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Current Management of Sickle Cell Anemia

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Abstract

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Proper management of sickle cell anemia (SCA) begins with establishing the correct diagnosis early in life, ideally during the newborn period. The identification of affected infants by neonatal screening programs allows early initiation of prophylactic penicillin and pneumococcal immunizations, which help prevent overwhelming sepsis. Ongoing education of families promotes the early recognition of disease-released complications, which allows prompt and appropriate medical evaluation and therapeutic intervention. Periodic evaluation by trained specialists helps provide comprehensive care, including transcranial Doppler examinations to identify children at risk for primary stroke, plus assessments for other parenchymal organ damage as patients become teens and adults. Treatment approaches that previously highlighted acute vaso-occlusive events are now evolving to the concept of preventive therapy. Liberalized use of blood transfusions and early consideration of hydroxyurea treatment represent a new treatment paradigm for SCA management.

The natural history of untreated sickle cell anemia (SCA) is well described and documents serious morbidity and early mortality (Powars 1975; Platt et al. 1994; Serjeant 1995; Powars et al. 2005). Hemolytic anemia, acute vaso-occlusive events (VOEs), and chronic end-organ damage begin early in life, and complications accumulate throughout childhood. Without early identification or specific interventions, many patients with SCA have poor quality of life, and most die as young adults of SCA-related complications (Diggs 1973; Rogers et al. 1978).

Fortunately great strides have occurred over the past 40 years, and better management strategies have altered this previously bleak outlook. Despite the complexity and multifactorial pathophysiology of vaso-occlusion (Ware 2010a), relatively straightforward measures have greatly improved outcomes for children with SCA: (1) early identification by neonatal screening programs; (2) education of parents and patients about medical complications and early recognition; (3) preventive measures with prophylactic penicillin and pneumococcal immunizations; (4) aggressive treatment of acute VOEs including hydration, analgesics, antibiotics, and transfusions; (5) screening programs for early signs of organ damage, especially primary stroke risk using transcranial Doppler (TCD) examinations; and (6) therapeutic intervention with transfusions, hydroxyurea, or stem cell transplantation. For children receiving medical care at comprehensive care programs, 95%–99% survival rates into adulthood are documented (Telfer et al. 2007; Quinn et al. 2010). For adults with SCA, screening programs and anticipatory guidance are less standardized but still critical, and the benefits of preventive therapy using hydroxyurea are even more compelling.

Here we will focus primarily on the management of SCA (HbSS or HbS/β^0-thalassemia). We emphasize and summarize general principles of care and management, rather than discussing details of pathophysiology or mechanisms of disease. The management of specific examples of acute VOEs will be highlighted.

EARLY IDENTIFICATION

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Perhaps the most critical aspect of optimizing SCA management is early identification of affected patients, before the onset of signs and symptoms of disease. Without early diagnosis and intervention, SCA often acts as a swift and invisible killer, with many infants dying suddenly of bacterial sepsis or acute splenic sequestration crisis (ASSC) within the first few years of life (Pearson et al. 1969, 1977; Rogers et al. 1978; Powars et al. 1981). Sometimes fatal complications occur even before families or medical providers are aware the infants have SCA.

With the recognition that infants with SCA have greatly increased risk of bacterial sepsis, the landmark multicenter double-blinded placebo-controlled PROPS trial proved that penicillin prophylaxis significantly lowered the risk of bacteremia and death (Gaston et al. 1986). This simple intervention provided the justification needed for newborn screening of SCA, to identify affected infants soon after birth and to allow lifesaving prophylactic antibiotic therapy. Although a 1987 NIH Consensus Conference recommended newborn screening for SCA, universal screening was not accomplished in all U.S. states and territories until 2006.

Newborn screening programs in the United States, Jamaica, and Europe have documented the utility of early identification of SCA, with a marked reduction in morbidity and mortality, especially in the first 5 years of life (Rogers et al. 1978; Vichinsky et al. 1988; Almeida et al. 2001; Bardakdjian-Michau et al. 2001). Figure 1 illustrates that early identification of SCA through neonatal screening programs has contributed to the improved survival rates (Quinn et al. 2010).

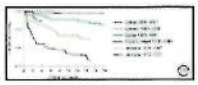

Figure 1.
Survival curves of infants with SCA in the United States and Jamaica, by era. This research was originally published in *Blood*. (From Quinn et al. 2010; reprinted, with permission, © American Society of Hematology.)

Testing of newborns in the United States for SCA began with targeted screening, which involves selecting at-risk populations to screen, such as babies whose parents are African-American. Such an approach is problematic in several ways, and has evolved now to universal screening for all newborns. In contrast, most European countries still perform targeted screening for infants most likely to be affected, such as those of African ancestry. Although potentially cost-effective, targeted screening almost certainly misses some babies with SCA, and presents difficulties related to both equity and logistics (Grosse et al. 2005). Despite the high burden of disease, newborn screening has yet to be implemented systematically in Africa, although pilot studies document a high incidence of trait and disease.

