An Evidence-Based Approach to the Treatment of Adults with Sickle Cell Disease

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The application of evidence-based medicine to the management of adults with sickle cell disease (SCD) is currently primarily driven by clinical expertise and patient preference, as there is a paucity of randomized controlled trial (RCT) data to guide decision-making. A summary of SCD management principles in the areas of health care maintenance, transfusion therapy, treatment and prevention of painful episodes, acute chest syndrome, stroke, renal disease, contraception and pregnancy, and priapism is predominantly based on the authors' interpretation of available observational studies as well as the opinions of experts in SCD. RCTs impacting current practices address use of hydroxyurea to prevent painful episodes and acute chest syndrome, intensity of pre-operative transfusion, transfusion during pregnancy, and angiotensin-converting enzyme inhibitor therapy for proteinuria, but most issues in adult SCD care have not been rigorously studied and management may not be appropriately extrapolated from pediatric data. While challenging clinical problems need to be addressed by RCTs, there is also the need for development of practice guidelines using formal methodological strategies. This brief review is not a substitute for the process but provides a literature-based approach to making treatment decisions when caring for adults with SCD.

Evidence-based medicine (EBM) has been described as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[1] The American Society of Hematology EBM curriculum provides an overview of the concepts and links to comprehensive references on the subject (www.hematology.org/education/ebm.cfm). A major premise is that a hierarchy of evidence exists, with the well-designed randomized control trial (RCT) recognized as the strongest research design to evaluate treatment efficacy. Unfortunately few RCTs directly address clinical issues of adults with sickle cell disease (SCD) (**Table 1**) and the published literature is predominantly represented by observational studies. The results of clinical trials involving pediatric patients with SCD influence the approach to the adult patient but there continues to be significant reliance on expert opinion to guide treatment of adults with SCD.

The expanding adult SCD population places unique challenges on the health care delivery system. Since the majority of patients do not receive care through comprehensive sickle cell centers, the management of acute complications, surgery, and other interventions often involve physicians with limited experience in caring for the adult patient with SCD. Thus, there is a clear need to provide clinical guidelines that are useful for a wide spectrum of health care providers. The following synthesis of information represents an initial step in the process. Pulmonary hypertension and hematopoietic cell transplantation will be covered elsewhere. Literature searches were performed using MEDLINE, the *Cochrane Database of Systematic Reviews*, and the National Guidelines Clearinghouse. Additional resources included The Management of Sickle Cell Disease monograph published by the NIH,[2] American Society of Hematology annual meeting SCD educational session materials, and opinions from sickle cell experts. Interventions were evaluated using the US Preventive Services Task Force (USPSTF) quality of evidence hierarchy[3] (**Table 2**). An additional designation (PED) is provided to indicate if the evidence is based on studies limited to a pediatric population.

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Health Maintenance Considerations

Periodic health screening and interventions as recommended by the USPSTF are applicable to patients with SCD (www.ahrq.gov/clinic/uspstfix.htm). USPSTF level A (strongly recommended) and B (recommended) interventions should be routinely implemented, including screening for high blood pressure, lipid disorders, colorectal cancer, breast cancer, depression, primary prevention of cardiovascular events, and counseling for tobacco use. The impact of SCD on screening criteria for intervention also needs to be considered. For example, persons with SCD have lower systolic and diastolic blood pressures as compared to matched controls.[4] Modest increases in blood pressure within the normal range for other individuals may be indicative of underlying renal disease or other comorbid medical conditions. There are additional health mainte-

Table 1. Randomized clinical trials in adults with sickle cell disease.

Clinical Trial	Outcome
Multicenter Study of Hydroxyurea in Sickle Cell Anemia[15]	Hydroxyurea reduces the frequency of painful episodes, acute chest syndrome, transfusions, hospitalizations
Preoperative Transfusion in Sickle Cell Disease[28]	Simple blood transfusion to increase the Hb level to 10 g/dL is as effective as exchange transfusion to reduce Hb S to 30%
Prophylactic Transfusion in Pregnancy[16]	Prophylactic blood transfusion to increase the Hb level to 10 g/dL compared to transfusion for Hb < 6 g/dL or for emergent indications did not improve obstetrical or perinatal outcomes but reduced the incidence of painful episodes
Captopril for Albuminuria in Sickle Cell Anemia[33]	Captopril reduces albuminuria in normotensive patients
Poloxamer 188* for Treatment of Acute Vaso-occlusive Crisis[12]	Poloxamer 188 reduces the duration of acute painful episodes

* Non FDA-approved

nance concerns specific to patients with SCD.[2] Ophthalmologic examination, and assessment of liver, pulmonary, and renal function should be performed at least annually (Level III).

