Sickle Cell Vasculopathy: An epiphenomenon in need of a management approach

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Abstract

The review of current literature unveiled another phenomenon that subsequently occurs as a result of the sickling of erythrocytes—vasculopathy. It is a secondary phenomenon initiated by endothelial damage in the hemolysis-induced dynamics of nitric oxide depletions, coagulation activations, and oxidative stress, to say the least, which plays a significant role in the cumulative disease process. One of the goals proposed by the National Institute of Health (NIH) is to be able to measure severity of the disease. Without knowing how effective our preventive approaches are—perhaps by a possible objective way of measuring improvements or severity of the vascular condition—it is a difficult disease to treat because an asymptomatic patient can have chronic narrowing of the vessels[1]. The treatments of Hydroxyurea and Blood transfusion can help delay morbidity. Vasculopathy is a morbidity requiring further understanding of the pathophysiology in order to improve management of this disease. Bone marrow transplant can possibly cure the disease, however with dire consequences, if unfortunate. Perhaps, improving our understanding of the vasculopathy aspect of the disease, we can further prolong life and delay reaching a point of severe conditions.

Keywords

Management, Sickle Cell, Treatment, Vascuolopathy

Introduction

This paper will review background information of Sickle Cell Anemia (SCA) by first defining the term and exploring historical events surrounding this disease including the involvement of regulatory agencies making current recommendations. Next, the observations of real patient clinical encounters, incidence, and prevalence of the disease will unveil the significance of the disease impact on healthcare systems. Lastly, this paper will highlight current treatment management options with a note that we may also need to be focusing on another phenomenon—vasculopathy for the proper symptomatic treatment of SCA.

Definition

Chromosome 11, known for one of the most gene- and disease- rich chromosomes in the human genome comprising of 23 pairs of chromosomes, houses the gene HBB or the beta-(hemo)globin[2]. Two units of this beta-globin molecules or chains and two units of an alpha-globin chains make up a single Hemoglobin A, which is the most common form present in erythrocytes in the human species[3]. A defect in a specific location in chromosome 11 or at the locus 11p15.5 on the short arms of this chromosome encodes a point mutation to the B-globin chain. Specifically, the point mutation occurs as a substitution of the glutamic acid with valine at the 6th position of the amino acid sequence. Receiving a copy of this genetic mutation from

both parents, the conceived child will have an autosomal (chromosome 11) recessive mutation in which we have coined the term Sickle Cell Anemia (SCA). Using Hemoglobin electrophoresis, a blood test measuring different types of oxygen-carrying proteins, will show hemoglobin S and can diagnose SCA.

Erythrocytes transport oxygen to our tissues and carbon dioxides out of our body. In a single erythrocyte, hemoglobins abound—a couple hundred million of them, all composed of a common denominator made up of two alpha-subunits and two beta- subunits forming a tetramer called Hemoglobin A. The most common form of sickle cell disease is sickle cell anemia resulting from a defect in chromosome 11 expressed as a point mutation in the beta-subunit chains[4]. Sickle cell anemia and many other variants suffer the phenotype conditions characteristic of "Sickle cell disease". Though the variant forms, such as thalassemias, may have a mutation in either the alpha- or the beta- subunits, nevertheless, the mutations change the affinity toward oxygen molecules and are manifested with similar disorderly symptoms.

