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Review on Hydroxyurea Usage in Young Children with Sickle Cell Disease: Examining Hemoglobin Induction, Potential Benefits, Responses, Safety, and Effectiveness

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Abstract

Sickle cell disease (SCD) is a prevalent condition, particularly in the countries of sub-Saharan Africa, where the presence of specific genes associated with Malaria contributes to its high prevalence. Patients with sickle cell disease frequently experience painful episodes necessitating hospitalization, and their hemoglobin levels are typically lower than those of the general population. There are different treatment options available to manage complications, such as transfusing blood, hydroxyurea, and strong anti-pains. However, with all these treatments, patients still commonly experience pain crises and suffer from organ damage. Hydroxyurea, the sole approved medication for sickle cell anemia in developed and developing countries, is widely used in children despite being primarily indicated for adults. Multiple studies have demonstrated the efficacy of hydroxyurea in inducing HbF production in young children with SCD. Elevated HbF levels have been associated with improved clinical outcomes, including a reduction in vaso-occlusive crises, acute chest syndrome, and the need for blood transfusions. Furthermore, increased HbF levels have been shown to ameliorate disease-related organ damage, such as pulmonary hypertension and sickle cell retinopathy. The response to hydroxyurea treatment in young children with SCD is variable. Some patients achieve substantial increases in HbF levels and experience significant clinical benefits, while others may have a more modest response. Factors influencing the response include baseline HbF levels, genetic modifiers, treatment adherence, and dose optimization. Safety is a crucial consideration when using hydroxyurea in young children. Studies have shown that hydroxyurea is generally well-tolerated, with the most common adverse effects being myelosuppression, gastrointestinal symptoms, and dermatological manifestations. However,

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long-term effects and potential risks, such as renal dysfunction and reproductive impacts, require further investigation. The effectiveness of hydroxyurea in young children with SCD has been demonstrated in various clinical trials and observational studies. These studies have shown a significant reduction in disease-related complications and improved quality of life. However, optimal dosing, treatment duration, and long-term outcomes are still areas of ongoing research. This review focuses on recent studies investigating the benefits, effectiveness, responses, and safety of hydroxyurea in pediatric individuals diagnosed with sickle cell disease.

Keywords

Effectiveness, Hydroxyurea, Sickle Cell Disease, Sickle Cell Anemia, Minimally Effective Dose, Maximum Tolerated Dose

1. Introduction

A widespread and heritable disease, Sickle cell disease (SCD) affects millions of people in the world, with significant impact and healthcare costs in the world. Particularly in European countries, hundreds of thousands of people, primarily of African descent, have Sickle cell disease, and newborn screening identifies approximately 1:375 African-American infants with the disease every year. While the average lifespan of sicklers for publically insured individuals with SCD is 56 years, males' life expectancy at birth is 49.3 years, which is lower than that for females (at birth 55 years), but in well-resourced countries can live up to 70 years as adults. However, underdeveloped countries, particularly in sub-Saharan Africa, experience a high mortality rate of 50% - 80% within the first five years of life. Recognizing the severity of this issue, the WHO declared Sickle cell disease a world health problem in 2006, emphasizing the urgent need for accessible and effective treatment options worldwide [1] [2] [3].

According to the Centers for Disease Control and Prevention (CDC) in the United States, SCD affects approximately 100,000 Americans. The CDC estimates that about 1 in 365 African-American births and 1 in 16,300 Hispanic-American births are affected by SCD [4]. The UK Sickle Cell Society estimates that there are around 12,500 individuals living with SCD in the UK [5]. Nevertheless, SCD is prevalent among individuals of African and Afro-descendant populations in Brazil. Exact prevalence figures for SCD in Brazil may vary as estimates range from 25,000 to 30,000 individuals affected [6].

Sub-Saharan Africa is where the majority of these births take place, and it ranges from 50% to 90% of children having anemia-associated Sickle cell disease, will not survive beyond the age of 5, often without being diagnosed. The presence of the heterozygous mutated sickle gene provides a significant survival advantage against malaria, which is why the frequency of this allele is highest in regions of Africa where malaria is prevalent [7].

Despite the existence of effective treatments to improve clinical outcomes, mortality remains alarmingly high among African children aged 6 months to 5 years, often before a confirmed diagnosis is made in this setting. This is likely due to delayed detection and intervention, which hampers efforts to alleviate the burden of this disease in the pediatric population [8].

The primary approach to treating patients with Sickle cell anemia (SCA) is generally supportive, hydroxyurea (HU) being the main drug used thus far. HU can modify the progression of the disease and has shown positive effects on clinical outcomes. It achieves this through raising levels of alpha-2 gamma-2 hemoglobin, which in turn reduces the occurrence of sickling events. In adults, HU decreases incidences of hospitalizations, episodes of acute chest syndrome, strokes, as well as painful crises, ultimately leading to improved quality of life [9].

In sickle cell anemia (SCA), fetal hemoglobin (HbF) levels play a protective role. However, it decreases significantly during the first year of life, but finally picks its lowest point at the age of 5. This particular value, commonly known as the “baseline” HbF level for each patient, is potentiated by genetic factors that are not well explained [10].

The primary mechanism by which fetal hemoglobin (HbF) provides protection against sickling is by downregulating the rate of hemoglobin S (HbS) combination inside the red blood cells. HbS concentration is diluted by HbF tetramers inside the cells and does not participate in the process of polymerization. Based on these discoveries, researchers aimed to find remedial substances that could stimulate HbF production. Among various effective compounds, hydroxyurea stood out. Although hydroxyurea is known for its potential toxicity, it has remained the primary focus of efforts to stimulate the production of alpha-2 gamma-2 hemoglobin due to its convenient oral administration and significant laboratory and clinical effects. In the early 1980s, straightforward yet impressive “proof-of-principle” research showcased the great advantages of hydroxyurea treatment for elderly patients having SCA [11].

Larger amounts of the drug in oral pulses of hydroxyurea have been shown to increase the presence of reticulocytes with elevated levels of alpha-2 gamma-2 hemoglobin in the systemic circulation. This leads to a whole rise in the amount of hemoglobin present in the bloodstream and the percentage of HbF, providing strong evidence of hydroxyurea’s ability to stimulate HbF production. Extensive research and clinical experience spanning three decades have established hydroxyurea as a great therapeutic agent for inducing alpha-2 gamma-2 hemoglobin in individuals with sickle cell anemia (SCA). It has demonstrated efficacy across all age groups, from infants to adults, and offers additional benefits such as mild suppression of bone marrow function, increased red blood cell size, reduced cellular adhesion, improved blood flow, and the potential to enhance nitric oxide release in affected areas [12].

Hydroxyurea functions by increasing the activity of the γ -globin gene, leading to a redirection of gene expression away from the β -globin gene. This shift re-

sults in higher levels of fetal hemoglobin (HbF: $\alpha 2\gamma 2$) and a reduction in the production of adult hemoglobin (HbA: $\alpha 2\beta 2$). Although hydroxyurea may lead to gastrointestinal side effects such as nausea and loss of appetite, the most notable adverse effect is myelosuppression, which impairs the bone marrow's ability to generate blood cells [13].