Newborn screening for SCA requires a small dried blood spot (DBS) for analysis, collected from cord blood or the infant's heel/toe. Collection technique is important; DBS specimens have variable quality by the amount and distribution of blood on the filter paper. Specimens are most easily collected in the neonatal period for babies born in the hospital, or during initial immunization visits for babies born at home. Testing in the United States is most commonly performed by hemoglobin electrophoresis using isoelectric focusing (IEF), which easily distinguishes abnormal sickle hemoglobin (Hemoglobin S, HbS) from normal hemoglobin (HbA) and fetal hemoglobin (HbF), as illustrated in Figure 2. High-performance liquid chromatography (HPLC), capillary electrophoresis (CE) techniques, and even DNA-based laboratory diagnosis also can be used for accurate diagnosis. When possible, parental studies should also be performed to confirm the diagnosis of SCA.

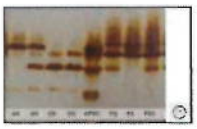

Figure 2.
Isoelectric focusing (IEF) electrophoresis technique for identification of SCA. Blood specimens from AA, AS, and SS patient controls are shown on

the *left*, along with a manufactured Hb AFSC control in the *center*. Newborn samples, typically obtained from ...

EDUCATION

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Parental and family sickle cell education should begin once the diagnosis is made and continue throughout childhood. Given variable parental education and literacy, education should be provided in written and spoken form, and should be repeated with each visit to ensure information is comprehended. When possible, both parents should receive education, plus extended family members and other caregivers, to become knowledgeable about SCA.

Education in the early newborn period should focus on the basics of SCA, including its genetics and inheritance, need for penicillin prophylaxis, and benefits of protein-conjugated pneumococcal immunizations. At each visit these key points should be repeated to parents and caregivers. The importance of regular medical care should be emphasized, especially the need for prompt medical evaluation for fever. Antipyretics should never be given for fever at home, because this treatment can mask a serious infection. Education for young patients should also include signs and symptoms of ASSC: pallor, fussiness or irritability, and tender splenomegaly. Teaching parents to palpate their baby's spleen regularly, ideally several times a day during routine diaper changes, allows early diagnosis of ASSC and potentially prompt and lifesaving intervention.

As the child grows, education should focus more on recognition and early medical intervention for acute vaso-occlusive complications such as dactylitis and other painful events, respiratory distress, acute chest syndrome, and stroke. Parents should learn to manage mild pain at home with oral hydration and analgesia. At an early age, families should be introduced to possible treatment options including hydroxyurea and transfusions, and even stem cell transplantation, if available. As affected children grow up and enter adolescence, it is critical to provide ongoing education about SCA and its complications, to provide young patients with the skills necessary to understand and advocate for their own medical care. Such self-awareness and investment in their medical care becomes critically important on transition from pediatric to adult hematology care. Unfortunately, evidence suggests increased morbidity and mortality in late adolescence and early adulthood following this transition of care (Brousseau et al. 2010; Quinn et al. 2010).

PREVENTIVE MEASURES

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As the result of vascular congestion, intraparenchymal sickling, and hypoxic injury to the spleen, infants with SCA have early loss of filtrative splenic function and are susceptible to acute life-threatening infections, particularly from encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Winkelstein and Drachman 1968; Pearson et al. 1969; Pearson 1977). This risk remains increased throughout life, but is most significantly increased in the first 5 years, when bacteremia incidence is the highest (Overturf et al. 1977; Powars et al. 1981; Gill et al. 1995).

The PROPS trial showed that prophylactic oral penicillin reduced the frequency of bacterial infection by 84% among young children (age 3–36 mo) with SCA (Gaston et al. 1986). However, the follow-up PROPS 2 study was unable to show benefit from penicillin after age 5 yr, primarily owing to their lower incidence of bacteremia (Falletta et al. 1995). After introduction of protein-conjugated pneumococcal vaccines, the incidence of invasive pneumococcal disease decreased by 93.4% among young children with SCA (Halasa et al. 2007). In Africa the dangers of pneumococcal sepsis for children with SCA have been questioned, but recent data confirm its prevalence and lethality (Williams et al. 2009).

Based on overwhelming evidence, early pneumococcal prophylaxis is recommended for all infants with SCA. Penicillin 125 mg by mouth twice daily should begin by 3–4 mo of age, as a liquid formulation or crushed tablet. The penicillin dose should be increased to 250 mg by mouth twice a day as the child grows, typically at 3 yr of age. Some international programs recommend monthly IM penicillin to help ensure compliance. Oral erythromycin can be used as a substitute if penicillin allergy or rash develops, but this is uncommon.