Etiology/Incidence

The geographical regions that represent most concentration of sickle cell trait / disease are sub-Saharan Africa, Central America, the Caribbean, South America, Saudi Arabia, India, and the Mediterranean countries, such as Turkey, Greece, and Italy[5]. According to the American Anthropological Association, areas in Africa, the Middle East, southern Europe and South Asia where Malaria is endemic to the region have a peculiar correspondence to sickle cell conditions. Scientists share similar views in which people of these origins had a survival benefit in carrying the sickle cell trait that would allow them to live longer even after a Malaria-infected mosquito bite. Despite a high number of the African-American population affected by this disease in the United States, an additional terminology—"Thalassemia"—is coined by the Greeks describing a blood disorder commonly seen in the "Thalassa" or the people of the Mediterranean. Thus, based on observation, an evolutionary force seemed to have taken place in the Malaria-stricken region causing the alteration in the genetic composition of the inhabitants. We may see SCA more prevalent in the African American population here in the United States—perhaps as a result of the transatlantic slave trade in which approximately 12 million African Americans arrived in the Americas according to the Journal of American History. However, carrying a single mutation of the gene or the sickle cell trait manifested with no symptoms was actually a survival benefit in a different region. They had a better chance of surviving and passing on genetic information to their descendants than those who were born healthy or with sickle cell anemia[6].

During the former President Nixon's administration, the National Sickle Cell Anemia Control Act (P.L. 92-294) was signed into law on May 16, 1972. The Sickle Cell Anemia Control Act provided for the "establishment of voluntary sickle cell anemia screening and counseling programs; information and education programs for health professional and the public; and research and research training in the diagnosis, treatment, and control of sickle cell anemia[7]." Subsequently, the Department of Health, Education, and Welfare assigned the National Heart, Lung, and Blood Institute the duties for research in sickle cell disease. Since then, monumental efforts have been implemented to decrease sickle cell disease-related mortality rates, beginning with an increase in budget for research and treatment of sickle cell anemia amounting to $923 million during the years 1972 -2001[7]. In the past, the exact number of people living with SCD has not been recorded. In order to evaluate how the disease impacts healthcare from different perspectives, the CDC in collaboration with the National Institute of Health and 7 states have begun the Registry and Surveillance System for Hemoglobinopathies (RuSH) project[7]. It is estimated, however, that SCD affects 90,000 to 100,000 Americans with SC trait occurring among about 1 in 12 African Americans. Other facts about sickle cell anemia include: mortality rates among African-American children younger than 4 years of age fell by 42%

from 1999 through 2002, coinciding with the implementation of pneummoccal vaccination; in economic costs during 2005, medical expenditures for children with SCD averaged $11,702 for children with Medicaid coverage and $14,772 for children with employer-sponsored insurance; an average of 75,000 hospitalizations due to SCD occurred in the United States, costing approximately $475 million[5].

Pathophysiology

The molecular composition of a sickle cell erythrocyte consists of two subunits of sickle globin molecules (Hb S) and two subunits of alpha globin molecules. The Hb S is formed because the autosomal recessive mutation at the allele level encodes a point mutation at the molecular level that substitutes a glutamc acid to a valine as aformentioned. With valine in place, the aggregation of the globin chains occurs within an erythrocyte—hydrophobic valine inviting similar hydrophobic species from an adjacent hemoglobin molecule, causing polymerization of sickle hemoglobins[2]. This aggregation of Hb S molecules forms the basis for "sickling" of erythrocytes[7,2]. The deformed and fragile erythrocytes subject to hemolysis, not only affect the patient solely by the change in the cell conformation, but also inflict damage to the vascular path the erythrocytes take[8]. Once the red blood cells burst and materials that were once compartmentalized are now exposed to the intravascular lumen, multitudes of reactions take place with notable consequences being: defects in nitric oxide availability, oxidative stress, ischemia-reperfusion injury, and hemostatic activation; as well as defects in leukocytes and in platelets[8].

Methods

A PubMed search, online journal articles, patient interviews and medical chart reviews were conducted as methods for collecting information. The design of this research incorporated case study, medical chart review, and multi-study review.