2. Molecular Explanation for HbF Gene Expression

The human HBB locus comprises five globin genes that undergo regulation throughout their development of different stages. During utero development, these genes are organized in a sequential manner that corresponds to the order of their expression: HBE1, HBG1, HBG2, HBD, and HBB. These genes are located on chromosome 11. The locus control region (LCR), located upstream of HBE1, plays a pivotal role in gene regulation. It consists of five DNase I hypersensitive sites that are specifically active in erythroid cells. Each LCR element contains enhancer sequences that bind to transcription factors, ensuring proper hemoglobin switching. The LCR plays a vital role in regulating the expression of the HBB locus by directly interacting with the promoters of individual globin genes. Several factors, such as transcription factors, epigenetic remodeling proteins, and DNA looping, contribute to facilitating this interaction [14].

DNA-binding proteins, including GATA1, TAL1, E2A, LMO2, LRF/ZBTB7, and LDB1, work together to boost gene transcription. They help create loops between the locus control region (LCR) and individual globin promoters. This looping is crucial for regulating the transcription of globin genes and ensuring their proper expression [15].

Extensive researches have focused on understanding the molecular mechanisms behind hemoglobin transition from fetal to adult form. These researches have been crucial for developing innovative drugs to treat sickle cell disease (SCD). Tightly regulated interactions between a locus control region and repressive transcription factors play a crucial role in governing the transcription of globin genes. One such factor, BCL11A, binds to the HBG promoters or the HBD/HBB intergenic region. BCL11A has emerged as a promising target for drug interventions that aim to increase HbF production effectively [15].

In 1948, Dr. Janet Watson noted that infants showed a delay in the emergence of clinical symptoms, which was linked to higher levels of HbF during their initial life of living [16].

Further support for the disease-modifying effects of alpha-2 gamma-2 comes from the occurrence of HbS in particular individuals, who also inherited a genetic variant causing the continuous presence of fetal hemoglobin (HbS-HPFH), generally exhibiting minimal symptoms associated with the condition [16]. The occurrence of alpha-2 gamma-2 in sickle red blood cells inhibits the development of deoxy-HbS polymers. Various hereditary persistence of fetal hemoglobin variants results from deletions in binding sites for factors within the HBB locus, reducing HbA production. In the process of globin gene switching, the

HBG promoter undergoes binding by negative transcription factors when mutations are present. However, across diverse populations, an increase in HBG expression in adults is observed due to a particular point mutation occurring in the Xmn1 site. The intergenic region of HBS1L-MYB and BCL11A has been identified through genetic mapping and studies as having quantitative trait loci that have a substantial impact on the regulation of HbF levels [17].

The ideal level of HbF to reduce the severity of clinical disease is a commonly asked question. Historical evidence suggests that HbF levels above 8.6% lead to fewer microvascular crises, episodes of pulmonary crisis with respiratory distress, and improved survival rates. HbF levels exceeding 20% also offer protection against strokes. Recent studies recommend using hydroxyurea in children to achieve an HbF level above 20%. Considering the allocation of HbF within erythrocytes is important for clinical effectiveness. Laboratory studies have shown that HbF can form hybrid hemoglobin molecules that inhibit the polymerization of HbS [17].

3. The Way by Which Hydroxyurea Induces the Production of Fetal Hemoglobin

Hydroxyurea is a potent compound that has anti-cancer and anti-metabolic properties. While the exact mechanism for its stimulation of fetal hemoglobin (HbF) production is not fully understood, however, it's believed that hydroxyurea induces a response known as "stress erythropoiesis," altering the timing of red blood cell differentiation and leads to the release of reticulocytes and erythrocytes having high levels of HbF. Hydroxyurea also interacts with heme-containing proteins, releasing nitric oxide (NO) that activates soluble guanosine monophosphate (sGC) and promotes HbF synthesis. In animal studies, it has been demonstrated that hydroxyurea activates the NO-sGC-cGMP and protein kinase cascades, leading to HBG activation. Hydroxyurea also affects the phosphorylation of specific proteins that participate in the maturation of erythrocytes and the expression of HBG (hemoglobin gamma). Ongoing research suggests that microRNAs, like miR-494, miR-26b, and miR-151-3p, may contribute to the variations in HbF levels observed in SCD patients treated with hydroxyurea. Hydroxyurea can downregulate genes such as BCL11A, KLF1, and MYB while upregulating miR-15a, miR-16-1, and TAL1. Methylation of CpG islands in the HBG2 promoter has also been correlated with HbF levels in individuals with sickle cell disease (SCD). To evaluate hydroxyurea's effectiveness, a hydroxyurea responsiveness index has been proposed, which considers changes in GATA-1, GATA-2, and BCL11A protein levels in cultured sickle cell precursors [18] (Figure 1).

Hydroxycarbamide induces fetal hemoglobin (HbF) through multiple mechanisms, impacting the symptoms of Sickle Cell Disease (SCD). Hydroxyurea triggers the generation of nitric oxide (NO), which activates soluble guanylyl cyclase (sGC). This activation sets off a signaling pathway known as cyclic guanosine monophosphate-protein kinase G (cGMP-PKG). As a result, p38 mitogen-activated

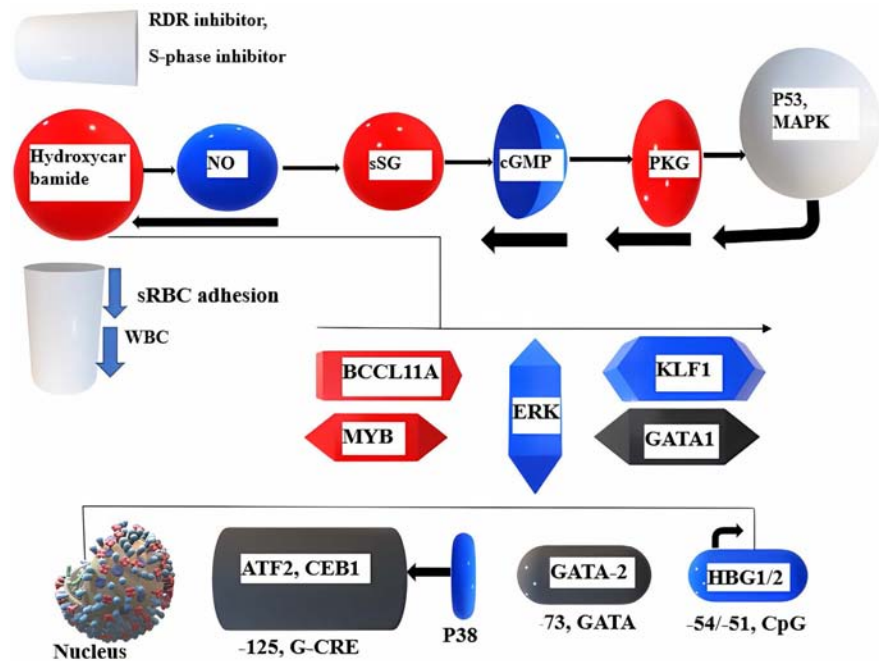


Figure 1. Fetal hemoglobin induction by Hydroxyurea.

protein kinase (MAPK) is phosphorylated, while extracellular signal-regulated kinase (ERK) MAPK is inhibited. The phosphorylated p38 MAPK then enters the nucleus and stimulates ATF2 and CREB1 transcription factors that are involved in the regulation of gene expression. Ultimately, this results in a rise in the expression of HBG2, the gene responsible for fetal hemoglobin production. Additionally, hydroxyurea targets ribonucleoside diphosphate reductase (RDR), affecting both red and white blood cells. Together, these mechanisms contribute to the therapeutic effects of hydroxyurea in sickle cell anemia.

