. (2020). Hydroxyurea Optimization through Precision Study (HOPS): study protocol for a randomized, multicenter trial in children with sickle cell anemia. Trials, 21(1), 983. https://doi.org/10.1186/s13063-020-04912-z
39. Michelon, I., Vilbert, M., Pinheiro, I. S., Costa, I. L., Lorea, C. F., Castonguay, M., Tran, T. H., & Forté, S. (2023). COVID-19 outcomes in patients with sickle cell disease and sickle cell trait compared with individuals without sickle cell disease or trait: a systematic review and meta-analysis. EClinicalMedicine, 66, 102330. https://doi.org/10.1016/j.eclinm.2023.102330
40. Munipalli, B., Seim, L., Dawson, N. L., Knight, D., & Dabrh, A. M. A. (2022). Post-acute sequelae of COVID-19 (PASC): a meta-narrative review of pathophysiology, prevalence, and management. SN Comprehensive Clinical Medicine, 4(1), 90. https://doi.org/10.1007/s42399-022-01167-4
41. Nevitt, S. J., Jones, A. P., & Howard, J. (2017). Hydroxyurea (hydroxycarbamide) for sickle cell disease. Cochrane Database of Systematic Reviews, 2017(4). https://doi.org/10.1002/14651858.CD002202.pub2
42. Ofakunrin, A. O. D., Oguche, S., Adekola, K., Okpe, E. S., Afolaranmi, T. O., Diaku-Akinwumi, I. N., Zoakah, A. I., & Sagay, A. S. (2020). Effectiveness and Safety of Hydroxyurea in the Treatment of Sickle Cell Anaemia Children in Jos, North Central Nigeria. Journal of Tropical Pediatrics, 66(3), 290–298. https://doi.org/10.1093/tropej/fmz070
43. Oikonomou, E., Souvaliotis, N., Lampsas, S., Siasos, G., Poulakou, G., Theofilis, P., Papaioannou, T. G., Haidich, A.-B., Tsaousi, G., Ntousopoulos, V., Sakka, V., Charalambous, G., Rapti, V., Raftopoulou, S., Syrigos, K., Tsioufis, C., Tousoulis, D., & Vavuranakis, M. (2022). Endothelial dysfunction in acute and long standing COVID−19: A prospective cohort study. Vascular Pharmacology, 144, 106975. https://doi.org/10.1016/j.vph.2022.106975
44. Osunkwo, I., Manwani, D., & Kanter, J. (2020). Current and novel therapies for the prevention of vaso-occlusive crisis in sickle cell disease. Therapeutic Advances in Hematology, 11, 204062072095500. https://doi.org/10.1177/2040620720955000
45. Otsuka, Y., & Kobayashi, T. (2020). Case Report: A Patient with COVID-19 under Myelosuppression Induced by Chemotherapy. The American Journal of Tropical Medicine and Hygiene, 103(5), 1983–1985. https://doi.org/10.4269/ajtmh.20-0678
46. Paldor, I., Awad, M., Sufaro, Y. Z., Kaye, A. H., & Shoshan, Y. (2016). Review of controversies in management of non-benign meningioma. Journal of Clinical Neuroscience, 31, 37–46. https://doi.org/10.1016/j.jocn.2016.03.014

47. Pedrosa, A. M., Leal, L. K. A. M., & Lemes, R. P. G. (2021). Effects of hydroxyurea on cytotoxicity, inflammation and oxidative stress markers in neutrophils of patients with sickle cell anemia: dose-effect relationship. Hematology, Transfusion and Cell Therapy, 43(4), 468–475. https://doi.org/10.1016/j.htct.2020.07.011
48. Pule, G. D., Mowla, S., Novitzky, N., Wiysonge, C. S., & Wonkam, A. (2015). A systematic review of known mechanisms of hydroxyurea-induced fetal hemoglobin for treatment of sickle cell disease. Expert Review of Hematology, 8(5), 669–679. https://doi.org/10.1586/17474086.2015.1078235
49. Sahu, T., Pande, B., Verma, H. K., Bhaskar, L. V. K. S., Sinha, M., Sinha, R., & Rao, P. V. (2023). Infection and Potential Challenge of Childhood Mortality in Sickle Cell Disease: A Comprehensive Review of the Literature from a Global Perspective. Thalassemia Reports, 13(3), 206–229. https://doi.org/10.3390/thalassrep13030019
50. Santos, F. K. de S., & Maia, C. N. (2010). Patients with sickle cell disease taking hydroxyurea in the Hemocentro Regional de Montes Claros. Revista Brasileira de Hematologia e Hemoterapia, 33(2), 105–109. https://doi.org/10.5581/1516-8484.20110029
51. Sayad, B., Karimi, M., & Rahimi, Z. (2021). Sickle cell disease and COVID-19: Susceptibility and severity. Pediatric Blood & Cancer, 68(8). https://doi.org/10.1002/pbc.29075
52. Shyam Sunder, S., Sharma, U. C., & Pokharel, S. (2023). Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. Signal Transduction and Targeted Therapy, 8(1), 262. https://doi.org/10.1038/s41392-023-01469-6
53. Silva-Pinto, A. C., Angulo, I. L., Brunetta, D. M., Neves, F. I. R., Bassi, S. C., Santis, G. C. De, & Covas, D. T. (2013). Clinical and hematological effects of hydroxyurea therapy in sickle cell patients: a single-center experience in Brazil. Sao Paulo Medical Journal, 131(4), 238–243. https://doi.org/10.1590/1516-3180.2013.1314467