Clinical Encounters

Despite current management approaches, such as Hydroxyurea and blood transfusions in reducing the severity of the symptoms on a chronic basis to reach stabilization, some patients will still require urgent treatment in the emergency room or require pain medications. A common example of a sickle cell patient having unbearable pain crisis is seen in the emergency room[9]. A 17 year old African American female presents to the emergency room complaining of abdominal and lower extremity pain. The problematic part of this visitation was a few weeks prior to this encounter, she had already received blood transfusion as part of her antisickling therapy. Another example at an urgency clinic that manages pain medications for sickle cell anemia patients reveals a 24 year old African American female expressing the need for pain medications due to occasional pain crisis despite the use of Hydroxyurea (HU) for couple of years[10]. The next logical set of questions from a medical provider's standpoint may be:

- Are there any barriers preventing effective implementation of Hydroxyurea (HU) from a patient as well as provider's point of view? Is HU being implemented aggressively and accessible to the patient?
- After the implementation and administration of HU over 30 years, what is the current information on HU adverse effects, primarily any mutagenic outcomes?
- What needs to be done to treat Sickle Cell Vasculopathy, if prevention of sickle cell disease through Hydroxyurea and blood transfusion is not attainable?
- Acknowledging the scarce resources of blood products, how effectively are we transfusing patients with sickle cell disease if blood transfusion therapy is not alleviating symptoms?

Vasculopathy is a sickle cell disease complication, and it would be ideal to control the disease before it reaches this point. Mortality and morbidity is due to the most vulnerable organs becoming infarcted—the brain and the lungs or as a stroke or acute chest syndrome/pulmonary hypertension, respectively[7]. Treating the defective red blood cells with hydroxyurea or promoting a more oxygenated environment through blood transfusion therapies solves only a part of the problem. With the intrinsic nature of this disease causing cells to sickle and eventually ensuing a state of hemolysis, unusual reactions take place that promote vasoconstriction, coagulation activation, and endothelial damage and activation[11,1,12,13]. Once severe vasculopathy is evident in a patient, management approach seems to be towards palliative care. The critical point for these individuals—the point of no return—is when the disease reaches the severe stages of vasculopathy which is the major contribution to mortality in these patients.

> *A 34-year old African American woman with homozygous sickle cell disease (SCD) undergoing hydroxyurea therapy for several years succumbs to the disease eventually as a result of chronic occlusion of bilateral internal carotid arteries with nearly absent blood flow.[13] During a subsequent hospitalization for vaso-occlusive crisis, the patient developed clinical feature of encephalopathy, renal insufficiency, and pulmonary infilterates on chest radiograph that was consistent with fat embolizaiton from ischemic myelonecrosis. The episode resolved after aggressive transfusion with packed red blood cells. Two weeks after recovering from this episode, the patient developed acute righ hemiparesis and dysarthria. Magnetic resonance imaging demonstrated an acute cerebral infarct that was accompanied by signs of previously unsuspected old focal and watershed zone infarcts. Magnetic resonance angiography demonstrated extremely severe chronic occlusion of bilateral internal cartod arteries with nearly absent blood flow. Contents obtained from Kato GJ, et al[1].*

Therefore, preventative measures should be tailored to combat the different mechanisms involved in the process of vasculopathy, including the pathophysiology after hemolysis. This is an important concept to understand to explain the mortality in the aforementioned and morbidities in some of the following epidemiological and clinical findings:

Epidemiological findings:

- Vaso-occlusive crisis ensues even after blood transfusion therapy[9]
- Silent cerebral infarcts occur despite regular blood transfusion therapy after first strokes in children with sickle cell disease[14]
- Effect of transfusion therapy on transcranial Doppler ultrasonography velocities in children with sickle cell disease[15]

Research focused on molecular mechanisms in vasculopathy

- Evolution of novel small molecular therapeutics[1]
- Sickle cell vasculopathy: a state of nitric oxide resistance[13]
- Vasculopathy in sickle cell disease: biology, pathophysiology, genetics, translational medicine and new research directions[1]

Future Therapies

Managing sickle cell vasculopathy begins with understanding the pathophysiology of this epiphenomenon—a secondary process occurring due to the sickling of red blood cells and hemolytic events. The pathophysiology involves meticulously studying the process of chemical reactions that are involved—initiated by the release of red blood cell contents from hemolysis and triggers multitudes of events which contributes to vascular compromise, such as oxidative toxicity, platelet activation, increased expression of endothelial cell adhesion molecules, and vasoconstriction (Figure 1; 1).