Recommendations from the Advisory Committee on Immunization Practices for adults with SCD include immunization with the 23-valent pneumococcal polysaccharide, *Haemophilis influenzae* type b, meningococcal and hepatitis B vaccines if not previously administered. Influenza vaccination on an annual basis and revaccination for pneumococcus one time after 5 years are also indicated (Level III). The transfused patient should be tested for hepatitis C (Level III).

Table 2. Levels of evidence.*

I	Evidence obtained from at least one properly designed randomized controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

*The PED designation indicates the evidence is limited to studies in the pediatric patient population

Transfusion Considerations

Transfusion remains a mainstay in the management of SCD patients and will be discussed in the context of specific indications in subsequent sections. Simple transfusion can be used to improve dyspnea, severe fatigue or heart failure associated with an oxygen-carrying deficit or to decrease the percentage of Hb S containing cells. To avoid excessive blood viscosity the post-transfusion Hb level should not exceed 10 to 11 g/dL[5,6] (Level III). Exchange techniques (manual or automated erythrocytapheresis) can be used to rapidly reduce the concentration of Hb S or when simple transfusion would result in hyperviscosity or volume overload. Clinical indications for transfusion (see **Table 3**) have been evaluated by respected authorities and a consensus panel[5,6] (Level III). Alloimmunization occurs in up to 30% of adult patients who receive frequent transfusions; this can be reduced by the use of phenotypically matched blood for at least the C, E, and Kell antigens[7] (Level III-PED). All patients should have complete RBC phenotyping performed prior to transfusion and antibody

Table 3. Clinical indications for transfusion.

Methods	Simple Transfusion	Chronic Simple Transfusion	Exchange Transfusion
Conventional Indications	Symptomatic anemia Acute neurologic event Acute chest syndrome Acute multiorgan failure Preparation for major surgery Acute splenic or hepatic sequestration Sepsis and meningitis	Prevention of recurrent stroke Recurrent acute chest syndrome or multiorgan failure Symptomatic anemia with renal failure unresponsive to erythropoietin Pulmonary hypertension or chronic hypoxia Chronic heart failure	Acute neurologic event Severe acute chest syndrome Acute multiorgan failure Preparation for major surgery Chronic use, as for simple transfusion, to avoid/reduce iron loading
Controversial Indications	Before use of contrast media Severe ophthalmological complications	Recurrent debilitating pain events Non-healing leg ulcers Recurrent priapism	Acute priapism

status should be reassessed 1-3 months after episodic transfusions (Level III). Appropriate selection of blood products (**Table 4**) can minimize complications (Level III). Significant iron loading may occur after 50 units of RBCs in most patients and is generally associated with steady-state serum ferritin values > 1500 ng/mL. Chelation therapy is indicated for significant iron overload (Level II-2). Serum ferritin levels in SCD do not accurately reflect iron stores and quantitative tissue liver iron concentration may be needed to guide chelation therapy. Non-invasive assessment using magnetic resonance imaging (MRI) or SQUID susceptometry may be considered as alternative measures of body iron burden (Level II-3, III). Deferoxamine has been administered to SCD patients subcutaneously by continuous infusion, by twice daily subcutaneous injection, and intravenously.[8] In the United States oral chelating agents are currently under investigation; however, deferiprone is available in other countries. Chronic erythrocytapheresis reduces iron accumulation (Level II-3).