3.1. Increased HbF Production by Hydroxyurea

Hydroxyurea increases HbF production by promoting the transcription of gamma-globin genes. The drug activates the enzyme ribonucleotide reductase, leading to an increase in intracellular levels of deoxyribonucleotide triphosphates (dNTPs). The elevated dNTP levels favor the incorporation of fetal hemoglobin subunits into newly synthesized hemoglobin molecules [19].

3.2. Impact of Hydroxyurea on SCD Pathophysiology

Hydroxyurea reduces the frequency of vaso-occlusive crises, acute chest syndrome, and the need for blood transfusions in SCD. It improves red blood cell hydration, therefore, reducing endothelial activation and adhesion molecule expression, and decreasing the release of pro-inflammatory cytokines. Hydroxyurea also decreases the expression of adhesion molecules on red blood cells, reducing their adherence to the endothelium and preventing vaso-occlusion [20] [21].

3.3. The FDA Has Given Its Approval for the Use of Hydroxyurea as a Treatment for Individuals with Sickle Cell Anemia

Hydroxyurea has been extensively used in clinical practice for over twenty years and has demonstrated its safety and efficacy. Although regular peripheral blood counts and chemistries monitoring are necessary, the side effects of hydroxyurea, such as bone marrow suppression, are mostly reversible. The standard of care for infants between the ages of 6 to 9 months diagnosed with sickle cell anemia (SCA) and adults experiencing severe clinical symptoms of sickle cell disease is highly recommended [22].

3.4. The Treatment Indications for Hydroxyurea

The clinical recommendations regarding the initiation of hydroxyurea therapy are continuously evolving, and there is currently no established consensus guideline. Hydroxyurea has undergone extensive experimental tests including infants, children, and adults, with sickle cell anemia (SCA). These trials consistently show that hydroxyurea is effective in reducing pain, episodes of pulmonary crisis, the requirement for blood infusions, and hospitalizations in individuals with SCA [23].

Clinical trials have confirmed the effectiveness of hydroxyurea therapy, which is considered based on various factors including the intensity and incidences of painful events and episodes of pulmonary crisis. Hydroxyurea is also prescribed for other conditions such as hand-foot syndrome, hemolytic anemia, increased cerebral blood flow velocities, failure to thrive or stunted growth, and repeated hospital stays. Additionally, hydroxyurea may help preserve or reverse organ insufficiency in patients with oxygen deficiency, albuminuria, or stroke. Disease severity markers, such as leukocytosis and reduced percentage of alpha-2 gamma-2, are taken into account. Ongoing researches will provide further insights into the effectiveness of hydroxyurea for different indications. Increasingly, families are requesting hydroxyurea treatment, particularly when one sibling is already receiving it. In these cases, practitioners are required to carefully assess potential advantages for patients who have not yet shown signs of severe symptoms [23].

Hydroxyurea therapy is safe to start at any age, including infants as young as 6 - 9 months old. Younger patients tend to respond better to treatment and are more likely to stick to their medication regimen. It is recommended to consider beginning hydroxyurea therapy early in life, ideally before the age of 5 - 10 years. However, clinical effectiveness has been observed at all ages, as demonstrated by significant reductions in pain, episodes of pulmonary crisis with respiratory distress, blood infusions, and repeated admission stay days even in elderly patients with severe symptoms who started hydroxyurea therapy [24].

3.5. Hydroxyurea Dosage

Hydroxyurea can be taken orally either in the form of capsules or through a liq-

uid formulation that is prepared as needed. The medication is typically administered once a day [25].

In developed countries, the typical starting dose of administration of hydroxyurea in the treatment of sickle cell anemia (SCA) patients is at initial of 20 mg/kg/day in children above 2 years, and it is generally well endured. The dose is gradually increased every two months until reaching the maximum tolerated dose (MTD), which is determined by a mild decrease in bone marrow function that is safe and does not cause severe infections. About 25% of patients may experience lower reticulocyte levels. Most young patients reach their MTD at a dose of 30 mg/kg/day, allowing them to achieve important laboratory thresholds without excessive bone marrow suppression. Most medical practitioners have a preference for a lower dose called the minimally effective dose (MED), which is determined by clinical improvement and overall well-being. However, patients receiving the MED may have lower treatment responses compared to those receiving the MTD [26].

3.6. The Treatment Responses Observed with Hydroxyurea

It is crucial for patients and their families to comprehend that hydroxyurea does not provide immediate results. Usually, it takes approximately 6 months to observe changes in laboratory measurements, including an increase in average red blood cell size and a reduction in absolute neutrophil count (ANC) and reticulocyte index. When the hydroxyurea dosage is increased towards the maximum tolerated dose (MTD), changes can be noticed in the examination of the peripheral blood film. These changes include an occurrence of macrocytosis without the presence of polychromasia, a decrease in half-mooned cells red blood cells, an increase in target cells, and a reduction in residing neutrophils and erythroid cells. It is worth noting that the positive effects on fetal hemoglobin (%HbF) may not be immediately noticeable during early treatment, and the maximum effects are typically observed after 6-12 months of therapy [27].

4. The Previous Researches

Research on hydroxyurea in sickle cell anemia (SCA) has accumulated almost three decades of experience. The initial study in 1984 provided the first evidence of its effectiveness, leading to subsequent infants, children, and adults phase one/two. A major breakthrough came in 1995 with the publication of the third-phase multicenter trial study of hydroxyurea (HU). The results of this trial, which employed an experiment utilizing a double-blind methodology and a placebo group for comparison, definitively validated the effectiveness of hydroxyurea in preventing pain, episodes of pulmonary crisis, blood infusions, and frequent admissions in elderly people diagnosed with SCA.

The National Institutes for Health (NIH) sponsored two clinical research investigating the effectiveness of hydroxyurea, one of which focused on babies diagnosed with sickle cell anemia, called the BABY HUG trial. Participants were

arbitrarily put to receive either hydroxyurea or a dummy treatment for a duration of 24 months. While the main goal of preventing organ dysfunction was not achieved, the secondary outcomes demonstrated encouraging findings. The group receiving hydroxyurea treatment experienced significantly reduced occurrences of agony, dactylitis, instances of pulmonary crisis, blood infusions, and repeated hospital stays in contrast to the placebo group [28].

As part of a research investigation comparing treatment options for young patients with sickle cell anemia, hydroxyurea has emerged as a viable option. The study, known as the Stroke with Transfusions Changing to Hydroxyurea (SWiTCH) study, divided the patients having a history of stroke and hemochromatosis into two groups. One group received standard treatment with transfusions and chelation, while the other group received complementary therapy with hydroxyurea and bloodletting. The objective was to avoid subsequent strokes and improve the management of excessive iron levels. However, the alternative treatment arm was stopped early due to its inability to improve iron overload management compared to the standard treatment. Significantly, there was a notable disparity in the incidence of strokes, with 10% of patients on hydroxyurea experiencing strokes compared to 0% of patients on transfusions at the end of the study [29].