Based on the pathophysiology currently proposed, treatment of vasculopathy can only begin from understanding the cascade of events. Not only do we need to undertake the molecular mechanisms involved in vascular compromise, but at what point on the severity scale does a patient begin such molecular-based treatments to keep the vessels more patent? Should these novel treatment, instead, be implemented as prophylaxis because nitric oxide inhalation does not improve sickle cell pain crisis for acute treatment (during the actual crisis) as demonstrated in a randomized control trial study[16]? Indeed, sickle cell vasculopathy is a complicated disease. However, in the 1970s, the first identifiable complication that was approached and to be treated was the deadly Streptococcus pneumonia sepsis in infants and toddlers. Penicillin Prophylaxis in Sickle Cell Disease Study (PROPS), a study that proved to be an overwhelming success was terminated 8 months early because the daily administration of oral penicillin to children 3 months to 3 years could reduce the incidence of infection by 84 percent[7]. Therefore, noting the vasculopathy aspect of this SCA as another identifiable complication needing treatment in order to prevent major complications in the future, such as a stroke or acute chest syndrome due to pulmonary hypertension, seems to be a critical issue in this genetic disease. A novel thinking of treating sickle cell vasculopathy, such as small molecular therapeutics, can be an eye opener in managing vasculopathy. Addressing the pathophysiology related to sickle cell vasculopathy because it is such a debilitating disease, can also be cross-referenced to another widely known disease—Atherosclerosis[1]. There are notable similarities in the observations made between the two diseases (Table 1; 1).

Results

The results were based on a review of journal articles published within a timeframe of 5-7 most recent years emphasizing the significance of the role of vasculopathy in treating sickle cell anemia

Treatments

Current antisickling therapies consist of Hydroxyurea, Blood transfusion, and Bone Marrow Transplant. The indication for these therapies are dependent on the subjective experience or objective observation of the disease severity (table 2; 13).

Ideally, bone marrow transplant (BMT) would be the best solution because it cures the disease. However, BMT involves a crude process—initially suppressing the hematopoietic stem cells in the defective bone marrow followed by the infusion of healthy donor stem cells—a process also suffered equally by cancer patients. BMT is an option, possibly curing the disease, but with some serious risks and side effects—rejection of the transplant, infection, infertility, neurologic complications (stroke or seizure), Graft-versus-host disease, and death[17]. Therefore, a decision as such is made when a critical point is reached in deciding whether the transplant will, at the minimum if not curative, prolong life. In addition, the actual transplant cannot begin immediately even after the consent has been completed—unless some healthy stem cells still exist in the patient's bone marrow and have been stored for future use. Using healthy stem cells provided by

the patient's own bone marrow will not require any delay, and so, an autologous transplant can take place immediately. Whereas, an allogenic transplant requires a Human Leukocyte Antigen (HLA) match—search for stem cells that begins from siblings to a national registry match. Stem cells are found in donor's blood or umbilical cord blood that match the patient's stem cells as closely as possible. This is an important process because the host can reject the blood if offending histocompatibility antigens are introduced to the host's immune system as demonstrated in a murine model[18]. The donors and recipients are matched through a blood test called HLA tissue typing. Once the match is successful, then the dreadful pre-treatments of chemotherapy/radiation therapy begin in order to create a receptive environment for the donor's healthy bone marrow stem cells to be introduced to the recipient.