Treatment of Acute Painful Episodes

Pain is the most common complication of SCD and frequent painful episodes are associated with increased mortality. An evidence-based clinical practice guideline for the management of acute and chronic pain in SCD has been published by the American Pain Society (APS) (www.ampainsoc.org/pub/sc.htm). This practice guideline addresses pain assessment, treatment of pain in various settings, and psychological, behavioral, and physical interventions. Other available treatment modalities have been examined in small-scale prospective studies. A RCT of 29 patients ages 8–21 with 38 hospitalizations for acute chest or back pain above the diaphragm compared the use of incentive spirometry versus standard care and demonstrated a reduction in pulmonary complications in the intervention group (P = 0.019).[9] The use of high-dose methylprednisolone therapy for severe painful episodes was evaluated with a placebo-controlled RCT in 36 patients under the age of 21.[10] The duration of analgesic therapy was reduced in the treatment arm (P = 0.03), but there was more rebound pain after discontinuing steroid administration. A RCT of inhaled nitric oxide in 20 pediatric patients did not show a significant reduction in pain scores for the treatment group compared to placebo at the primary endpoint.[11] In a RCT enrolling children and adults, purified poloxamer 188, a non-FDA approved surfactant, showed a small overall effect in reducing the duration of a painful episode.[12] A dedicated day hospital has been shown to be effective in reducing hospital admissions and length of stay for painful episodes.[13]

Table 4. Selection of blood products.

- Sickle cell trait negative (for exchange)
- Leukocyte reduced
- Limited phenotype matching for all patients: ABO,C, D,E, and Kell antigens
- Extended phenotype matching for patients with alloantibodies

Management principles

Information pertaining to symptoms requiring prompt medical attention as well as plans for pain management should be provided to the patient and family (Level III). Implementation of clinical pathways and standardized orders for hospital-based management of pain episodes based on APS algorithms and using multi-disciplinary approaches should be considered (Level III). Opioid medications are indicated for management of moderate to severe pain. The use of meperidine is not recommended (Level III). Close monitoring of oxygen saturation and avoidance of excessive sedation are necessary (Level III). Oxygen supplementation is not indicated unless there is documented hypoxemia (Level III). Intravenous fluids should be hypotonic and after correcting volume depletion, limited to 1-1.5 times maintenance fluid requirements to avoid overhydration[14] (Level III). Incentive spirometry should be used during waking hours (Level I-PED). Blood transfusion is not indicated in the management of an uncomplicated pain episode[5] (Level III). The administration of steroids is not recommended for an uncomplicated painful episode. NSAIDs may be beneficial for patients without contraindications (Level III). Acute pain management in a day hospital or an equivalent facility is effective in reducing hospital admissions (Level II-2).

Prevention of Painful Episodes

The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) was a landmark RCT that enrolled patients with Hb SS age 18 years or older experiencing 3 or more painful episodes/year to test the efficacy of hydroxyurea (HU).[15] There were statistically and clinically significant reductions in pain episodes for the HU arm compared to placebo as measured by decrease in the rate of crises/year, time to first crisis, and time to second crisis. A 9-year follow-up observational study showed continuing benefit for patients taking HU. Patients with Hb S/β^+-thalassemia or Hb SC treated with HU have been reported in small case series. The effectiveness of HU therapy in patients with these genotypes has not been determined. Case series and reports indicate that repeated phlebotomy to lower the Hb level and induce iron deficiency can reduce the frequency of painful episodes in selected patients with high steady state Hb levels. Non-pharmacologic approaches to management of chronic pain in adults with SCD have not been evaluated in controlled trials. A RCT examining the efficacy of prophylactic transfusion in pregnancy showed a decrease in painful episodes for the prophylactic transfusion group; however, there was a 29% incidence of alloimmunization.[16]

Management Principles

HU therapy is indicated for patients with Hb SS and Hb S/β^0 thalassemia experiencing frequent moder-

ate to severe painful episodes or chronic pain (Level I, III). A phlebotomy program may be considered for symptomatic patients with Hb level >10 g/dL (Level III). Selected patients may benefit from non-pharmacologic therapies utilized in the management of other pain syndromes (Level III). Chronic transfusion to suppress Hb S levels may be considered for the patient with debilitating refractory pain not responding to other interventions (Level III).