The findings from the SWiTCH trial provided valuable insights into pediatric patients with sickle cell anemia (SCA) who previously experienced stroke. The study revealed that many of these children had severe vasculopathy and clinical fragility. Additionally, the trial highlighted the challenges associated with using the combined primary outcome in a randomized clinical trial conducted across multiple centers.

4.1. Ongoing Researches on Clinical Trials

There are several clinical trials funded by the NIH that are currently underway to explore the effectiveness of hydroxyurea in treating patients with SCA. One of these trials, known as TWiTCH (NCT01425307), is specifically focused on children who currently receive chronic transfusions and have abnormal Transcranial Doppler velocities. These children will be randomly assigned to either continue with transfusions or switch to hydroxyurea treatment. The primary goal of this trial is to assess the alteration in TCD velocity.

Another trial, called SCATE (NCT01531387), is targeting children with conditional TCD velocities. Similar to the TWiTCH trial, these children will also be randomly assigned to either continue with observation or switch to hydroxyurea treatment in order to prevent their TCD velocities from reaching abnormal levels. The SCATE trial is being conducted in the US, Jamaica, and Brazil.

The HUSTLE trial (NCT00305175) seeks to collect data on the pharmacokinetics, pharmacogenetics, as well as lasting impacts of hydroxyurea treatment on organ functionality in children with SCA. Additionally, the ongoing study (NCT00890396) is closely monitoring the BABY HUG cohort to evaluate

the potential benefits and drawbacks of initiating hydroxyurea treatment at an early age, specifically before the age of six months.

4.2. The Follow-Up over an Extended Period of Time

It is crucial to regularly monitor SCA patients who are receiving hydroxyurea therapy for possible long-term toxicities. Fortunately, studies involving extended treatment periods ranging from 15 to 20 years in adults and 10 to 15 years in children have not indicated an elevated risk of stroke, myelodysplasia, or carcinogenicity. When evaluating rare instances of malignancy in hydroxyurea-treated patients, it is of paramount importance to take into account the background cancer rate in SCA. This approach helps prevent unnecessary concerns or inaccurate connections [30].

Although concerns have been raised about hydroxyurea's potential negative effects on fertility, particularly in terms of sperm production, there is currently no conclusive evidence to support these claims. Clinical experience suggests that hydroxyurea does not affect fertility in both men and women with SCA. Additionally, while there is a theoretical risk of teratogenicity, no clinical observations have confirmed this concern. Recent findings from an adult cohort study offer reassurance regarding the outcomes of pregnancies in individuals receiving hydroxyurea treatment [31].

While it is crucial to exercise prudence regarding pregnancy or conception during hydroxyurea therapy, the existing data suggest negligible adverse consequences. When it comes to pregnant women with SCA who are undergoing hydroxyurea treatment, it is of utmost importance to thoroughly consider the potential hazards of continuing the therapy versus the risks associated with ceasing an efficacious treatment in a pregnancy that carries a high degree of risk.

Regarding long-term benefits, hydroxyurea therapy has shown promising outcomes. Numerous studies have provided evidence of consistent enhancements for indicators in the laboratory and clinical settings for patients adhering to the treatment, including enhanced growth and development in young individuals. Notably, newly conducted studies over an extended period, conducted in the USA and Greece have shown even better endurance rates among individuals afflicted with sickle cell anemia (SCA) who are administered hydroxyurea as treatment. A positive impact on mortality further reinforces the importance of considering hydroxyurea treatment for all affected patients [32] [33].

4.3. Comparable Therapies for SCD with Hydroxyurea in Children and Adults

Gene therapy and hydroxyurea: Gene therapy aims to correct the genetic mutation responsible for SCD by introducing a functional copy of the gene into the patient's cells. Recent advances in gene therapy, such as lentiviral vectors, have shown promising results in early clinical trials in both children and adults. Gene therapy has the potential to provide a long-term cure for SCD by enabling

the production of healthy red blood cells with normal hemoglobin. However, gene therapy approaches are still in the experimental stage and require further research and refinement. On the other, hydroxyurea has been extensively studied in both children and adults and has been shown to increase fetal hemoglobin (HbF) production, reducing the proportion of sickle hemoglobin (HbS) and improving symptoms in SCD. Hydroxyurea has been shown to reduce vaso-occlusive crises, acute chest syndrome, and the need for blood transfusions [34] [35]. It's important to note that while gene therapy holds promise, it is still in the early stages of development and has not yet been approved as a standard treatment for SCD. Hydroxyurea remains the established and widely used treatment for both children and adults with SCD. Further research and clinical trials are ongoing to evaluate the long-term safety and efficacy of gene therapy in SCD.

Blood transfusion and hydroxyurea: Regular blood transfusions involve the administration of healthy red blood cells with normal hemoglobin to replace the sickled red blood cells in patients with SCD. Transfusions can alleviate symptoms, reduce the risk of stroke, and improve overall well-being in both children and adults with SCD. However, long-term transfusion therapy may lead to complications such as iron overload and alloimmunization [36]. In general, both blood transfusion and hydroxyurea have shown benefits in the treatment of SCD in children and adults. However, blood transfusions provide immediate relief by replacing sickled cells with healthy ones, while hydroxyurea offers a long-term approach by increasing HbF production. The choice of treatment depends on various factors, including the severity of the disease, the patient's age, and individual patient needs.

Bone Marrow Transplant (BMT) and hydroxyurea: BMT, also known as hematopoietic stem cell transplantation, involves replacing a patient's diseased bone marrow with healthy donor cells. BMT provides a potential cure for SCD by restoring the production of healthy red blood cells. It is most effective when performed in younger patients with a matched sibling donor. However, BMT is associated with significant risks, including graft-versus-host disease and transplant-related complications. In a study by Lena *et al.*, found that the overall survival (OS) and disease-free survival (DFS) in the Roma cohort were 84% and 69%, respectively, while OS and DFS were 100% in the Berlin cohort. Immune reconstitution was satisfactory. Although asymptomatic viral reactivation was common, no severe viral infection occurred. These data confirm that TCR- α/β^+ /CD19⁺ depletion is a well-suited haplo-HSCT (HLA-haploidentical hematopoietic stem cell transplantation) strategy for children with hemoglobinopathies [37]. While BMT offers the potential for a cure, it is associated with significant risks and challenges, including the need for a suitable donor. Hydroxyurea, on the other hand, provides symptom relief and has a well-established safety profile. The choice between BMT and hydroxyurea depends on factors such as the severity of the disease, availability of a suitable donor, and patient-specific considerations.

Erythropoietin (EPO) and hydroxyurea: Erythropoietin is a hormone that stimulates the production of red blood cells in the bone marrow. In SCD, EPO has been used to increase red blood cell production and improve anemia. However, the use of EPO in SCD is limited and controversial, as it may increase the risk of vaso-occlusive events and thrombosis [38]. In a study by John N *et al.*, it was found that α -thalassemia not only increases hemoglobin in patients with HbSS but also reduces erythropoietin values, demonstrating a measurable response to improved tissue oxygenation. Furthermore, α -thalassemia had a reduced annualized transfusion burden in both HbSS and HbSC, but α -thalassemia had no impact on annualized admission rates in either group [39]. In a nutshell, hydroxyurea is the preferred treatment for SCD due to its well-established efficacy and safety profile. Although Erythropoietin, on the other hand, has limited evidence and potential risks, however, in certain cases where anemia is severe and hydroxyurea is contraindicated or ineffective, erythropoietin may be considered under close medical supervision.