54. Silva, D. G. H., Belini Junior, E., de Almeida, E. A., & Bonini-Domingos, C. R. (2013). Oxidative stress in sickle cell disease: An overview of erythrocyte redox metabolism and current antioxidant therapeutic strategies. Free Radical Biology and Medicine, 65, 1101–1109. https://doi.org/10.1016/j.freeradbiomed.2013.08.181
55. Smith, W. R., Ballas, S. K., Mccarthy, W. F., Bauserman, R. L., Swerdlow, P. S., Steinberg, M. H., & Waclawiw, M. A. (2011). The Association Between Hydroxyurea Treatment and Pain Intensity, Analgesic Use, and Utilization in Ambulatory Sickle Cell Anemia Patients. Pain Medicine, 12(5), 697–705. https://doi.org/10.1111/j.1526-4637.2011.01096.x
56. Steinberg, M. H., Chui, D. H. K., Dover, G. J., Sebastiani, P., & Alsultan, A. (2014). Fetal hemoglobin in sickle cell anemia: a glass half full? Blood, 123(4), 481–485. https://doi.org/10.1182/blood-2013-09-528067
57. Sysol, J. R., & Machado, R. (2017). Sickle Cell Disease and Acute Chest Syndrome: Epidemiology, Diagnosis, Management, Outcomes (pp. 67–87). https://doi.org/10.1007/978-3-319-41912-1_4
58. Taylor, C. M., Kasztan, M., Sedaka, R., Molina, P. A., Dunaway, L. S., Pollock, J. S., & Pollock, D. M. (2021). Hydroxyurea improves nitric oxide bioavailability in humanized sickle cell mice. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 320(5), R630–R640. https://doi.org/10.1152/ajpregu.00205.2020
59. Tayyaba Rehan, S., Hussain, H. ul, Malik, F., Usama, R. M., Tahir, M. J., & Asghar, M. S. (2022). Voxelotor versus other therapeutic options for sickle cell disease: Are we still lagging behind in treating the disease? Health Science Reports, 5(4). https://doi.org/10.1002/hsr2.713
60. Telen, M. J. (2016). Beyond hydroxyurea: new and old drugs in the pipeline for sickle cell disease. Blood, 127(7), 810–819. https://doi.org/10.1182/blood-2015-09-618553
61. Telen, M. J., Malik, P., & Vercellotti, G. M. (2019). Therapeutic strategies for sickle cell disease: towards a multi-agent approach. Nature Reviews Drug Discovery, 18(2), 139–158. https://doi.org/10.1038/s41573-018-0003-2
62. Teresa Santiago, M., Feld, L., Dhar, A., Nyka Christian-Weekes, L., Appiah-Kubi, A., Mitchell, E., Aygun, B., & K. Fiorino, E. (2024). Cardiopulmonary Complications of Sickle Cell Disease in Children. In Current Practices in Sickle Cell Disease [Working Title]. IntechOpen. https://doi.org/10.5772/intechopen.1005507
63. Thaweethai, T., Jolley, S. E., Karlson, E. W., Levitan, E. B., Levy, B., McComsey, G. A., McCorkell, L., Nadkarni, G. N., Parthasarathy, S., Singh, U., Walker, T. A., Selvaggi, C. A., Shinnick, D. J., Schulte, C. C. M., Atchley-Challenner, R., Horwitz, L. I., Foulkes, A. S., Aberg, J. A., Adolphi, N. L., … Zisis, S. (2023). Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. JAMA, 329(22), 1934. https://doi.org/10.1001/jama.2023.8823

64. Toumi, M. L., Merzoug, S., & Boulassel, M. R. (2018). Does sickle cell disease have a psychosomatic component? A particular focus on anxiety and depression. Life Sciences, 210, 96–105. https://doi.org/10.1016/j.lfs.2018.08.066
65. van Dijk, M. J., de Wilde, J. R. A., Bartels, M., Kuo, K. H. M., Glenthøj, A., Rab, M. A. E., van Beers, E. J., & van Wijk, R. (2023). Activation of pyruvate kinase as therapeutic option for rare hemolytic anemias: Shedding new light on an old enzyme. Blood Reviews, 61, 101103. https://doi.org/10.1016/j.blre.2023.101103
66. Voskaridou, E., Christoulas, D., Bilalis, A., Plata, E., Varvagiannis, K., Stamatopoulos, G., Sinopoulou, K., Balassopoulou, A., Loukopoulos, D., & Terpos, E. (2010). The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). Blood, 115(12), 2354–2363. https://doi.org/10.1182/blood-2009-05-221333
67. Wang, C., Ramasamy, A., Verduzco-Gutierrez, M., Brode, W. M., & Melamed, E. (2023). Acute and post-acute sequelae of SARS-CoV-2 infection: a review of risk factors and social determinants. Virology Journal, 20(1), 124. https://doi.org/10.1186/s12985-023-02061-8
68. Ware, R. E. (2010). How I use hydroxyurea to treat young patients with sickle cell anemia. Blood, 115(26), 5300–5311. https://doi.org/10.1182/blood-2009-04-146852
69. Xu, J. Z., & Thein, S. L. (2022). Revisiting anemia in sickle cell disease and finding the balance with therapeutic approaches. Blood, 139(20), 3030–3039. https://doi.org/10.1182/blood.2021013873.