Sickle-Cell Disease:
Prognosis and Treatment

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Reports from Africa during the 1940s and 1950s indicated that very few persons who had sickle-cell disease survived to reach adulthood. In the United States, as medical care improves, increasing numbers of sickle-cell patients are now surviving for four, five, or even six decades of life.

The prognosis of a given patient may be greatly affected by inherited factors. The unusually low morbidity and mortality found among sickle-cell patients in Saudi Arabia, for example, have been attributed to high fetal hemoglobin levels in that country.

What is the prognosis for a child who is found to have sickle-cell disease? In a population of 207 children under the age of 14 in Chicago who were found to have sickle-cell disease, there were 19 deaths (9.1 percent) over a five-year period. A retrospective review of 422 sickle-cell patients in the Los Angeles area over 20 years disclosed 24 deaths and an expected death rate of 10 percent over the first decade of life. The causes of death in these two studies are shown in Table 1. The modal age of death during childhood was two years. The infectious causes were sepsis, pneumonia, meningitis, gastroenteritis, and hepatitis. The majority of infections were due to pneumococcus. All but two of the infectious deaths were in children between one and six years of age; deaths due to splenic sequestration occurred between one and four years of age. Many of these deaths occurred in children not previously recognized as having sickle-cell disease. There were no deaths in a prospective study of 12 sickle-cell patients identified by cord-blood screening and followed for as long as three years.

The prognosis after the first decade is less clear. A multi-institution national prospective study of the natural history of sickle-cell disease is under way and should define the prognosis in older patients more accurately.

TREATMENT

Health maintenance, through the provision of regular, comprehensive medical care, is of particular importance to the patient with sickle-cell disease. During visits to the physician's office, usually scheduled every six to 12 weeks during early childhood and less frequently later, the function of each organ system is reviewed, with emphasis on potential problems associated with the hemoglobinopathy. Baseline values for the complete blood count, reticulocyte count, urinalysis (with specific gravity), and various serum chemistries should be obtained. Particular attention should be paid to growth, which may be retarded, and to the psychosocial adaptation of the patient and his family to his disability. Evaluation by an ophthalmologist every one to two years after age five is recommended, in view of the high frequency of sickle retinopathy. Proper education of the parents in the early detection of signs of infection or splenic sequestration of sickle cells is of particular importance in the newly diagnosed infant. In all patients, health education should stress pain management, provision of adequate fluid intake, and counseling regarding such factors as exposure to cold or travel by air, which may be associated with an increased likelihood of sickle-cell crisis. An appropriate attitude toward such problems as enuresis can be developed in the patient and his family through counseling. Prompt and complete immunization of children with sickle-cell disease should also be stressed.

TABLE 1

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percent of total deaths</th>
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<tr>
<td>Infection</td>
<td>44</td>
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<tr>
<td>Splenic sequestration</td>
<td>16</td>
</tr>
<tr>
<td>Sudden, unexpected death</td>
<td>14</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>12</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>7</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>7</td>
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Source: five-year study in Chicago and 20-year study in Los Angeles.
Because of their particular susceptibility to pneumococcal sepsis, children with sickle-cell disease should receive the polyvalent pneumococcal vaccine at or soon after the age of two. Although no study has yet shown a protective role for prophylactic oral penicillin in children with sickle-cell disease, it is sometimes used in young children, in whom the risk of pneumococcal infection appears to be the highest. Finally, although a well-balanced diet will provide sufficient nutrients and vitamins to sickle-cell-disease patients in most instances, they do have an increased requirement for folic acid as the result of chronic hemolysis and increased erythropoiesis. For this reason, folic acid (1 mg. / day) is usually recommended.

ACUTE CRISSES

Because of the risk of death from overwhelming infection, the sudden appearance of high fever (oral temperature greater than 102°F.), particularly in the absence of an obvious explanation, should be treated as an emergency. Cultures should be obtained and intravenous therapy with penicillin or ampicillin instituted. Such extreme therapy will usually not be necessary in patients in whom fever has developed more gradually and is accompanied by symptoms and signs of localized infection.

In the treatment of vaso-occlusive or painful crises, emphasis is placed on eliminating factors that promote sickling. If hypoxia is suspected, supplemental oxygen should be administered. The value of hyperbaric-oxygen therapy has not yet been established. Acidosis should be corrected promptly, but there is no benefit to alkali administration in the absence of acidosis. Dehydration commonly accompanies vaso-occlusive crisis as a consequence of hyposthenuria and reduced oral fluid intake in an acutely ill patient. Fluid replacement should be aggressive and take into account the continuing urinary losses of water in the hyposthenuric patient. Tylenol, with or without codeine, is sometimes effective in pain management, but often stronger, potentially addicting, narcotics must be utilized. Because repeated dosing with meperidine (Demerol) may be associated with seizures, morphine or hydromorphone are the preferred agents for the relief of severe pain. Although the first goal should be to control pain, care should be taken to minimize the likelihood of narcotic addiction. It is occasionally helpful to supplement analgesic medication with a tranquilizer—such as hydroxyzine pamoate (Vistaril), 50-100 mg. three or four times a day—while remembering to appropriately reduce the dosage of analgesic. The potential of nonpharmacologic means of pain control has not yet been explored in sickle-cell disease.