Acute Chest Syndrome

Acute chest syndrome (ACS), the association of a new pulmonary infiltrate associated with acute respiratory symptoms, is a leading cause of mortality for adult patients. A prospective multicenter study analyzed 671 episodes of ACS in 538 patients to determine the cause, clinical course and outcomes.[14] For those patients ≥ age 20 with an etiology identified, infection was most common and included a substantial incidence of atypical organisms; however, 26% sustained pulmonary fat embolism. A standardized treatment protocol was used in that study (see **Table 5**). Transfusion was given based on physician discretion to 72% of the patients with similar outcomes for simple and exchange techniques. Analysis of outcomes revealed that those patients ≥ age 20 had more complications than the younger age groups, with 22% requiring mechanical ventilation and 9% mortality.

There have been no controlled clinical trials addressing the use of inhaled bronchodilators, although a case-control study revealed an association of asthma and increased risk of developing ACS during a painful episode in children.[17] Intravenous dexamethasone was found to be beneficial in a RCT of 43 episodes of ACS in children, reducing the length of hospital stay and need for transfusion.[18] Blood transfusion, the use of inhaled nitric oxide, and steroid therapy in adults have not been evaluated in clinical trials.

In the MSH there was a 50% decrease in the incidence of ACS for the HU treatment group compared to the control group ($P < 0.001$).[15] A retrospective analysis of 27 pediatric patients receiving chronic transfusion for a history of severe or recurrent ACS showed a reduction in the incidence from 1.3 to 0.1/patient year ($P < 0.0001$).[19] The severity of the ACS and duration of hospitalization were not changed. Secondary analysis of data from the STOP trial revealed a significant reduction in the frequency of ACS in the children on transfusion therapy compared to the control group.[20]

Management Principles

Interventions used in the treatment protocol of the National Acute Chest Syndrome Study Group are recommended (see **Table 5**) (Level III). Transfusion therapy is recommended if there is clinical deterioration, multilobar infiltrates, or a history of underlying pulmonary or cardiac disease (Level III). For patients with significant anemia, simple transfusion can be used but exchange transfusion to decrease the Hb S level to 30% or less should be considered if there is respiratory decompensation or other organ failure (Level III). For patients with a history of severe or recurrent episodes of ACS, HU therapy is recommended (Level III). The role of chronic red blood cell transfusion in reducing the recurrence of ACS in adults has not been defined but can be considered (Level III-PED).

Stroke

One of the essential interventions in the management of acute ischemic stroke in children with SCD is emergent blood transfusion to reduce the Hb S level below 30%. Although there have not been controlled trials addressing secondary stroke prevention, chronic transfusion with the goal of maintaining Hb S < 30% has been recommended due to the high incidence of recurrence in the subsequent 2 years. There are no RCTs addressing the duration or intensity of chronic transfusion necessary to prevent recurrent strokes. However, a prospective study of 10 children stopping transfusion after 5 to 12 years demonstrated a 50% recurrence rate.[21] The intensity of transfusion was addressed in a report of 15 pediatric patients with the Hb S target level set at 30% for at least 4 years and subsequently allowed to rise to 50%. There were no recurrent ischemic events reported with a median follow-up of 7 years.[22] A contemporary retrospective multicenter study of 137 children with stroke continuing to receive prophylactic transfusions to maintain Hb S levels at 30%-50% revealed a recurrence rate of 2.2/100 patient-years.[23] An alternative approach using HU therapy and phlebotomy as a substitute for transfusion has been evaluated in 35 children who were previously in a chronic transfusion program for a mean duration of 4.2 years.[24] After HU therapy and phlebotomy for a mean duration of 3.5 years, there was a stroke recurrence rate of 5.7/100 patient-years. The protocol was modified to assure overlap of HU to maximally tolerated doses prior to discontinuing transfusions, and the recurrence rate was 3.6/100 patient-years among that subset of patients.[24]

Table 5. Management of acute chest syndrome.*

- Oxygen supplementation to correct hypoxia
- Respiratory therapy including use of incentive spirometry
- Antibiotic therapy (include coverage for community-acquired and atypical pathogens)
- Monitor intake and output: maintain euvolemia
- Pain management: minimize chest splinting and avoid oversedation
- Bronchodilator therapy if reactive airway disease (consider empiric trial in all patients)
- Red blood cell transfusion if respiratory compromise or clinical deterioration