Due to the serious risks and side effects of bone marrow transplant as aforementioned, less aggressive measures are taken initially. Hydroxyurea (HU) is given on a non-acute basis and blood transfusion and pain medications for acutely symptomatic patients. Hydroxyurea has been in use to treat myeloproliferative neoplasms, chronic myelogenous leukemia, and HIV[1]. By definition, HU is a potent inhibitor of ribonucleotide reductase, an enzyme required for DNA synthesis and repair. However, through several suggested mechanisms at this time (table 2), HU triggers a response by the bone marrow to produce more functional hemoglobins[17]. Despite its unresolved mechanisms and no serious reported adverse effects thus far in the course of three decades, Hydroxyurea has proved its safety and efficacy and has been well documented in several clinical trials (Table 3; 12).

Blood transfusion is the next level management, especially when more frequent pain crisis is experienced or further complications begin to impair the individual. However, how can we explain or what would be the next level management if blood transfusion no longer works for a patient who presented to the ER with vaso-occlusive pain crisis after recent blood transfusion therapy[9]? Blood transfusion therapy is always not a solution for some people, depending on the severity level. In a study to learn the effect of transfusion therapy on cerebral vasculopathy in children with sickle cell anemia, 24 patients with severe symptoms and a baseline of abnormal MRA/MRI showing mild-moderate stenosis of vessels were observed after blood transfusion took place[15]. Severe symptoms were defined as acute stroke at 2.1 years old and abnormally high velocity on transcrannial Doppler screening at age of 8.5 years old. Three patterns were detected—improvement in 11 patients, stabilization in 6, and worsening in 7 patients after transfusion therapy. The researchers concluded that improvement was less likely seen in severe stenosis of the vasculature. In another study, transfusion seemed most beneficial in patients who are younger, with higher pre-transfusion Hemoglobin level, and lower abnormal Transcrannial Doppler velocities[23]. That is, the ideal candidates are patients who are in the infant stages of the disease with less compromised vessels and some functional hemoglobin in their system. As you can imagine, severity of the disease is difficult to measure and vasculopathy is an underlying factor to consider as the disease progresses (Figure 2).

Discussion

SCD Complications

After the scrutiny of current treatment efficacies for Sickle Cell Anemia, what if the treatment was not implemented by the providers or administered by the patients appropriately as it is proposed in the literatures? Afterall, "the true success of an intervention relies heavily on the effectiveness of the intervention in real clinical practice outside of a controlled clinical trial environment[24]." Thus, it is important to unveil the candid truth about what works in an "uncontrolled" environment in order to evaluate the

effectiveness of an intervention." The effectiveness of Hydroxyurea "can be inhibited at the provider, patient or systems level[20]." Provider-related barriers may surround fear of carcinogenesis (a side effect which has not yet been proven) and biases of not offering the drug because of patient noncompliance. At the patient-related barrier level, fear of cancer, not wanting to take the medication, not wanting to follow up laboratory monitoring, or not thinking the medication would work were some of the reasons for refusal of medication in a survey study in children. Lastly, at the systems level, some of the contributing factors to barriers to treatment were limited access to transportation, lack of healthcare insurance, lack of medical home, limited access to comprehensive sickle cell centers, lack of care coordination between comprehensive sickle cell centers and community-based physicians, and poor transition from pediatric to adult care.

Conclusion

While preclinical and clinical studies are currently utilizing lentiviral vectors to transfer the human beta-globin genes in treating sickle cell disease, gene therapy would be the ultimate answer to the cure for any genetic disease. Until gene therapy becomes a proven method in curing sickle cell anemia, current issues to be addressed are on long-term toxicities (duration of a human lifetime) in the use of Hydroxyurea, the efficacy of blood transfusion for severe vasculopathy, and vascular complications leading to eye damage, stroke, priapism, and acute chest syndrome. In order to improve the lives of sickle cell anemia patients under current technological and medicinal approaches, management of sickle cell anemia may involve early administration of hydroxyurea treatment, screening for vascular occlusions mainly of the most vulnerable organs (head and pulmonary artery functions), and the availability of blood products. Pain medication is not an option but a necessity for this group until we can figure out a way to treat sickle cell vasculopathy. The National Heart, Lung, and Blood Institute currently are investing in new treatment methods to further research in improving blood and marrow stem cell transplants, perfecting gene therapy, and approaches to new medicines. Researchers are also looking for a way to predict the severity of the disease.

