# Beneficial Effect of Intravenous Dexamethasone in Children With Mild to Moderately Severe Acute Chest Syndrome Complicating Sickle Cell Disease

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**Acute chest syndrome (ACS) in patients with sickle cell disease (SCD) has historically been managed with oxygen, antibiotics, and blood transfusions. Recently high-dose corticosteroid therapy was shown to reduce the duration of hospitalization in children with SCD and vaso-occlusive crisis. Therefore, we chose to assess the use of glucocorticoids in ACS. We conducted a randomized, double-blind placebo-controlled trial to evaluate the efficacy and toxicity of intravenous dexamethasone (0.3 mg/kg every 12 hours × 4 doses) in children with SCD hospitalized with mild to moderately severe ACS. Forty-three evaluable episodes of ACS occurred in 38 children (median age, 6.7 years). Twenty-two patients received dexamethasone and 21 patients received placebo. There were no statistically significant differences in demographic, clinical, or laboratory characteristics between the two groups. Mean hospital stay was shorter in the dexamethasone-treated group (47 hours *v* 80 hours; *P* = .005). Dexamethasone therapy prevented clinical deterioration and reduced the need for blood transfusions (*P* < .001 and = .013, respectively). Mean duration of oxygen and analgesic therapy, number of opioid doses, and the duration of fever was also significantly reduced in the dexamethasone-treated patients. Of seven patients readmitted within 72 hours after discharge (six after dexamethasone; *P* = .095), only one had respiratory complications (*P* = 1.00). No side effects clearly related to dexamethasone were observed. In a stepwise multiple linear regression analysis, gender and previous episodes of ACS were the only variables that appeared to predict response to dexamethasone, as measured by lengh of hospital stay. Intravenous dexamethasone has a beneficial effect in children with SCD hospitalized with mild to moderately severe acute chest syndrome. Further study of this therapeutic modality is indicated.**


ACUTE CHEST SYNDROME (ACS) is one of the most frequent complications requiring hospitalization and a leading cause of death in children with sickle cell disease (SCD).[1-4] ACS is an acute illness characterized by fever, cough, chest pain, dyspnea, and new pulmonary infiltrates.[3-6] Significant hypoxemia may occur, and the hemoglobin concentration often falls below steady state values, which necessitates blood transfusions.[5,7,8] Pulmonary fibrosis and cor pulmonale may result from repetitive episodes.[9-12]

Despite its substantial morbidity and mortality, relatively little is known about the etiology and pathophysiology of ACS. Some cases of ACS are clearly due to infection.[5,13,14] Additional factors that may precipitate ACS include hypoventilation after opioid analgesics, splinting due to rib infarction, and excessive intravenous hydration.[4,15] More recently, fat embolism has been implicated in some cases.[16,17] Although multiple factors may cause ACS, pulmonary sequestration and/or sickling with resultant pulmonary infarction probably play a key role.[1,4,5,8]

Historically, the management of ACS has included oxygen, intravenous fluids, antibiotics, and blood transfusions.[2,4,5,7,18-20] The role of transfusion therapy (including exchange transfusion) is unclear.[21] Specific therapy that decreases the severity and/or duration of ACS has not been identified. We have previously demonstrated that high-dose intravenous methylprednisolone shortens the duration of hospitalization and reduces opioid requirements in children with painful events.[22] This effect may have resulted from the inhibitory effects of glucocorticoids on the inflammatory response that accompanies tissue ischemia/infarction. We hypothesized that because the pathophysiology of ACS and vaso-occlusive crisis is similar, corticosteroids might also reduce the severity of ACS. Therefore, we undertook a randomized, double-blind placebo-controlled study to assess the efficacy of intravenous dexamethasone in children with mild or moderately severe ACS.

## MATERIALS AND METHODS

### *Study Population*

Patients between 1 and 21 years of age with sickle cell anemia, sickle hemoglobin-C disease, and sickle $\beta^0$-thalassemia who were followed in the sickle cell program of Children's Medical Center of Dallas were eligible if they had mild or moderately severe ACS (see definitions below). Children with severe ACS (see definitions below) were excluded because we deemed it appropriate to study the therapeutic role and possible adverse effects of dexamethasone first in patients without life-threatening illness. However, patients who were enrolled with mild or moderately severe ACS but developed severe ACS during the study continued to receive study drug and remained evaluable. Other exclusion criteria were exacerbation of reactive airways disease, strong suspicion of bacterial infection, or any condition that might preclude the use of glucocorticoids, such as diabetes mellitus, hypertension, gastrointestinal bleeding, etc. The many patients who developed ACS while hospitalized for another reason (eg, surgical procedure, vaso-occlusive pain crisis, fever, or respiratory distress without a pulmonary infiltrate on the initial chest radiograph) were also excluded. Patients with mild or moderately severe ACS and concomitant vaso-occlusive crisis at the time of admission were not excluded.