4.4. Other Emerging Strategies for SCD

CRISPR/Cas9 Genome Editing: CRISPR/Cas9 is a gene-editing technology that allows precise modification of the DNA sequence. Researchers are exploring the potential of CRISPR/Cas9 to correct the genetic mutation responsible for SCD. Preclinical studies have demonstrated successful correction of the sickle cell mutation in stem cells [40].

Small Molecules and Targeted Therapies: Various small molecules and targeted therapies are being investigated to interfere with specific pathways involved in SCD pathophysiology. These therapies aim to reduce inflammation, oxidative stress, and adhesion of sickle red blood cells. Some examples include Nrf2 activators, anti-inflammatory agents, and adhesion molecule inhibitors [41].

These emerging therapies hold promise for the future treatment of SCD. However, it's important to note that further research and clinical trials are needed to establish their safety, efficacy, and long-term effects.

4.5. Potential Long-Term Side Effects of Hydroxyurea Use in Children with Sickle Cell Disease (SCD)

Hematologic Effects: Hydroxyurea can cause bone marrow suppression, leading to decreased production of red blood cells, white blood cells, and platelets. Prolonged use of hydroxyurea may increase the risk of developing myelosuppression and hematologic malignancies [42].

Reproductive Effects: Hydroxyurea may have reproductive effects in both males and females. In males, it can cause reduced sperm count and motility, leading to infertility. In females, it may disrupt the menstrual cycle and affect fertility [43].

Renal Effects: Some studies have suggested a potential association between long-term hydroxyurea use and renal dysfunction. Hydroxyurea may cause kid-

ney damage and impaired renal function, although the exact mechanism is not fully understood [44].

It is important to note that while these potential long-term side effects have been reported in some studies, the overall benefits of hydroxyurea in reducing SCD-related complications often outweigh the risks. Regular monitoring and close follow-up with healthcare providers are essential to manage and mitigate any potential side effects.

5. Situation in the Developing Countries

Although there is substantial evidence that supports the advantages of the administration of hydroxyurea to pediatric patients suffering from sickle cell anemia (SCA), there is insufficient information pertaining to its utilization in underdeveloped nations where SCD is a significant issue. Considering that there are over 300,000 annual cases of sickle cell disease worldwide, it is crucial to prioritize the provision of the only treatment that can modify the disease. Nonetheless, the safety and practicability of employing hydroxyurea as a form of treatment alongside co-existing conditions like malnutrition, vitamin deficiencies, and infections such as malaria and helminthiasis have not been thoroughly evaluated. While the idea of utilizing hydroxyurea, especially in Africa, may seem appealing, it is necessary to conduct a comprehensive evaluation of the potential risks and benefits, preferably through prospective studies like the proposed pilot trial known as Unleashing Cross-Continental Effectiveness through Hydroxyurea (UCCEH), to obtain a comprehensive understanding. As African nations implement programs that screen newborns for SCA, the wide-ranging implementation of hydroxyurea has the potential to serve as an effective therapeutic option in resource-limited settings, helping to alleviate the impact of the disease [45].

6. Knowledge Gaps That Still Exist

Further investigation is needed to fill important knowledge gaps in several areas. One area of interest is the variation in how individuals respond to hydroxyurea treatment, which is influenced by differences in their phenotypes. Moreover, patients' tolerance to different doses of hydroxyurea varies as much as their response in terms of HbF levels. Recent research indicates that this variability may be attributed to differences in pharmacokinetics and pharmacogenetics [46].

Compared to our knowledge of hydroxyurea's effectiveness in individuals suffering from sickle cell anemia (SCA), our understanding of its use in individuals with HbSC and HbS/ β^+ -thalassemia is insufficient. Existing data for these patient populations is mostly anecdotal or based on small series, and it is not appropriate to extrapolate findings from SCA patients. To address this gap, there is an urgent need for prospective studies specifically focused on HbSC patients, as hydroxyurea is increasingly being prescribed to them. While the benefits of HbF for HbSC patients are not well-established, there are potential therapeutic ad-

vantages such as reduced white blood cell count and decreased cellular adhesion. In clinical trials involving HbSC patients, measuring blood viscosity may be valuable due to the common increase in hemoglobin concentration caused by hydroxyurea, which could have potentially negative effects [46]. Another critical knowledge gap is understanding the factors that contribute to the decline of HbF with age, as this area of research holds promise for identifying preventive agents.

7. Conclusion

At present, hydroxyurea stands as the sole approved treatment for altering the progression of SCD. Its safety and effectiveness have been demonstrated in children with SCA, irrespective of whether they reside in developed or developing nations. Hydroxyurea use has resulted in significant improvements in outcomes and safety for both adults and children, offering hope for enhancing the survival of SCD patients. However, it is important to recognize the global impact of this condition and the inadequate management often seen in countries with a high prevalence of SCD. Therefore, fostering scientific collaboration and research efforts between countries is crucial for future advancements in this field. The safety and effectiveness of hydroxyurea are consistently supported by reliable long-term data, establishing it as a cost-effective treatment option that should be taken into consideration for the majority of SCA patients. Ongoing and upcoming research will further contribute to understanding its role in preserving organ function and comprehending the variability in how SCD patients respond to hydroxyurea.

Author Contributions

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Conflicts of Interest

The authors declare no conflict of interest.

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Abbreviations

SCD—Sickle Cell Disease	TCD—Transcranial Doppler
SCA—Sickle Cell Anemia	LDH—Lactate Dehydrogenase
MED—Minimally Effective Dose	ANC—Absolute Neutrophil Count
MTD—Maximally Tolerated Dose	LCR—Locus Control Region
HbF—Fetal Hemoglobin	HU—Hydroxyurea
WHO—World Health Organization	HbS—Hemoglobin S
sGC—Soluble Guanosine Monophosphate	NO—Nitric Oxide
HBG—Hemoglobin Gamma	HBB—Hemoglobin Subunit beta
CDC—Centers for Disease Control and Prevention	
dNTPs—Deoxyribonucleotide Triphosphates	
Nrf2—Nuclear Factor Erythroid 2-Related Factor 2	

Gastric Cancer Disparities in the United States: Overcoming the Barriers

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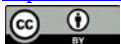
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Abstract

In this narrative review, we highlight the disparities in the incidence and mortality of gastric cancer across various racial and ethnic populations in the United States (US). Despite the low and decreasing trend in the incidence of gastric cancer in the US, the incidence remains significantly high among Asian and Hispanic Americans, showing a striking racial and ethnic disparity. The low survival rate of gastric cancer further accentuates the magnitude of this disparity. In addition, there is a marked funding disparity among different cancers in the US, reflecting the significantly lower level of support for cancers, such as gastric cancer, which are more prevalent in minority populations, compared to the cancers more prevalent among non-Hispanic Whites (NHW). Moreover, the economic burden from health disparities remains high. Although studies from the US and Asia suggest that screening for stomach cancer may be cost-effective, there is no currently available guideline for screening high-risk populations in the US. A multidimensional framework involving the community, physicians, and policymakers is proposed to tackle these gastric cancer disparities and to develop population-based screening and surveillance programs to reduce the burden of gastric cancer.