*Adapted from Vichinsky et al.[14]

In a retrospective analysis of patients with an initial stroke before age 18 maintained on chronic transfusions, the presence of moyamoya syndrome was associated with an increased rate of recurrent strokes.[25] A small case series and other reports with limited follow-up indicate benefit of vascular bypass surgery for moyamoya syndrome.[26] The multicenter STOP trial demonstrated that transfusion to maintain Hb S < 30% decreased the incidence of first stroke in high-risk pediatric patients, identified by transcranial Doppler (TCD).[27] STOP II was a follow-up RCT that showed discontinuing transfusion after 30 months resulted in an unacceptable incidence of reversion to the high-risk range of TCD velocity.

There are no clinical trials addressing primary stroke prevention for patients with SCD over 16 years of age. Furthermore, there are no published studies addressing the treatment of acute ischemic stroke in adults with SCD, including the safety of recombinant tissue plasminogen activator or anti-platelet agents. There are no clinical trials addressing the management of cerebral aneurysms in patients with SCD, but angiography is recommended in the evaluation of subarachnoid hemorrhage (SAH) due to the high incidence of multiple aneurysms.

Management Principles

Emergent exchange transfusion to reduce the Hb S level below 30% is indicated for acute ischemic stroke (Level III). For patients with a history of stroke as a child, long-term transfusion to maintain the Hb S level at 30%-50% is recommended (Level III-PED). For adult patients who decide to discontinue transfusions, or those with problematic alloimmunization, iron overload, or other impediments to chronic red blood cell administration, HU therapy should be considered to prevent recurrent events although it has not been adequately studied (Level III-PED). There should be an overlap period to attain maximally tolerated doses and laboratory evidence of effect prior to discontinuing transfusions (Level III-PED). The role of vascular bypass surgery in the management of moyamoya syndrome has not been addressed in a clinical trial and remains to be defined. The use of TCD is not recommended to screen adults to determine the risk of stroke. The diagnostic testing for transient ischemic attack or stroke in adults with SCD should be the same as for those without a hemoglobinopathy (Level III). The use of anti-platelet agents as prophylaxis following ischemic events has not been evaluated in SCD patients with stroke but may be considered if there are no contraindications (Level III). The role of chronic transfusion for the prevention of recurrent events has not been defined for patients with their initial stroke as an adult. Conventional angiography should be considered for patients with evidence of SAH to identify an arteriovenous malformation or aneurysm(s) amenable to surgery or other interventions (Level III). Exchange transfusion prior to invasive angiography is recommended (Level III).

Preoperative Transfusion for Surgery

Analysis of data from the Cooperative Study of Sickle Cell Disease demonstrated that administration of preoperative transfusions resulted in fewer complications in both adults and children. There are no peer-reviewed published clinical trials comparing outcomes for preoperative transfusion to no transfusion. The Preoperative Transfusion in SCD Study Group performed a RCT in Hb SS patients that addressed aggressive (reduction of the Hb S level below 30%) compared to conservative (increase the Hb level to 10 g/dL) preoperative transfusion techniques.[28] There were 551 patients, with 75% under the age of 20, and 25% of 604 surgical procedures were characterized as low risk. Approximately one-third of the procedures were associated with a complication. There were no significant differences between the treatment groups in the incidence of painful episodes, acute chest syndrome, or other complications. Alloimmunization occurred in 10% of the aggressive arm versus 5% in the conservative arm, whereas hemolytic transfusion reactions occurred in 6% of the aggressive arm compared to 1% in the conservative arm. The applicability of these findings to older patients undergoing major procedures is uncertain. The Study Group analyzed data for 364 patients undergoing cholecystectomy including patients not enrolled in the RCT with 37 who did not receive transfusions.[29] Overall there were complications in 39% of patients with the highest incidence of SCD-related events in the non-transfused group. There are no RCTs addressing preoperative management for patients with Hb SC or S/β^+ thalassemia. The Study Group analyzed data on 92 procedures for patients with Hb SC or other sickle variants, with 38% receiving preoperative transfusions.[30] Complications associated with intra-abdominal procedures occurred in 35% of patients not transfused compared to none in patients transfused.