The study protocol was approved by the Institutional Review Board

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of The University of Texas Southwestern Medical Center at Dallas. Written informed consent was obtained from the parents or guardians.

### *Definitions*

*ACS.* ACS is defined as the presence of a new pulmonary infiltrate (confirmed by a pediatric radiologist) and two or more of the following: fever, tachypnea, dyspnea, retractions, nasal flaring, grunting, or chest pain.[4-6]

*Mild to moderately severe ACS.* This is defined as some respiratory distress present (age adjusted tachypnea, dyspnea, nasal flaring, retractions, and/or grunting), but normal mental status and no extensive pulmonary infiltrates (complete lung involvement) or marked arterial hypoxemia (transcutaneous oxygen saturation $<85\%$ despite supplemental oxygen).

*Severe ACS.* Severe ACS is defined as lethargy, marked respiratory distress, extensive bilateral pulmonary infiltrates (or complete lung involvement unilaterally) and marked arterial hypoxemia.

*Clinical deterioration.* Clinical deterioration is defined as an increase in oxygen requirement and respiratory rate 12 hours or more after the administration of the first dose of the study drug.

*Respiratory clinical severity score.* Score 0, no respiratory distress; 1, age-adjusted tachypnea; 2, age-adjusted tachypnea and retractions.[10]

*Opioid therapy.* Opioid therapy consists of intravenous morphine and/or oral acetaminophen with codeine.

### *Treatment Protocol*

After the decision was made to admit the patient to the hospital and the consent form was signed, the patient was randomly assigned in a double-blind fashion to receive dexamethasone or placebo. The hospital pharmacist dispensed either dexamethasone or normal saline placebo according to a computer-generated list of random assignments. The pharmacist was the only unblinded study participant, but had no direct involvement in patient care.

Patients randomized to the study drug received dexamethasone, 0.3 mg per kg of body weight intravenously in 20 mL of normal saline on admission and 12, 24, and 36 hours after the first dose. Patients randomized to placebo received an equivalent volume of normal saline on the same schedule. The dexamethasone and saline solution had an identical appearance. All syringes were labeled ''steroid study drug.'' The drug was infused over 30 minutes.

Each patient received identical monitoring and supportive care, which included intravenous cefuroxime (50 mg per kg per day administered every 8 hours), oral erythromycin (40 mg per kg per day in three divided doses), intravenous fluids (5% dextrose with 0.45 saline) at maintenance rate, and supplemental oxygen by mask or nasal cannula to maintain oxygen saturation greater than 90%. Patients were placed on transcutaneous oxygen saturation monitors. Opioid agents, morphine intravenously or acetaminophen with codeine orally, were administered as needed. Simple and/or exchange red blood cell transfusions were ordered at the discretion of the attending physician based on the patient's clinical condition and laboratory parameters. Patients were discharged on erythromycin (40 mg per kg per day) to complete a 7-day course. A follow-up clinic appointment including a chest radiograph was scheduled for all patients 7 days after discharge from the hospital.

### *Clinical Assessment*

Clinical severity at diagnosis was determined or categorized as described above.[10] Physical examination, including weight determination, was performed at least daily. During the hospitalization, vital signs every 4 hours and continuous oxygen saturation measurement were recorded. Patients were discharged at the discretion of the attending physician when respiratory distress (ie, tachypnea, dyspnea, use of respiratory accessory muscles, nasal flaring), fever, chest pain, and oxygen requirement had resolved. Completion of the four doses of study drug was not required for patient discharge.

*Radiographic and laboratory assessment.* Admission baseline studies included a chest radiograph, complete blood cell count, reticulocyte count, blood culture, and percutaneous oxygen saturation determination. During hospitalization, daily laboratory monitoring included a chest radiograph, complete blood cell count, and reticulocyte count. Complete blood count was determined on a Coultermax (Coulter, Hialeah, FL). Reticulocyte count was performed by the new methylene blue stain technique. Oxygen saturation measurement was determined using a Nelcor pulse oximeter (Nelcor Inc, Hayward, CA). Hemoglobin concentration and percutaneous oxygen saturation measured during hospitalization were compared with the patient's steady state values. Chest radiograph results at discharge and during follow-up were compared with those obtained on admission.