Keywords

Gastric (Stomach) Cancer, Epidemiology, Prevention, Health Disparity, Immigrants, Minority Health, Endoscopic Screening

1. Introduction

Gastric cancer is the fifth most common cancer worldwide, with around 1.1 million new cases reported in 2020, the most recent year for which data are available, and remains a leading cause of cancer deaths [1]. A large percentage of gastric cancer cases is found in Asia, followed by Latin America, central and eastern

Europe, and other countries. At only 20%, the five-year survival rate from gastric cancer is a severe global public health concern [2] [3] [4]. By 2040, projections suggest 1.8 million cases and 1.3 million deaths, which are 66% and 71% higher, respectively, than the estimates made in 2020 [5]. These data identify countries and regions with increased incidence and mortality of gastric cancer, highlighting the need for cancer control initiatives consisting of primary prevention and screening.

Cardia Gastric Cancer (CGC) and Non-Cardia Gastric Cancer (NCGC)

There are two main anatomical subtypes of gastric cancer: cardia gastric cancer (CGC) and non-cardia gastric cancer (NCGC). Their incidences vary between regions and sexes [6] [7]. While both types share risk factors, such as smoking and alcohol consumption, they also have unique risk factors. CGC, often associated with gastroesophageal reflux disease (GERD) and obesity, develops near the gastroesophageal junction and behaves like esophageal adenocarcinoma. On the other hand, NCGC is strongly associated with *Helicobacter pylori* infection and a high salt diet [8] [9] [10]. Some studies have shown a worse prognosis in early CGC compared to NCGC, although there are controversies on the clinical outcome of these two types [9].

While exact global incidence estimates by subsite are lacking, there are significantly more NCGC cases than CGC. CGC and NCGC have a higher incidence in men than in women, and the sex difference is more significant in CGC [6]. In the US, the incidence of NCGC, primarily adenocarcinomas, is higher in minority groups (Asian Americans and Pacific Islanders (AAPI), Hispanics, Blacks, and American Indian natives) than in NHW. On the other hand, the incidence of CGC is higher in the NHW than in minority groups [9]. The epidemiology of gastric cancer changes over time, however, depending on ethnic group, sex, and age. For instance, among NHWs in the US, NCGC incidence has been rising in younger persons and falling in older persons. These increases were more pronounced among women than men, so female incidence may exceed male incidence rates in the future [7] [11].

Gastric Cancer in the US Minority Populations

While the incidence of gastric cancer is low in the US, with an estimated 26,500 cases in 2023 [12], it varies significantly between different ethnicities and races. For instance, the incidence is substantially higher in specific minority populations than in NHW. The highest number of cases of gastric cancer in the US occurs among Asian and Hispanic Americans [13] [14]. Looking at the subjects aged 50 and older, the incidence of NCGC adenocarcinoma was at least 1.8-fold to 7.3-fold higher in non-white groups than in NHW. Compared to NHW, the incidence of NCGC was as much as 14.5-fold higher in Korean American men and women [15].

Based on the Surveillance, Epidemiology, and End Results (SEER) data from people diagnosed with gastric cancer between 2012 and 2018, the five-year survival rate in the US in all stages combined remains low at 33% [16]. There is also a disparity in mortality rates between the various racial and ethnic groups. For

instance, analysis of the age-standardized mortality attributable to gastric cancer between 2000 and 2019 was highest in specific Asian and black groups while it was the lowest among NHW [13]. Although mortality declined in these groups, disparities compared to the NHW persisted across the entire two decades, further highlighting crucial differences in the burden of gastric cancer among racial-ethnic groups in the US [9] [10].

Despite these alarming statistics, there is no structured system in the US to screen gastric cancer in high-risk populations. The mechanisms that make these minority populations so vulnerable must be understood to overcome the barriers responsible for these disparities. It may be crucial to combat poverty and lack of built-in infrastructure in political and social systems, which, by various mechanisms, place minority populations at increased risk for developing gastric cancer [10] [13].

2. Gastric Cancer Disparities in the US

The high incidence of NCGC among minority groups and a persistently high mortality rate demand immediate attention. Among all the minority groups, including Korean, Japanese, Southeast Asian, Chinese, Hispanics, non-Hispanic Blacks (NHB), Filipino, and South Asian Americans, Korean Americans had the highest incidence rate of 49 cases per 100,000 [15]. Meanwhile, NHW had the lowest incidence rate, with only 3.7 cases per 100,000 people, revealing a 13-fold difference between Korean Americans and NHW. The incidence of NCGC was also substantially higher in other minority groups compared to NHW: Vietnamese (6.5×), Japanese (5.2×), Chinese (4.8×), Hispanics (3.8×), and NHB (3.0×).

Some of the ethnic groups exhibit significant sex differences in NCGC. For instance, in Korean and Japanese Americans, the male-to-female incidence was more than twice as high: Korean men and women had incidences of 70 and 33.5 per 100,000, respectively, while the corresponding incidences among Japanese men and women were 33.6 and 11.4 per 100,000. It should be noted that these incidence rates are similar to the current incidence of colon cancer in Asian Americans [17]. For comparison, the colorectal cancer incidence between 2015 and 2019 in those aged 45 - 49 of the US population, for which universal screening was recently initiated, was 33.4 per 100,000 [18].

Lack of a Structured Strategy for Screening High-risk Populations

In the US, gastric cancer is typically identified when symptoms such as weight loss, bleeding, and persistent epigastric pain are experienced rather than through routine screening. As a result, many gastric cancers are diagnosed at advanced stages, sharply reducing the chance for a cure. The survival of gastric cancer patients depends on the stage of cancer progression at diagnosis. According to the American Cancer Society, the five-year survival rate for individuals diagnosed with gastric cancer in the United States between 2012 and 2018 varied based on the extent of the disease: 72% for localized, 33% for regional, and 6% for distant [16].

In contrast to the US, South Korea and Japan, which have high incidences of gastric cancer, have implemented nationwide screening programs for gastric cancer, facilitating early diagnosis. In Korea, the National Cancer Screening Program (NCSP) was launched in 1999 and recommended that people aged 40 years and older undergo biennial upper endoscopy [19]. Similarly, a national screening program for gastric cancer began in Japan in 2014, approving gastroscopy in population-based screening [20].

These population-based screenings significantly reduced gastric cancer mortality compared with no screening. A meta-analysis of 6 cohort studies and four nested case-control studies comprising 342,013 individuals from Asia indicated that endoscopic screening was associated with a 40% reduction in gastric cancer mortality [21], shedding light on the opportunity to reduce the burden of gastric cancer through effective screening policy [22]. More recently, a study from South Korea revealed that the age-standardized mortality of GC per 100,000 persons declined from 29.0 in 2000 to 7.9 in 2020 [23]. This reduction in gastric cancer mortality was attributable to endoscopies, especially in people aged over 40 years [19]. As a result, these population-based screenings significantly increased survival rates in Korea (71.5%) and Japan (65.0%) compared to other countries [20].

Is Endoscopic Screening Cost-effective?