Pneumococcal immunization should begin with locally available pneumococcal conjugate vaccines (7, 10, or 13 valency) and supplemented at age 2 and 5–7 yr with the 23-valent pneumococcal polysaccharide vaccine (Pneumovax). Additional recommended vaccinations include the *H. influenzae* type b series, meningococcal conjugate vaccine (Menactra), and yearly influenza. When locally feasible, the published immunization schedule for high-risk children as recommended by the American Academy of Pediatrics (www2.aap.org/immunization/IZSchedule.html) should be followed.

Penicillin prophylaxis should continue through age 5, when the risk of invasive bacterial disease is lower. Once the immunization series is up to date, including the Pneumovax booster, children with SCA may discontinue penicillin prophylaxis. However, penicillin should be continued indefinitely if a child has had culture-positive sepsis or a surgical splenectomy.

The dramatically increased risk of overwhelming and rapidly fatal infection among young patients with SCA must be understood by all caregivers and medical providers. Fever >38.5°C is a medical emergency requiring prompt medical evaluation, including physical examination with vital signs and splenic palpation, blood culture, complete blood count, reticulocytes, urinalysis, and chest X-ray if clinically warranted. Type and crossmatch should be obtained if there is extreme pallor, splenomegaly, clinical instability, or acute respiratory or neurologic symptoms. After obtaining the blood culture, broad-spectrum antibiotics (e.g., ceftriaxone) should be administered intravenously. Addition of another broad-spectrum antibiotic (e.g., vancomycin) should be considered if the child appears toxic, has high fever, or suspicion of central nervous system (CNS) infection.

Hospitalization is recommended if clinical or laboratory indicators suggest sepsis, such as hemodynamic compromise including hypotension, child <1 yr of age, prior history of sepsis, temperature >40°C, WBC >30 × 10^9/L, or <3 × 10^9/L, concurrent symptoms such as pain or acute anemia, or if close follow-up is not reliable (Lane et al. 2001).

ACUTE VASO-OCCLUSION

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Pain Events

The sudden onset of pain that occurs frequently in patients with SCA results from acute intravascular sickling, so is often referred to as painful VOE or vaso-occlusive "crisis" (VOC). Although many providers and patients use the simple phrase "pain crisis," VOE is preferable because it broadly defines the process and avoids stigma about pain perception and management.

The VOE results from erythrocyte sickling, microvascular occlusion, and tissue ischemia/reperfusion, and is a hallmark clinical feature of SCA. Pain is the most common cause of acute morbidity of SCA, and is associated with severity of disease and early mortality among young adults (Platt et al. 1991). Pain often accompanies acute chest syndrome (ACS), a serious and potentially life-threatening complication of SCA, in 72% of cases (Platt et al. 1994; Vichinsky et al. 2000). This association usually follows sternal or truncal pain, which leads to splinting and poor inspiratory effort, and lack of active and complete inspiration following opioid-induced sedation. The frequency and severity of pain in SCA is more than just episodic and acute, however; pain in SCA is often chronic, underrecognized and underreported, and therefore undertreated (Solomon 2008). Pain diaries of 232 adult patients showed that SCA pain is common and often chronic; pain was present on 54.5% of days and 29.3% of patients reported pain on >95% of days (Smith et al. 2008).

The pathophysiology of vaso-occlusive pain is multifactorial and complex, and includes various blood cells including reticulocytes and neutrophils, plus plasma factors and vascular endothelium (Ware 2010a). Several factors have been identified as triggers of painful VOE, with individual patients often recognizing their own specific triggers. The most commonly described triggers include cold temperatures and especially cold water, as well as dehydration, overexertion, and menses (Redwood et al. 1976; Resar and Oski 1991; Yoong and Tuck 2002).

A combination approach of nonpharmacologic and pharmacologic agents should be used for acute management of vaso-occlusive painful events. Nonpharmacologic interventions with shown effectiveness include oral hydration, heat, massage, and various cognitive-behavioral and self-relaxation techniques (Rees et al. 2003; Dampier et al. 2004). Cold packs can increase local sickling and may exacerbate pain, so should be avoided. Pharmacologic interventions should begin at home with nonopioid analgesics, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs); ibuprofen (10 mg/kg or 800 mg for adults >40 kg every 6–8 h) is an effective oral agent given its potent analgesic and anti-inflammatory properties. Corticosteroids may reduce the duration of painful VOE but on discontinuation, are associated with an increased frequency of rebound painful episodes requiring readmission (Griffin et al. 1994), and so are relatively contraindicated for routine pain management. If pain is not controlled with increased hydration, oral analgesia, and other conservative measures, opioids should be used. Oral narcotic therapy such as codeine and its derivatives can often be used effectively at home, in selected settings and patients.