### *Measurement of Outcome and Statistical Analysis*

A retrospective chart review of 30 patients with ACS who met inclusion criteria was used to determine the sample size required. The primary outcome measurement was length of hospital stay (in hours). Based on an observed standard deviation equal to 28 hours, 21 subjects per treatment group would be required to detect an overall difference of 24 hours with a power equal to 80% and a two-sided test of significance at the .05 level.

Descriptive summary statistics include frequencies and percents for categorical variables and mean, median, range, and standard deviation for numerical values. The .05 level was selected for significance tests.

Comparison of baseline and outcome variables was made using $\chi^2$ contingency table analysis (with Yates correction) or Fisher's exact test for categorical variables. Student's *t*-test for independent samples was used for comparison of numerical outcomes. The relationship of age, sex, number of previous episodes of ACS, presence of pain, and treatment assigned (dexamethasone or placebo) to length of hospital stay was assessed using stepwise multiple linear regression analysis. Exploratory subgroup analyses were made to provide direction for further research. Collected data were stored in Paradox for Windows; statistical analyses were performed using the SAS statistical package (SAS/STAT Guide for Personal Computers, Version 6.04; SAS Institute Inc, Cary, NC, 1987). Except when otherwise specified, the statistical analyses were based on the number of episodes and not on the number of patients. All times recorded begin with the administration of the first dose of study medication, that is, the time when the nurse executed the physician's order and not when the order had been written.

## RESULTS

### *Description of Patients*

Between October 1992 and July 1995, 131 episodes of ACS were diagnosed in our center. Fifty-seven episodes occurred in patients already hospitalized with another disease complication (usually pain crisis). Two additional patients had severe ACS at presentation and received an immediate exchange transfusion. The 72 remaining episodes fulfilled the study eligibility criteria. Twenty episodes of ACS occurred in patients who were not enrolled because parents or guardians were not present or declined to participate. When these 20 episodes were analyzed separately, the clinical, laboratory, and demographic measures at diagnosis were similar to the study population. In addition, the length of hospitalization and overall hospital course were similar to the study patients who received placebo (Table 1).

Fifty-two of these episodes of ACS were included in the study. Of the 52 episodes in which randomization occurred, 9 were not fully evaluable for the following reasons: parents

**Table 1. Clinical Characteristics During the Hospital Course of the Placebo-Treated Patients and Episodes Occurring in Eligible Patients Who Were Not Enrolled on the Study**

| | Placebo-treated Patients (n = 21) | Not Enrolled on Study (n = 20) | *P* Value |
|---|---|---|---|
| Length of hospitalization (h) | | | |
| Mean | 80 | 96 | .62* |
| Range | 34-245 | 19-688 | |
| SD | 50 | 137 | |
| Duration of fever (h) | | | |
| Mean | 53 | 84 | .37* |
| Range | 13-128 | 5-672 | |
| SD | 34 | 154 | |
| Duration of oxygen therapy (h) | | | |
| Mean | 60 | 62 | .88* |
| Range | 9-162 | 19-139 | |
| SD | 43 | 38 | |
| Mean duration of opioid therapy (h) | | | |
| Mean | 77 | 79 | .89* |
| Range | 37-123 | 14-144 | |
| SD | 31 | 48 | |
| ACS episodes that required blood transfusions | 10 (47%) | 11 (55%) | .88† |
| Number of patients requiring intensive care | 2 (9.5%) | 2 (10%) | .96† |

*Student *t*-test for two independent groups.
†Chi-square contingency table analysis or Fisher exact test.

withdrew consent (n = 3), no infiltrate was present on chest radiograph at admission on retrospective review by the pediatric radiologist (n = 4), or intravenous methylprednisolone had been administered for expiratory wheezing (n = 2). Thus, 43 episodes of ACS were evaluable for analysis in 38 children (29 males and 9 females; 34 with sickle cell anemia, 3 with sickle hemoglobin C disease, and 1 with sickle-$\beta^0$ thalassemia) aged 1.4 to 15 years (median, 6.7 years) (Table 2).