Several studies have demonstrated that endoscopic screening may be cost-effective in high-risk populations. A Japanese study showed that an endoscopic screening program would be cost-effective when implemented among patients between 50 and 75 years of age, underscoring Japan's need for gastric cancer screening [22]. A large-scale, population-based study conducted using the Korean National Health Insurance Big Data Base also showed similar results. This study included information on the treatment of gastric cancer and the costs incurred for patients aged 40 and above between 2004 and 2013. Patients with gastric cancer who participated in the NCSP at least once (*i.e.*, the screening group) were compared with those who did not undergo screening. The study revealed that the screening group had notably lower medical expenses and demonstrated a significantly better prognosis compared to the non-screening group. The cost-effectiveness analysis, based on the GDP per capita, showed that the NCSP for gastric cancer was cost-effective [24].

A US study using modeled data estimates showed that it was cost-effective to bundle an upper endoscopy for NCGC screening with colonoscopy for average-risk colorectal cancer screening in specific ethnic groups aged 50 years or older. This was particularly true for NHB, Hispanic, and Asian Americans, considered as an aggregated group, but not cost-effective for the NHW population [25]. These findings suggest that it may be cost-effective to implement targeted screening for ethnic groups at high risk of developing gastric cancer in the US, similar to the screening model in Korea and Japan [21] [22] [23]. However, there are many barriers to implementing such screenings in the United States, including issues with healthcare infrastructure and insurance coverage.

The argument for cost-effectiveness may be stronger if one considers the increasing population of affected ethnic groups. The projected increase in the population of minority ethnic groups with a high risk for gastric cancer could provide a more accurate evaluation of the economic burden of health disparities. Between 2000 and 2019, for instance, Asian Americans had the highest population growth rate among all racial and ethnic groups in the United States [26]. Moreover, the Asian population could grow by as much as 162 percent between 2016 and 2060, going from 5.7 percent of the total U.S. population to 10.8 percent. The Hispanic community witnessed the second-fastest population growth in the United States. As of 2021, the Hispanic American population has reached 62.5 million, which accounts for 19% of the total population of the United States, a significant increase from 13% in 2000. Since then, it has been the most critical contributor to population growth in the United States, accounting for 54% of overall growth. According to the projections, by 2060, the Hispanic American population is expected to increase to 111.2 million, making up 28% of the total U.S. population [27]. In contrast, the NHW population is projected to decrease such that by 2060, it will no longer be the majority [26]. When projecting future cost-effectiveness studies, it is essential to consider these surges in Asian and Hispanic populations and the potential financial losses stemming from disparities unless they are resolved.

3. Cancer Funding Disparity

The differences in the incidence and mortality of gastric cancer could be linked to the disparity in federal funding for different types of cancers in the US. A recent study, which analyzed funding allocation for 19 cancer types by the National Cancer Institute (NCI) between 2014 and 2018, revealed disparities compared to disease burden [28]. This study utilized a Funding-to-Lethality (FTL) score to identify funding disparities in cancer research [29].

Significant differences in the level of funding were observed across cancer types, with breast cancer receiving the highest annual funding of \$542.2 million and lung cancer receiving \$292.9 million. In contrast, gastric cancer received the lowest funding, with an average of only \$13.2 million. The FTL score for breast cancer, the highest-funded cancer, was 179.65, while gastric cancer, the lowest-funded, had an FTL score of only 1.78. This shows a 100-fold difference in FTL score between the two types of cancers [28].

Based on their observations, the researchers found a strong correlation between cancer incidence and the FTL score for NHW. This correlation was not present for other racial and ethnic groups, however. Additionally, they noticed a strong correlation between mortality and FTL score in NHW but only a weak one for other ethnic groups. The study also revealed that NCI funding was highly associated with cancers primarily affecting NHW, such as breast cancer, leukemia, and lymphoma. In contrast, cancers that had a high incidence rate among minority populations, such as gastric, uterine, and liver cancers, received much

less funding [28]. More recent data on NCI funding between 2019 and 2021 demonstrate that the funding pattern has not appreciably changed, and funding for gastric cancer remains at the lowest of all cancer sites [30]. In support of these findings, another report demonstrated that NCI and non-profit funding increased proportionately as incidence increased for NHW patients, whereas cancers with higher incidence in the ethnic minority populations were relatively underfunded [31].

While these reports showed a lower level of funding among ethnic minority groups, the data do not differentiate between the specific ethnic groups, potentially masking even more marked disparity between a specific minority group and the NHW group. At any rate, it is evident that there is a pressing need to prioritize equity across various types of cancers when allocating NCI funds. It is necessary to put in more effort to ensure that funding distribution for disease control is aligned with the lethality of the disease and addresses the historical disadvantage faced by minority groups. This is particularly critical since there have been significant differences in cancer outcomes for minorities, especially in cancers that receive less funding. For example, Black Americans, Hispanics, Asians, and Pacific Islanders are 2 - 3 times more likely to die from gastric cancer than NHW individuals [9].

Cancer research funding is crucial for improving prevention, detection, and treatment and ultimately, the quality of life for cancer survivors. New health policies could foster more equitable distribution of federal funding across all racial and ethnic groups to mitigate the cancer burden in minority populations. Not only do these disparities impose life-threatening health burdens on minority populations, but they also impose a significant financial toll on the nation. Recent research showed that America's economic burden of health disparities is unacceptably high. This study, funded by the National Institute on Minority Health and Health Disparities, demonstrated that in 2018, racial and ethnic health disparities cost the US economy \$451 billion, a 41% increase from \$320 billion in 2014 [32]. What fraction of these figures is attributable to gastric cancer is unknown. Nevertheless, reducing health disparities in minority populations will mitigate the health burden and help the national economy.

4. Overcoming the Barriers: A Multidimensional Approach

The disparities in the incidence and mortality of gastric cancer and the allocation of federal funding among different racial-ethnic groups have persisted in the US for decades without improvement. The reasons behind these disparities can be many-fold, including a continuous influx of immigrants from countries with high incidences of gastric cancer, genetic predisposition, and dietary habits. In addition, these disparities are associated with unequal social, political, and economic resource distribution and may illustrate a lack of government input or political will toward minority health. It is important that we acknowledge the existing disparities and work towards implementing new policies that can help

mitigate such issues and reduce the burden of gastric cancer.

Gastric cancer disparities are reminiscent of other minority health issues, including chronic hepatitis B (CHB), a major cause of liver cancer and cirrhosis. A significant difference in the prevalence of CHB and its complications across different racial and ethnic groups has long been recognized in the US. For example, while 5% - 10% of Asian Americans have HBV infection, only 0.2% of NHW Americans are infected [33] [34]. CHB has been significantly underdiagnosed and undertreated [35]. The obstacles to screening and treatment for CHB are numerous and complex, including a lack of awareness about the disease, language and cultural barriers, and financial challenges [36] [37]. US public health systems are often ill-equipped to cater to the needs of diverse populations [38] [39]. Moreover, poor communication exists between healthcare providers and patients from different cultural, ethnic, or racial backgrounds, causing inadequate healthcare access for minority groups. Despite extensive documentation of CHB and its complications in immigrant populations over the decades, it was not until 2014 that the USPSTF released a grade B recommendation for screening individuals at high risk for HBV infection [40].