At present, blood transfusion is the only generally available effective means of terminating or preventing vaso-occlusive crisis. It is also, of course, the treatment of choice for anemic crises and may, under certain circumstances, reverse temporarily organ dysfunction, such as hyposthenuria or functional asplenia. Simple transfusion of packed red cells is often all that is required for the treatment of anemic crisis, but in vaso-occlusive crises, where the goal of treatment is dilution of sickle cells by normal hemoglobin-A-containing red cells, partial exchange transfusion is usually preferred (Table 2). Recommendations vary widely as to the extent of replacement required, but there is a rough consensus that reducing the number of sickle cells to approximately 30 to 40 percent of the total is sufficient. Until recently, use of blood transfusion was limited to the treatment of acute crises or to the short-term prevention of potential crises—as, for example, in preparation for surgery or during the last trimester of pregnancy. Long-term transfusion therapy, extending over a period of years, is now being evaluated in several high-risk groups of sickle-cell patients who have exhibited central-nervous-system manifestations as a result of their hemoglobinopathy.12,13 The advent of more effective methods for the prevention of transfusion reactions and transfusion-induced hepatitis, as well as the development of more effective means of preventing iron overload, may lead to a more widespread use of transfusion therapy in the future.

Surgery poses some special hazards for sickle-cell-disease patients.14 Because it is often difficult to establish the cause of their recurrent episodes of

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**TABLE 2**

INDICATIONS FOR TRANSFUSION THERAPY IN SICKLE-CELL DISEASE

1. Anemic crises
2. Termination of severe vaso-occlusive crises,4-8
3. Prevention of vaso-occlusive crises
   —in pregnancy16
   —in surgery11
   —in stroke12,13
4. Reversal of organ dysfunction*
   —functional hyposthenuria14
   —hyposthenuria16

*Although reversal of functional hyposthenuria or hyposthenuria is feasible, it is not usually attempted and is—at present—primarily of theoretic interest.
pain, they are more likely than others to undergo unnecessary surgery. Even short periods of moderate hypoxia associated with general anesthesia may be sufficient to induce a vaso-occlusive crisis. Re-duction in blood flow—which can, for example, accompany the use of a tourniquet—may have similar consequences. For these risks, the potential benefits can be eliminated by taking special care to maintain adequate oxygenation and body warmth and by such obvious measures as avoiding the use of tourniquets. Preoperative blood transfusion will also effectively reduce the risk of surgery to that of the general population.

There are several settings in which surgery is frequently considered. Well over 25 percent of sickle-cell patients have detectable gallstones by the time of adolescence. In view of the morbidity associated with cholecystectomy, it seems prudent to recommend this procedure only in patients who have experienced at least one episode of acute cholecystitis. Splenectomy, although helpful in other types of hemolytic anemia, has only a limited role in sickle-cell disease. It has little or no effect on the rate of hemolysis, and its chief value lies in the prevention of life-threatening splenic sequestration crises in patients who have already undergone one or two such episodes. In considering splenectomy in young children with sickle-cell disease, one should recall that functional asplenia and increased susceptibility to overwhelming sepsis are features of the disease even in patients who have not undergone splenectomy, and there is no evidence that the operation further adds to the risk of infection.

The therapeutic potential of antisickling agents has been established by the recent thorough evaluations of one such agent, cyanate. This agent, given orally, will prolong the survival of sickle red cells in vivo, resulting in a rise in hemoglobin and a fall in reticulocyte count. However, there is significant toxicity associated with the oral use of cyanate, and at doses acceptable to patients there is no demonstrable reduction in the frequency of vaso-occlusive crises. This limitation has led to development of methods for the extracorporeal use of cyanate in the treatment of sickle-cell disease. Such methods require removal of blood from the patient, treatment of the removed red cells with cyanate, and then removal of unreacted cyanate prior to return of the blood to the patient. Although this type of therapy has been shown to prevent painful crises, it remains experimental. The limitations it places on a patient's life, as well as its complexity and expense, will almost surely limit its eventual application to a very small group of unusually sick patients.

A substantial number of other antisickling agents, effective in vitro, have recently been discovered. For the most part, their mechanism of action is inhibition of gelation of hemoglobin S or prevention of sickling by membrane modification. The possibility also exists that inhibition of microvascular entrapment of sickle cells may have a beneficial therapeutic effect. Most agents currently under development react not only with hemoglobin but with other proteins as well. It is likely that the nonspecificity of such reactions will result in sufficient toxicity to limit their eventual therapeutic usefulness in sickle-cell disease. Other therapeutic approaches, such as bone-marrow transplantation, carry risks that are, at present, unacceptable.

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REFERENCES