Management Principles

Preoperative hydration, monitoring of oxygenation, and meticulous post-operative management including respiratory therapy are indicated for all patients undergoing general anesthesia (Level III). For the patient undergoing minor surgery not requiring general anesthesia preoperative transfusion is not routinely indicated (Level III). For younger uncomplicated patients with Hb SS undergoing low-intermediate risk procedures (including laparoscopic cholecystectomy) pre-operative transfusion to increase the Hb level to 10 g/dL is often used (Level I). Exchange transfusion to reduce the level of Hb S to 30% or less should be considered for high-risk procedures and patients with a history of pulmonary disease requiring prolonged anesthesia (Level III). Pre-operative transfusion should be considered for patients with Hb SC undergoing intra-abdominal surgery (Level III).

Renal Disease

Chronic renal insufficiency (CRI) occurs in up to 30% of adult patients, manifested by microalbuminuria, proteinuria, hypertension, worsening anemia, and, in some cases, focal segmental glomerulosclerosis and nephrotic syndrome. As in other disease states, microalbuminuria and proteinuria may be indicative of early glomerular injury and renal dysfunction. In small case series, administration of enalapril has been associated with normalized or markedly reduced albuminuria and proteinuria without changes in potassium excretion or significant changes in mean arterial blood pressure.[31,32] A RCT of captopril in 22 adult sickle cell anemia patients demonstrated a mean 37% reduction in albumin excretion with captopril as compared to placebo.[33] However, there are no long-term data to demonstrate that reduction of proteinuria slows or prevents progression to CRI and renal failure. Both hemodialysis and transplantation can be performed successfully.[34] Short-term graft and patient survival are comparable to other patients, but increased graft loss has been noted at 3 years, especially with cadaveric transplantation, with increased mortality 1 to 3 years after transplantation.

Steady-state hemoglobin values diminish with age, especially among patients older than 40 years. This progressive anemia may represent diminished renal function and erythropoietin production. Case reports indicate there is a blunted Hb response to recombinant erythropoietin in SCD patients with CRI even at doses much higher than those used for patients without SCD.

Management Principles

Annual renal function should be assessed by measurement of serum creatinine and urinalysis for microalbuminuria or proteinuria (Level III). Since fractional excretion of creatinine is increased, even mild elevation of serum creatinine may be indicative of renal insufficiency and warrants further investigation (Level III). Patients with proteinuria should be treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker (Level III). NSAIDs should be avoided and dosing of hydroxyurea requires more frequent monitoring and reduction in patients with CRI. Recombinant erythropoietin therapy for progressive anemia should be titrated as needed (Level III). The optimal target Hb value for SCD patients with CRI and renal failure has not been established but Hb levels > 10 g/dL should be avoided (Level III). Renal replacement therapy, including dialysis and transplantation, should be pursued when indicated (Level III).

Contraception and Pregnancy

There are no controlled trials addressing the safety of oral contraceptives (OC) in SCD. Case series indicate no detrimental effects. Contemporary data addressing pregnancy outcomes in women with SCD are predominately gathered from retrospective case series,[35,36] one prospective cohort study,[37] and one RCT of transfusion support.[16] Maternal mortality is < 2%, and neonatal mortality rate is generally < 5%.[16,37] An increased tendency to pre-eclampsia, preterm labor and low-birth-weight babies has been reported in women with Hb SS.[35-37] There is no correlation between the degree of anemia in women with SCD and obstetrical complications, perinatal complications or birth weight.[35,37] In a non-randomized series, use of chronic erythrocytapheresis was associated with a significant reduction in pain events, ACS, low birth weight babies and perinatal death.[38] The use of transfusion was evaluated in an RCT of 72 women with Hb SS, prior to 28 weeks gestation, assigned to receive prophylactic transfusion or transfusion for acute events.[16] The prophylactic transfusion protocol called for a target Hb level of 10-11 g/dL and Hb S < 35%. The control group received transfusion for Hb < 6 g/dL or for medical/obstetrical complications. Adjusted analysis of the data was carried out by removing patients with previous perinatal mortality and multiple gestations. There was no significant difference in obstetrical or perinatal outcomes between the two groups, but prophylactic transfusion reduced the incidence of painful episodes ($P < 0.01$).