In the event of severe vaso-occlusive pain requiring formal medical evaluation, aggressive pain management should be implemented promptly with intravenous hydration and opioid (morphine or hydromorphone) analgesia, and adjuvant intravenous NSAID therapy. Historically, the most painful VOEs have been evaluated and treated in the local emergency room, but given the relative lack of sickle cell knowledge and familiarity among some healthcare providers, such evaluations have delays in initiating appropriate analgesia, poor pain control, and a high rate of hospital admission. A sickle cell day hospital approach, which features staffing by experienced sickle cell providers, is increasingly used and results in improved pain management, better patient satisfaction, and decreased rates of hospitalization for both adults and children with SCA (Benjamin et al. 2000; Raphael et al. 2008).

During treatment of VOE, frequent evaluation of pain is important to assess the degree of relief and potential side effects of narcotic analgesia. When hospitalization is required, continuous opioid infusion by patient-controlled analgesia (PCA) is recommended (van Beers et al. 2007; Jacob et al. 2008). Figure 3 illustrates a convenient algorithm to consider for management of mild to severe painful VOE, but flexibility should exist for individual patient preferences. When opioids are used, an aggressive bowel regimen should be used concurrently to reduce gastrointestinal complications, especially hypomotility (O'Brien et al. 2010). Teaching and encouraging frequent incentive spirometry with ambulation can reduce the risk of developing complications including ACS (Bellet et al. 1995; Ahmad et al. 2011).

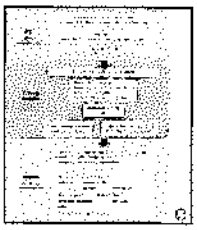

Figure 3.
Algorithm for the management of painful vaso-occlusive events.

Acute Splenic Sequestration Crisis

ASSC remains an important cause of morbidity and mortality for young children with SCA. Most ASSC events occur in infants or toddlers before age 2 yr. In some cases, ASSC may be the first clinical manifestation of SCA, and hence should be emphasized in the education of families during the first year of life.

The pathophysiology of ASSC involves erythrocyte sickling and rapid accumulation within the spleen. ASSC is clinically defined as a decrease in baseline hemoglobin concentration by ≥2 g/dL, in the presence of active reticulocytosis and splenomegaly; mild thrombocytopenia is common. The acute sequestration event can result in severe anemia, occasionally with hypovolemia, and even can evolve to circulatory shock or death (Topley et al. 1981; Emond et al. 1985; Powell et al. 1992).

Medical management of ASSC begins with early recognition and diagnosis; parents and caregivers must be educated about early signs and symptoms and the need to seek urgent medical evaluation. After initial assessment including vital signs and physical examination, laboratory studies should include complete blood count with

reticulocytes, blood culture if febrile, and type and crossmatch. Transfusion volumes should not be excessive because a transfusion "overshoot" phenomenon can occur when the spleen abruptly unloads trapped erythrocytes, raising the hemoglobin level above the target goal. Small aliquots (from the same unit) should be administered every 12–24 h to treat anemia and hypovolemia, while avoiding hyperviscosity following splenic release.

Recurrent ASSC events are common, occurring in about half of the children who survive the first episode. Chronic transfusions can be implemented after the first episode, but their benefits on reducing recurrent events or avoiding splenectomy are limited (Kinney et al. 1990). The benefits of splenectomy for ASSC must be compared to its infectious and other postoperative risks; surgery is usually recommended only after one severe or life-threatening ASSC event, or after several recurrent ASSC events. Pneumococcal immunizations should be completed before surgery, and then lifelong penicillin prophylaxis is recommended (Ammann et al. 1977; Deodhar et al. 1993). Partial or subtotal splenectomy could potentially preserve some filtrative and immunological splenic function, but published reports in SCA are sparse and anecdotal experiences have been unsuccessful (Rice et al. 2003).

Acute Chest Syndrome

ACS is a common cause of morbidity and a leading cause of death among adults with SCA (Castro et al. 1994; Gill et al. 1995; Vichinsky et al. 2000; Powars et al. 2005). First described over 30 years ago (Charache et al. 1979), ACS has a complex pathophysiology that remains poorly defined. Numerous etiologies have been proposed including typical and atypical bacterial pathogens (Miller et al. 1991; Vichinsky et al. 2000; Neumayr et al. 2003), viral infection (Lowenthal et al. 1996), fat embolism (Vichinsky et al. 1994), intrapulmonary sequestration of erythrocytes (Vichinsky et al. 1994), and nitric oxide–hemoglobin interactions (Gladwin et al. 1999).