Acknowledgement

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Tables and Figures

Figure 1. Pathological Cascade Caused by Intravascular Hemolysis and Targets for Pharmacologic Intervention in Sickle Cell Disease

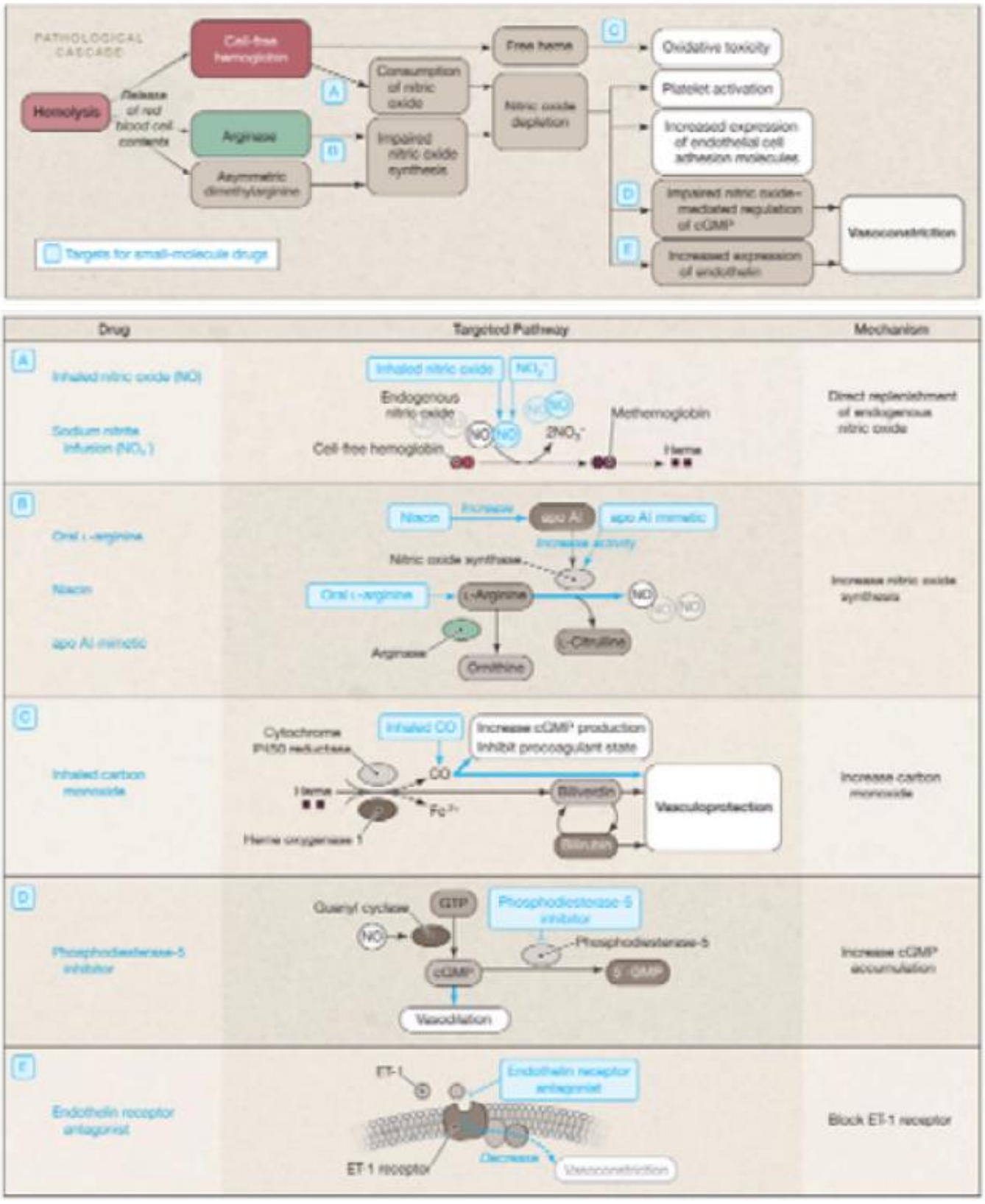

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Table 1 Comparison of Atherosclerosis and Sickle Cell Pulmonary Hypertension