Management Principles

Use of OC, depot medroxyprogesterone acetate, and barrier contraceptive methods are acceptable for women with SCD who have no contraindications or risk factors (Level III). Combined management by a hematologist and high-risk obstetrician is recommended for all pregnant patients with SCD (Level III). Management of acute sickle cell complications, including pain, should be the same as for non-pregnant SCD patients, avoiding medications contraindicated during pregnancy (Level III). Prophylactic transfusion for uncomplicated pregnancy is not recommended (Level I); **Table 6** lists indications for transfusion during pregnancy (Level III). Fetal monitoring should include periodic ultrasound to detect intrauterine growth retardation (Level III). Timing and route of delivery should be based on obstetrical indications as in women without SCD (Level III).

Table 6. **Indications for transfusion during pregnancy.**

- Anemia associated with cardiac or respiratory compromise
- Severe sickle cell disease (SCD)-related complications (e.g., acute chest syndrome)
- Preparation for Cesarean section
- Refractory pre-eclampsia
- Controversial
  - increasing frequency of painful episodes
  - SCD-related complications during previous pregnancy
  - multiple gestation pregnancy

Priapism

Priapism in SCD is due to trapping of sickled cells in the corpora cavernosa. Stuttering priapism presents as recurring episodes lasting between 30 minutes and 4 hours whereas the prolonged form persists more than 4 hours and can result in corporeal fibrosis or impotence. Hydration, analgesics, and alkalinization of urine have been recommended to end an episode but have never been evaluated in clinical trials. For prolonged priapism, surgical intervention within 4 to 12 hours has been recommended to avoid sequelae. A single institution's experience with aspiration and irrigation using a dilute solution of epinephrine in 15 pediatric patients was successful in 37 of 39 episodes.[39] Transfusion has been used as an urgent intervention, but has not been studied in clinical trials. Two case series reporting an association of neurological events with partial exchange transfusion and high end hemoglobin levels raise concerns about the use of aggressive transfusion for this indication. Secondary prevention including the use of chronic transfusion has not been examined in rigorous clinical trials. There are case reports and series suggesting the utility of a variety of vaso-active agents. A crossover design clinical trial of stilbesterol demonstrated short term efficacy and there are case reports indicating benefit of gonadotropin releasing hormone agonists (GnRH) or anti-androgens. HU has been reported to prevent recurrences in 4 of 5 patients.[40]

Management Principles

Hydration, encouragement to urinate, and analgesics are recommended as initial efforts to resolve acute priapism (Level III). Patients should be instructed to seek emergent care for unrelenting priapism of 2 hours' duration and urology consultation at the time of presentation is recommended. If conservative measures fail, aspiration of blood from the corpora cavernosa should be considered after 4 hours of symptoms Guidelines from the American Urological Association (AUA) (www.guideline.gov) recommend aspiration (with or without irrigation) or intracavernous injection of a dilute solution of phenylephrine (Level III). A corporoglandular shunt should be considered if repeated injections fail (Level III). Blood transfusion in the acute management of priapism is controversial. If considered for unresponsive priapism, attention to avoiding hyperviscosity is recommended (target Hb ≤ 10 g/dL) (Level III). Preventive measures for recurrent stuttering priapism have not been adequately studied. The use of alpha or beta adrenergic agonists such as pseudoephredrine or terbutaline may be considered (Level III). The AUA supports a trial of GnRH agonists or antiandrogens (Level III). Chronic transfusion and HU therapy are additional prophylactic considerations (Level III).

Conclusion

This review highlights the reliance on observational studies and expert opinion for formulating treatment plans for the adult with SCD. The growing adult SCD population provides an opportunity to perform prospective clinical trials to address specific management issues but there remains a current need to provide best practices guidelines. Programs to enhance dissemination of proven therapies (e.g., hydroxyurea) are also necessary.

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