ACS is defined as a constellation of signs and symptoms including respiratory distress with tachypnea and dyspnea, hypoxemia, fever, elevated WBC count, mild anemia, and new infiltrate on chest X-ray (Castro et al. 1994; Vichinsky et al. 2000; Ballas et al. 2010). ACS is often characterized by rapid clinical decline, so a high index of suspicion is needed for early identification and intervention. The onset of ACS may be insidious, often including pain, with nearly 50% of patients admitted with a different diagnosis. Sternal and rib pain often leads to splinting and poor inspiration, which coupled with mild respiratory depression from opioids, can quickly deteriorate into a serious condition requiring aggressive respiratory and hematological support. To avoid this sequence of events, incentive spirometry can reduce the incidence of ACS and should be mandatory for all hospitalized patients with SCA (Bellet et al 1995; Ahmad et al. 2011).

Worsening hypoxemia or tachypnea, and early radiographic changes should lead to aggressive incentive spirometry, and oxygen therapy to correct hypoxemia. Close management of fluid status is warranted to prevent fluid overload. Although hyperhydration is typically recommended for painful VOE to improve blood flow, intravenous fluids should be limited to 50%–75% maintenance in the setting of evolving ACS, to reduce the risks of developing pulmonary edema or pleural effusions and worsening respiratory distress. Despite the lack of randomized clinical trials investigating the efficacy of antibiotics for ACS (Martí-Carvajal et al. 2007), coverage is provided for typical community-acquired and atypical pathogens, such as a broad-spectrum third-generation cephalosporin and macrolide (Lottenberg and Hassell 2005). Bronchodilators are not effective for all patients but are recommended for patients with ACS and concurrent reactive airways disease or asthma (Knight-Madden and Hambleton 2003; Knight-Madden et al. 2005).

Transfusions are often used for ACS (Lanzkowsky et al. 1978; Vichinsky et al. 2000), improving both anemia and oxygen-carrying capacity. Early simple transfusions are beneficial and can avert clinical deterioration that might warrant later exchange transfusion. Significant respiratory distress or clinical decompensation, hemoglobin ≥2 g/dL below baseline, and oxygen saturation >5% below baseline are all indications for packed red blood cell (PRBC) transfusion (Miller 2011). Automated erythrocytapheresis should be used for severe ACS associated with significant respiratory distress or hypoxia (Kleinman et al. 1984; Velasquez et al. 2009). There is no current evidence that inhaled nitric oxide (NO) has a beneficial role in the current management of ACS (Gladwin et al. 1999; Al Hajeri et al. 2008), but several clinical trials are ongoing. For recurrent ACS, both chronic transfusion

programs (Miller et al. 2001a; Hankins et al. 2005a) and hydroxyurea (Steinberg et al. 2003; Hankins et al. 2005b; Wang et al. 2011) can reduce the frequency and severity of additional ACS events.

Stroke

Cerebrovascular accidents are a relatively common and devastating complication of SCA, with an overt stroke incidence rate of 11% by age 20 years and 24% by age 45 (Ohene-Frempong et al. 1998). Clinical stroke events represent only a fraction of the cerebrovascular complications of SCA, which include silent cerebral infarctions (Miller et al. 2001b; Pegelow et al. 2001; DeBaun et al. 2012) and other neurocognitive deficits (Schatz et al. 2001; Thompson et al. 2002).

In the setting of acute clinical stroke, quickly reestablishing cerebral blood flow is crucial; new-onset weakness or aphasia suggests stroke and intervention should never depend on confirmatory radiological imaging. Modest IV hydration can help acutely, and should be provided while blood is being crossmatched for transfusion. Particularly for children with severe anemia, a simple PRBC transfusion can rapidly reduce intravascular sludging and help improve cerebral blood flow, which is critical to help reverse acute symptoms and prevent stroke progression. When available, exchange transfusion should be performed promptly to reduce HbS <30%, with a target hemoglobin concentration of ~10 g/dL (Swerdlow 2006). A retrospective analysis of children with overt stroke suggested children receiving exchange transfusion had a significantly lower risk of recurrent stroke, compared to children receiving only simple transfusion (Hulbert et al. 2006).