Observation	Atherosclerosis	Sickle Cell Pulmonary Hypertension
Vacular smooth muscle proliferation	Yes	Yes
Decreased nitric oxide bioactivity	Yes	Very severe
Oxidant stress	Yes	Yes
Endothelial dysfunction	Yes	Yes
Endothelial activation	Yes	Yes
Endogenous nitric oxide synthase	Yes	Yes
inhibitors	Yes	Yes
Disordered apolipoproteins	Yes	Yes
Platelet activation	Yes	Yes
In situ thrombosis	Yes	Yes
Accelerated in renal insufficiency	Yes	No
Hypercholestolemia	Yes	No
Atheroma formation	Coronary, cerebral	Pulmonary, cerebral
Commonly affected vascular beds		

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Table 2. Currently available antisickling therapies

	Chronic transfusion	Hydroxyurea	Hematopoietic stem cell transplantation
Indications	Ischemic CVA Recurrent ACS Splenic sequestration Severe anemia due to renal failure	Recurrent ACS Frequent pain	Ischemic CVA Recurrent ACS Frequent pain Avascular necrosis No matched donor
Contraindications	Multiple RBC allo-antibodies Poor venous access	Pregnancy	No matched donor
Advantages	Reduce severity of sickle cell complications Prevent stroke in children	Reduce severity of sickle cell complications Improve longevity Increase hemoglobin Gain weight	Curative Prevent further cerebro-vascular disease
Disadvantages	Requires good venous access RBC alloimmunization Iron overload except when using erythrocytopheresis Transfusion-transmitted infection Not curative	Requires monitoring Myelosuppression Not curative	Risk of transplant related death: infection, organ failure, graft versus host disease Risk of chronic graft versus host disease
Beneficial effect on hemolysis	Mild-moderate, depends on sickle RBC fraction Hemolysis persists	Mild, Hemolysis persists	Curative
Beneficial effect on oxidative stress	Mild-moderate, depends on sickle RBC fraction Hemolysis persists	Mild. Hemolysis persists	Curative
Beneficial effect on oxidative stress	Mild. Inflammation persists	Mild. Inflammation persists	Curative

Risks and benefits of each, including their effects on hemolysis and oxidant stress, are presented. Abbreviations: ACS, acute chest syndrome; CVA, cerebral vascular accident; RBC, red blood cell.

Table and contents obtained from the article Wood KC, et al (13); Copyright permission obtained from Free Radical Biology of Medicine.

Table 3. Mechanisms and benefits of HU (above) and Clinical trials of HU efficacies (below)