Grassroots Action

Solving health disparities in ethnic minority populations can be challenging because of numerous obstacles at different levels, including socioeconomic, cultural, linguistic, and political. Understanding these barriers and how they relate to each other is crucial before proposing any solutions. Moreover, it is essential to consider any past experiences in addressing health disparities.

We propose that a successful gastric cancer campaign should have three following specific objectives. First, it should increase public awareness of gastric cancer and its disparities. The campaign should prioritize accessible gastric cancer screening for high-risk populations with a focus on equity. We need a multi-faceted grassroots approach involving communities, physicians and other healthcare professionals, and policymakers to achieve these goals. The primary community component would be education, increasing awareness of gastric cancer and its risk in specific populations. It is crucial to spread information to the affected ethnic minority populations, where language, culture, and financial barriers may preclude them from accessing appropriate care. Poor health literacy has been well documented as a key hindering factor in accessing care in immigrant populations [41]. As awareness increases, at-risk patients are more likely to make appropriate health decisions and request surveillance from their primary care physicians.

Second, it is essential to reach out to physicians in the community. They need to know the level of risk their communities have in developing gastric cancer. This could be through seminars and forums for physicians with the most frequent contacts with at-risk ethnic communities, including Asian and Hispanic Americans. In addition to updating physicians on gastric cancer disparities, screening, treatments, and monitoring, these educational activities can help motivate providers to participate in community outreach. Updated with the heigh-

tened risk of gastric cancer in specific ethnic groups, physicians are also likely to be more attentive to the need for screening for gastric cancer in these populations. For instance, physicians can also advocate for the changes needed to promote the health of their patients, communities, and society at large.

Patient advocacy is another excellent example of how we can engage with the community. Collaborating with patient advocacy groups is crucial to support patients and their families. Such collaborations help providers gain insights into patients' conditions by better understanding their lives. Additionally, they help inform the community about advances in current therapy and work towards dispelling misinformation, stigma, and discrimination associated with gastric cancer.

To achieve these goals, it is necessary to foster strategic partnerships with key community organizations that promote community ownership and sustained campaign engagement. We have seen this approach succeed in other contexts. From 2007 to 2017, we led a community-based health screening and education campaign in NY and NJ Asian American communities, which helped to reduce CHB-related health disparities. This large-scale community-based Hepatitis B Screening and Awareness Campaign led by Center for Viral Hepatitis (CVH) [37] [42], devoted to promoting CHB screening and linkage to care in Asian American community, provided an effective model for screening and linkage to care in ethnic minority populations [43] [44]. CVH established collaborative relationships with local hospitals, community organizations, and physicians to work cooperatively in a multidisciplinary manner to foster the highest quality of care for screening, education, screening, and linkage to care for the individuals chronically infected with HBV. This concept is not confined to infectious diseases and can also be applied to the gastric cancer awareness campaign.

Thirdly, we propose involving local and federal governments in reducing these health disparities. To determine how future government legislation might affect health equity, it may be necessary to conduct an equity audit of current policies. This would involve asking several questions, such as whether the data collected on the nation's health disparities are accurate and complete and whether these data are being used to distribute the relevant portions of the budget proportionately. By doing so, we can gain insight into how previous policies may have contributed to health disparities and identify new policies that can be implemented to reduce them.

Improving health equity cannot be achieved by the government's health agencies alone. The key to achieving health equity is to engage communities by seeking their input, listening to their needs, and collaborating with them. It is crucial to incorporate community perspectives in the policy-making process.

5. Conclusions

Gastric cancer has a disproportionately negative impact on minority groups in the US, particularly Asian Americans and Hispanic Americans, as compared to NHW. The incidence of gastric cancer in some Asian American groups aged 50

and above is similar to the incidence of colon cancer in the general American population, which has access to universal screening. Despite the persistently high incidence and mortality from gastric cancer among these minority groups, the federal funding allocated to gastric cancer research is significantly lower than funding for other types of cancers found more commonly in NHW. This health disparity may increase with expected immigration-related minority population rise in the US.

Developing a strategy that focuses on facilitating more research, screening for gastric cancer, and making primary prevention more accessible in high-risk populations is a vital step in the right direction. There should also be greater transparency in the process by which research funds are distributed. It will be pivotal to allocate more funds for basic and clinical research and studies on the cost-effectiveness of regular screening for gastric cancer in high-risk populations while considering the expected increase in these populations. The goal in fund allocation is not to distribute research dollars in some manner that reflects a mathematical calculation of ratios and percentages but, in making such decisions, to factor in the vulnerabilities of patients whose risk profiles differ from those of the majority.

In addition, a multidimensional grassroots campaign involving the community, healthcare professionals, and policymakers may be required to encourage local and national governments to implement strategies for gastric cancer screening in these minority populations. Such a collective action to reduce disparity described in this report may also be effectively implemented in other ethnic populations to address their health disparities.

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Author Contributions

Both authors conceived of the study, participated in the review of the literature, and drafted the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data used and/or analyzed in the current review are available from the references.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

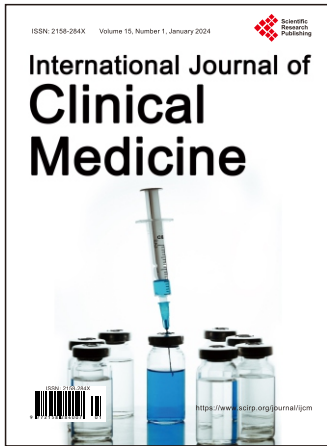
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- Clinical Obstetrics and Gynaecology
- Clinical Oncology and Cancer Research
- Clinical Ophthalmology
- Clinical Oral Implants Research
- Clinical Oral Investigations
- Clinical Orthopaedics and Related Research
- Clinical Otolaryngology
- Clinical Pathology
- Clinical Pediatric Emergency Medicine
- Clinical Periodontology
- Clinical Pharmacology & Toxicology
- Clinical Pharmacy and Therapeutics
- Clinical Physiology and Functional Imaging
- Clinical Practice and Epidemiology in Mental Health
- Clinical Psychology and Psychotherapy
- Clinical Psychology in Medical Settings
- Clinical Radiology
- Clinical Rehabilitation
- Clinical Research and Regulatory Affairs
- Clinical Research in Cardiology
- Clinical Respiratory
- Clinical Rheumatology
- Clinical Simulation in Nursing
- Clinical Sleep Medicine
- Clinical Techniques in Small Animal Practice
- Clinical Therapeutics
- Clinical Toxicology
- Clinical Transplantation
- Clinical Trials
- Clinical Ultrasound
- Clinical Virology
- Complementary Therapies in Clinical Practice
- Consulting and Clinical Psychology
- Contemporary Clinical Trials
- Controlled Clinical Trials
- Diabetes Research and Clinical Practice
- Evaluation in Clinical Practice
- Fundamental & Clinical Pharmacology
- Hereditary Cancer in Clinical Practice
- Human Psychopharmacology: Clinical and Experimental
- Innovations in Clinical Neuroscience
- Laboratory and Clinical Medicine
- Neurophysiologic Clinique/Clinical Neurophysiology
- Nutrition in Clinical Practice
- Pacing and Clinical Electrophysiology
- Psychiatry in Clinical Practice
- Therapeutics and Clinical Risk Management
- Veterinary Clinical Pathology

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