After an initial stroke, the risk of recurrent stroke events is 47%–93% without specific treatment (Powars et al. 1978; Balkaran et al. 1992; Pegelow et al. 1995). Chronic transfusions provided every 3–4 wk to maintain HbS of ~30% are recommended to prevent recurrent events (Lusher et al. 1976; Pegelow et al. 1995; Strater et al. 2002; Platt 2006). Once initiated, transfusions should be continued indefinitely, because discontinuation of transfusions is associated with increased risk of recurrent events (Wang et al. 1991; Adams and Bramilla 2005). Although efficacious, 10%–20% of patients will develop a second stroke despite transfusions (Pegelow et al. 1995; Scothorn et al 2002). Recent evidence further shows progression of vasculopathy and silent cerebral infarctions among chronically transfused patients (Hulbert et al. 2011). Hydroxyurea for the prevention of recurrent stroke, coupled with phlebotomy to remove iron overload, has shown efficacy (Ware et al. 1999, 2004), but in a phase III randomized clinical trial was inferior to transfusions and chelation therapy (Ware and Helms 2012). In certain clinical settings in which chronic transfusions are unsafe or otherwise not feasible, however, hydroxyurea may be a viable treatment option (Ali et al. 2011).

SCREENING PROGRAMS

Go to:

Prevention of complications is the ideal way to reduce the morbidity of acute VOE and potentially limit chronic organ damage; this is especially true when considering devastating neurologic events like stroke. Because blood flow velocity is inversely related to vessel diameter, the measurement of intracerebral arterial blood flow by transcranial Doppler ultrasonography (TCD) allows easy and noninvasive identification of large vessel stenosis and can accurately identify children at increased risk of developing primary stroke (Adams et al. 1992). Children with SCA have increased mean flow velocities when compared to children without anemia (Adams et al. 1989, 1992), and markedly elevated TCD values represent a biomarker of cerebrovascular disease and a significant risk factor for primary stroke.

Based on its utility of screening for stroke risk, both with efficacy in clinical trials (Adams et al. 1998) and effectiveness in clinical practice (McCarville et al. 2008; Enninful-Eghan et al. 2010; Bernaudin et al. 2011; Kwiatkowski et al. 2011), TCD screening is recommended annually for children with SCA starting at the age of 2–3 years. Figure 4 illustrates the recommended screening regimen and algorithm for management of TCD results (Platt 2006; McCarville et al. 2008). The risk of first stroke can be nearly eliminated by the initiation of a chronic transfusion program to decrease HbS <30% for time-averaged maximum blood flow velocities >200 cm/sec in the internal carotid or middle cerebral artery (Adams et al. 1998; Lee et al. 2006). Despite its clear efficacy for

prevention of primary stroke, the risks of chronic transfusion therapy are significant and include iron overload, alloimmunization, and cost (Rosse et al. 1990; Harmatz et al. 2000; Wayne et al. 2000). Hydroxyurea therapy at maximum tolerated dose (MTD) also can reduce TCD velocities (Zimmerman et al. 2007) and the ongoing TWiTCH trial (ClinicalTrials.gov NCT00122980) compares the efficacy of hydroxyurea versus transfusions for prevention of primary stroke in children with abnormal TCD velocities.

Figure 4.
Transcranial Doppler screening algorithm for children with SCA.

ADULT CARE

Go to:

Improved care of the child with SCA has led to increased survival rates into adulthood, and now attention must be focused on appropriate management of this older population. The success of neonatal and pediatric care leads to the formidable task of transitioning patients to the adult healthcare arena, in which providers often are neither trained adequately nor prepared to manage their unique needs. Written guidelines exist for managing adults with SCA (Lottenberg and Hassell 2005) but most of these recommendations do not derive from evidence-based research. The upcoming National Heart, Lung, and Blood Institute (NHLBI) guidelines document for SCA care, anticipated for release and distribution in 2013, will provide current evidence-based guidelines.

Adults with SCD should receive immunization boosters including pneumococcal, meningococcal, and even varicella vaccines based on age-specific recommendations. Management of acute VOEs such as pain, ACS, stroke, and priapism are similar for adults as for pediatric patients, but new issues may emerge related to chronic lung disease, especially restrictive pattern; leg ulcers that are difficult to manage and heal; and hepatic, endocrine, and even cardiac damage related to transfusional iron overload.

Additional screening for specific organ damage is recommended for teens and adults. Baseline pulse oximetry readings will help establish a baseline value and identify chronic hypoxemia. Blood pressure and serum creatinine are typically lower than age-related published values; hence, values at the upper limit of normal may indicate renal dysfunction. Dipstick urinalysis identifies gross proteinuria, but quantitative testing for microalbuminuria, using a 24-h urine collection if warranted, detects subclinical renal disease. Screening for hepatitis B, C, and HIV is warranted for patients who receive chronic blood transfusions; serum ferritin with review of transfusion history may identify patients who need iron chelation. Periodic screening for tricuspid regurgitation jet (TR jet) velocities can identify patients with pulmonary hypertension and possible early mortality (Gladwin et al. 2004). Ophthalmological screening for retinal disease is warranted every 1–3 yr with specialist referral for patients with abnormalities. Additional screening tests for the general adult population should also be provided, including strategies to prevent or identify cancer, hyperlipidemia, bone density loss, and even diabetes. (In the latter case, the lack of HbA makes screening with HbA1c innacurate, but serum fructosamine can be used.)