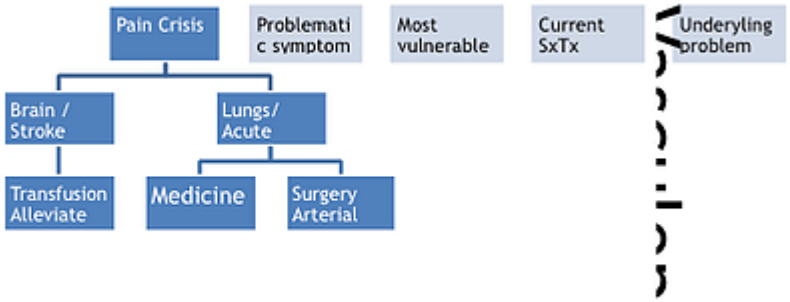
	Suggested Mechanism of HU	Effect/benefits of HU
Most notable mechanism proposed	Cytotoxic effects of HU results in 'stress erythropoiesis'	Increase in HbF levels
Possible mechanism	More complex effects involving the production of nitric oxide and soluble guanylyl cyclase and cGMP-dependent protein kinase pathway thought to play a role	Induced expression of gamma-globin gene (normally expressed during fetal years)
Various mechanisms resulting in several benefits	Several different mechanisms	• erythrocyte morphology and less deformabililty • lowering of circulating leukocyte and reticulocyte counts • reduction in hemolysis • potentially local release of nitric oxide
Clinical Trials on the efficacies of Hydroxyurea for patients with SCA		
HU in infants BABY HUG (19) (HU in infants)	• Multicentre, randomized, controlled trial examining population group of 200 infants from 9-18 months old between October 2003 and September 2009. Eligible participants had hemoglobin SS (HbSS) or hemoglobin thalassemia (HbSB(0)) and were not selected for severity. • Assessed the effect of hydroxycarbamide therapy on organ dysfunction and clinical complications, and examined laboratory findings and toxic effects. • Benefit: Significantly decreased pain and dactylitis with some evidence for decreased acute chest syndrome, hospitalization rates, and transfusion. Increased hemoglobin and fetal hemoglobin, decreased white blood-cell count. • Adverse effect: Minimal. Limited to mild-to-moderate neutropenia.	
HU in Pediatrics HUSTLE Hydroxyurea Study of Long Term Effects(12)	• Prospective observational study of children with SCA treated with hydroxyurea based on clinical severity. • to evaluate the long-term cellular and molecular effects of HU • Benefits: Examining for any chromosomal abnormalities, the report did not identify evidence of cumulative chromosomal damage in the HU-exposed group with up to 12 years of treatment exposure.	
HU in Adults LaSHS (20)	• Single-center trial, prospective study of adult population group of sickle cell anemia and thalassemias patients conducted in Greece. • To evaluate the prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes. Results of a 17 year follow up period with median of 8 years for HU patients and 5 years for non-HU patients. • Benefit: HU produced a dramatic reduction in the frequency of severe painful crisis, transfusion requirements, hospital admissions, and incidence of acute chest syndrome. Probability of 10-year survival was 86% and 65% for HU and non-HU respectively (P=0.001), although HU patients had more severe forms of SCD.-->prob because they are living longer and disease will progress as well.	
MSH Multicenter Study of Hydroxyurea in Sickle Cell Anemia (21)	• Double-blind, randomized clinical trial of 148 men and 151 women studied at 21 clinics. • Tested the efficacy of hydroxyurea in reducing frequency of painful crisis in adults with history of three or more such crisis per year. The trial was stopped after a mean follow-up of 21 months. • Benefits: HU treatment had lower annual rates of crisis (2.5 vs 4.5 crisis per year, P<0.001). Fewer incidences of chest syndrome (25 vs 51, P<0.001) and fewer transfusions (48 vs 73, P=0.001).	
The Risks and Benefits of Long-term Use of Hydroxyurea in Sickle Cell Anemia: A 17.5 Follow-Up (22)	• Adverse Effect: the long term safety of hydroxyurea needs investigation. • A randomized, controlled trial • A follow-up study to search for adverse outcomes and estimate mortality. For each outcome and for mortality, exact 95% confidence intervals were calculated, or tests were conducted at alpha=0.05 level (P-value <0.05 for statistical significance). • Benefits: mortality was reduced in individuals with long-term HU exposure. 25% of deaths due to pulmonary complications, 87.1% occurred in patients who never took HU or took it for <5 years. Stroke, organ dysfunction, infection, and malignancy were similar in all groups.	

Table created by Author.

Contents (above) obtained from the article McGann, et al (12)

Contents (above and below) obtained from the articles: Wang WC, et al (19) ;Voskaridou E, et al (20); Charache S, et al (21); Steinberg MH, et al (22).

Figure 2. An algorithm showing the connection to vascular pathology.



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