Twenty-two episodes were randomized to dexamethasone and 21 to placebo. Four patients who were enrolled on two or more occasions were males with homozygous SCD. One patient who was enrolled three times received dexamethasone once and placebo twice. Three other patients were enrolled twice; two were randomized to placebo during one episode and to dexamethasone the other, and the third child received placebo on both occasions. Polyvalent pneumococcal vaccine had been administered to all patients over age 2 years at some time before their hospitalization. Nine patients (3 of 22 in the dexamethasone group and 6 of 21 in the placebo group; $P = .28$) were not receiving prophylactic penicillin when they developed ACS, either because they were participating on the National Institutes of Health-sponsored Prophylactic Penicillin Study Group II (PROPS II) trial and were assigned to placebo[23] or because they were over 5 years old and were not receiving penicillin prophylaxis according to institutional policy.

There were no statistically significant differences between the two groups (dexamethasone *v* placebo) in any measured demographic, clinical, or laboratory characteristic. The degree of respiratory distress on admission, assessed by the previously

**Table 2. Demographic, Clinical, and Laboratory Characteristics on Admission of 43 Episodes of ACS in 38 Children With SCD**

| | Dexamethasone Treatment n = 22 Episodes | Placebo Treatment n = 21 Episodes | *P* Value |
|---|---|---|---|
| Age | | | |
| Mean | 6.7 | 5.7 | .4* |
| Range | 1.4-15 | 1.4-13 | |
| SD | 3.8 | 3.9 | |
| Gender | | | |
| Male | 17 | 12 | .33† |
| Female | 5 | 9 | |
| Type of hemoglobinopathy | | | |
| SS | 19 | 18 | |
| SC | 2 | 3 | |
| S $\beta^0$-thalassemia | 1 | 0 | |
| Previous episodes of ACS | | | |
| Mean | 2.7 | 3.7 | .33* |
| Range | 0-10 | 0-15 | |
| SD | 2.8 | 3.8 | |
| No. of patients with pain | 16 (73%) | 17 (81%) | .72† |
| Chest/shoulder | 12 | 9 | |
| Back | 2 | 2 | |
| Abdomen | 4 | 3 | |
| Other | 3 | 6 | |
| Hemoglobin concentration (g/dL) | | | |
| Mean | 7.93 | 7.38 | .19* |
| Range | 5.3-11.4 | 5.6-10.4 | |
| SD | 1.48 | 1.23 | |
| Room air transcutaneous oxygen saturation (%) | | | |
| Mean | 89.6 | 89.5 | .96* |
| Range | 70-98 | 57-100 | |
| SD | 6.5 | 9 | |
| Patients requiring supplemental oxygen | 13 (59%) | 15 (71%) | .60* |
| Chest radiograph findings | | | |
| Single lobe involvement | 14 (64%) | 13 (62%) | .91† |
| Multiple-lobe involvement | 8 (38%) | 8 (38%) | |
| Previous SCD-related hospitalizations other than ACS | | | |
| Mean | 3.6 | 2.3 | .19* |
| Range | 0-14 | 0-6 | |
| SD | 3.9 | 2.2 | |
| Duration of symptoms before admission (h) | | | |
| Mean | 32 | 26 | .47* |
| Range | 11-112 | 12-120 | |
| SD | 24 | 30 | |
| Respiratory score | | | |
| Mean | 1.43 | 1.43 | 1.0* |
| Range | 1-2 | 1-2 | |
| SD | 0.45 | 0.48 | |
| Fever | 19 (86%) | 17 (81%) | .70† |
| Expiratory wheezing | 3 (14%) | 4 (19%) | .70† |
| Patients requiring opioid therapy | 12 (54%) | 11 (52%) | .89* |

*Student *t*-test for two independent groups.
†Chi-square contingency table analysis or Fisher exact test.

described scoring system,[10] was not significantly different between the two groups (Table 2).

*Clinical Course and Duration of Hospitalization*

The length of hospitalization, determined from the time of administration of the first dose of study drug to the time of hospital discharge, was significantly shorter in the dexamethasone-treated group (47 *v* 80 hours; $P = .006$; Table 3). None of the study patients remained hospitalized for any other reason (eg, pain, psychosocial problems, etc) after the respiratory distress had resolved. Four of the nine patients whose episodes of ACS were not fully evaluable for reasons other than having received methylprednisolone for wheezing received at least 2 doses of study drug. When these episodes were included in the analysis (totaling 47 episodes), the difference in the mean hospital stay continued to be statistically significant, favoring the dexamethasone group (45 *v* 77 hours; $P = .005$).