THERAPEUTIC INTERVENTION

Go to:

Urgent erythrocyte transfusions are indicated for many acute complications of SCA including ACS, ASSC, transient aplastic crisis owing to parvovirus B19 infection, and acute stroke. In these settings, transfused blood helps to alleviate anemia, improve circulating blood volume, increase oxygen-carrying capacity, and provide erythrocytes that cannot sickle. If the posttransfusion target is high enough, transfusions also help suppress endogenous sickle erythropoiesis. Elective transfusions are often given for preoperative management, to prevent perioperative sickle-related complications. Chronic transfusions given on a monthly basis are also highly efficacious for primary and secondary stroke prevention. In contrast, transfusions are not indicated for acute painful events or anemia per se (recognizing that almost all patients have a baseline steady-state partially compensated hemolytic anemia), and have little role in the management of standard VOE (Smith-Whitley and Thompson 2012).

In most acute settings, simple transfusions with packed erythrocytes (PRBC) should be administered. PRBC are readily available across the United States, and are routinely tested for HIV as well as hepatitis B and C. As a general principle, simple transfusions should be given with a target of alleviating anemia or treating the underlying condition; whole units (or half units for small pediatric patients) should be administered whenever possible, instead of fixed volumes (e.g., 10 mL/kg), to help limit foreign antigen exposure. The posttransfusion target hemoglobin concentration should not exceed 10–11 g/dL in the untreated patient because hyperviscosity can occur; in chronically transfused patients with low %HbS, however, the posttransfusion target can be raised to help suppress endogenous erythrocyte production. It is also important for the Blood Bank to be aware that the patient has SCA, because extending red blood cell (RBC) phenotype matching for minor blood group antigens is recommended to help prevent alloimmunization (Yazdanbakhsh et al. 2012).

For patients with neurological indications for chronic transfusion therapy such as abnormal TCD velocities or stroke, repeated simple transfusions are effective in preventing primary and secondary stroke, respectively, but ultimately result in transfusional iron overload. For this reason, partial exchange transfusions or isovolemic erythrocytapheresis is recommended to minimize iron accumulation. In most patients, intravenous access for exchange transfusions is facilitated by the placement of an implantable device. With chronic transfusions, the goal is typically HbS ≤30% as a pretransfusion value, which typically requires transfusion every 3–5 weeks depending on the type and volume of each transfusion, the patient's own erythropoietic drive, and the response to transfusion therapy. Chelation therapy for transfusional iron overload should be considered for all patients on chronic transfusions, but also for teens and adults who have a large cumulative number of episodic or sporadic transfusions.

HYDROXYUREA

Go to:

Increased fetal hemoglobin (HbF) levels have been associated with a less severe phenotype of SCA (Conley et al. 1963; Diggs 1973; Platt et al. 1991, 1994) and HbF induction has become a desired pharmacologic end point for SCA therapy (Charache 1990; Charache et al. 1992). Hydroxyurea has been shown to potently increase HbF and is currently the most effective disease-modifying therapy for both adults and children with SCA (Platt et al. 1984; Steinberg et al. 2003; Zimmerman et al. 2004; Hankins et al. 2005b). The first clinical experience with hydroxyurea for SCA was reported nearly 30 years ago in seminal proof-of-principles studies (Platt et al. 1984). Subsequently, a multicenter phase II study documented laboratory efficacy (increased Hb, %HbF, and MCV; decreased WBC, ANC, ARC, and platelets) of hydroxyurea using a dose escalation schedule to MTD (Charache et al. 1992). The Multi-Center Study of Hydroxyurea (MSH) double-blinded, placebo-controlled randomized clinical trial showed clinical efficacy of hydroxyurea for adults with severe SCA, with significantly reduced time to first painful event, plus fewer episodes of ACS, transfusions, and hospitalizations (Charache et al. 1995).

In children with SCA, similar laboratory and clinical efficacy have been shown in open-label trials (Kinney et al. 1999; Wang et al. 2001; Zimmerman et al. 2004; Hankins et al. 2005b; Thornburg et al. 2009). In hydroxyurea study of long-term effects (HUSTLE), all pediatric patients with medication adherence had HbF responses, although responses were variable and possibly related to differences in drug absorption, pharmacokinetics, and pharmacogenetics (Ware et al. 2011). The results from the double-blinded, placebo-controlled multicenter randomized BABY HUG study show the safety and clinical efficacy of hydroxyurea for young infants with SCA, regardless of previous clinical severity (Wang et al. 2011). The primary end point of BABY HUG was the ability of hydroxyurea to prevent chronic organ damage (kidney, spleen), and the short-term study results were equivocal. Anecdotal reports suggest prevention and even reversal of chronic organ damage with hydroxyurea therapy (Zimmerman et al. 2007; Hankins et al. 2008; Thornburg et al. 2009), so further investigation of the BABY HUG cohort is necessary.

Long-term follow up from MSH and the Greek Laikon Study of Hydroxyurea in Sickle Cell Syndromes documented reduced mortality for adult patients with SCA on hydroxyurea (Steinberg et al. 2010; Voskaridou et al. 2010). There is now indisputable evidence that hydroxyurea has laboratory and clinical efficacy for all ages; a growing body of evidence also supports the long-term safety of hydroxyurea and the ability of hydroxyurea to prevent chronic organ damage and reduce mortality (McGann et al. 2011). Whereas hydroxyurea previously has

been reserved for older patients with a severe clinical course, hydroxyurea use should be liberalized and offered to all adults with SCA. An increasing number of pediatric hematologists believe hydroxyurea should now be considered as a treatment option for all children with SCA, regardless of age or previous clinical course.

Hydroxyurea should be initiated by an experienced clinician familiar with laboratory monitoring and appropriate dose escalation to MTD. Hydroxyurea treatment should commence at ~20 mg/kg/d by mouth, once daily. Complete blood count (CBC) should be checked every 4 wk to monitor for myelosuppression, which is typically mild and dose dependent, and always reversible by holding the hydroxyurea dose temporarily (Heeney and Ware 2008). Dose adequacy and medication compliance can be assessed by reviewing changes in CBC parameters and reviewing the peripheral blood smear (Fig. 5). To reach MTD, the daily dose should be escalated by ~5 mg/kg every 8 wk until MTD is mild neutropenia (e.g., ANC of 1500–3000 $\times 10^6$/L) or reticulocytopenia (ARC of 100–150 $\times 10^9$/L) is reached on a stable dose. Drug toxicity is usually defined by cytopenias such as ANC <1.0 $\times 10^9$/L, hemoglobin <7.0 g/dL with low reticulocyte count, ARC <80 $\times 10^9$/L, and platelets <80 $\times 10^9$/L (Heeney and Ware 2008). Given the unlikelihood of true hydroxyurea "nonresponders," efforts must be made to encourage medication compliance to reach and maintain a stable and efficacious hydroxyurea MTD (Ware 2010b).

Figure 5.

Blood smear changes with hydroxyurea therapy. *A* illustrates the untreated patient with anemia and numerous sickled forms; *B* is after initiation of hydroxyurea treatment with macrocytosis and more target cells; and *C* is after reaching a stable hydroxyurea ...

OTHER TREATMENTS

Go to:

HbF induction can be achieved by a group of short-chain fatty acids that inhibit the enzyme histone deacetylase; such HDAC inhibitors, primarily butyrate, can alter chromatin structure and induce HbF production by altering the transcription of the γ-globin gene (McCaffrey et al. 1997; Ataga 2009; Bradner et al. 2010). Clinical experience with HDAC inhibitors for SCA is limited but anecdotal reports suggest robust HbF induction in some patients with SCA (Atweh et al. 1999; Hines et al. 2008).

Decitabine is a nucleoside analog that induces HbF induction via epigenetic modulation, specifically hypomethylation of the γ-globin gene promoter. Experience with decitabine for SCA is also relatively limited, but several reports suggest clinical and laboratory efficacy of subcutaneously administered decitabine in adults who were not responsive to hydroxyurea (Creusot et al. 1982; DeSimone et al. 2002; Saunthararajah et al. 2003, 2008). Prospective trials of decitabine are warranted to determine if it has efficacy for a broad spectrum of patients with SCA.

Additional treatments that target specific pathways of the pathophysiology of SCA are just entering into clinical trials. One new promising inhibitor of the Gardos channel was found to have favorable effects on hemolysis and RBC survival, yet did not have clinical efficacy in a phase III randomized clinical trial (Ataga et al. 2011).

CONCLUDING REMARKS

Go to:

Decades of observational studies and therapeutic trials have contributed to a greater understanding of the pathophysiology and management of SCA. Based on these results, relatively simple interventions can substantially improve the survival of SCA, especially among children. Newborn screening, early preventive treatments, education about complications, and screening programs improve both the morbidity and mortality of SCA. Going forward, attention must focus on the care and management of teens and adults with SCA, and address quality of life as well as medical complications. More aggressive treatment of SCA is supported by current evidence, and therapeutic options with hydroxyurea should be considered early in life.

Footnotes

Go to:

Editors: David Weatherall, Alan N. Schechter, and David G. Nathan

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