To further assess the efficacy of dexamethasone, the length of the second hospital admission of the patient who was readmitted with exacerbation of ACS 72 hours after discharge (patient 6, Table 4) was added to the initial hospital admission as if it were a single prolonged admission. The difference in duration of hospitalization in the two groups remained significant (53 *v* 80 hours; $P = .033$). However, when a similar analysis was performed considering all six patients readmitted within 72 hours after discharge due to exacerbation of ACS or development of vaso-occlusive events (patients 1 to 6, Table 4), the difference in duration of hospitalization in the two groups was no longer significant (66 *v* 80; $P = .31$).

Eight (8 of 22) patients in the placebo group, but none (0 of 21) in the dexamethasone group ($P < .001$) experienced clinical deterioration (see definition above) of their respiratory status (Table 3). Two patients in the placebo group required endotracheal intubation with mechanical ventilation and double-volume exchange transfusions. Both recovered.

**Table 3. Effects of Dexamethasone in 43 Episodes of ACS Occurring in 38 Children With SCD**

| | Dexamethasone (n = 22) | Placebo (n = 21) | *P* Value |
|---|---|---|---|
| Length of hospitalization (h) | | | |
| Mean | 47 | 80 | .005 |
| Range | 18-87 | 34-245 | |
| SD | 16 | 50 | |
| Duration of oxygen therapy (h) | | | |
| Mean | 30 | 60 | .004 |
| Range | 11-83 | 9-162 | |
| SD | 18 | 43 | |
| Duration of opioid therapy (h) | | | |
| Mean | 19 | 76 | <.001 |
| Range | 2-37 | 37-123 | |
| SD | 14 | 31 | |
| No. of administered opioid doses | | | <.001 |
| Mean | 2.46 | 20.2 | |
| Range | 1-5 | 2-53 | |
| SD | 1.37 | 15.6 | |
| Persistent fever | 1 (4.5%) | 14 (67%) | <.001 |
| Occurrence of clinical deterioration | 0 | 8 (38%) | <.001 |
| Blood transfusion requirements | 2 (9%) | 10 (47%) | .013 |
| Readmission within 72 hours after discharge | 6 (27%) | 1 (4.7%) | .095 |
| Readmission with ACS within 72 hours after discharge | 1 (4.5%) | 0 | 1.000 |

*Fever and Documented Infections*

All 43 patients had a history of fever before admission, and 36 children (84%) were documented to be febrile (> 38.5°C) on presentation (including 19 in the dexamethasone group; Table 2). After administration of the first dose of dexamethasone, all patients except one became afebrile within 4 hours and remained so during the remainder of the hospital admission. In comparison, 14 of the 17 children who received placebo had persistent fever (intermittent or persistent fever over 38.5°C after the administration of the first dose of placebo or dexamethasone) for a median of 36 hours (mean, 52 hours; range, 13 to 120 hours; Table 3). The difference in the percentage of patients with persistent fever was highly significant ($P < .001$). One patient, randomized to placebo, had a positive blood culture (obtained at admission) due to *Staphylococcus aureus*. His chest radiograph at presentation showed infiltrates in the right middle and lower lobes. Because the patient did not appear seriously ill, became afebrile during the second hospital day, and had two negative repeat blood cultures, no modification was made in antibiotic coverage. He had no complications during the hospital course. During his follow-up clinic visit, he remained asymptomatic, and a chest radiograph showed improvement of the pulmonary infiltrates.

*Oxygen, Analgesic, and Transfusion Requirements*

There was no significant difference in the transcutaneous oxygen saturation or supplemental oxygen requirement between the two groups at the time of admission (Table 2; $P = .96$ and .60, respectively). However, after randomization, the mean duration of oxygen therapy was significantly less in patients receiving dexamethasone (30 *v* 61 hours; $P = .004$; Table 3).

The mean duration of opioid therapy was significantly less in the dexamethasone-treated group (16.8 *v* 76.8 hours; $P < .001$; Table 3). Also, the mean number of opioid doses administered was significantly less in the dexamethasone-treated patients (2.5 *v* 20 doses; $P < .001$; Table 3). Patients receiving placebo were more likely to require modifications (eg, changing the route of opioid administration from oral to intravenous or from intermittent intravenous to a continuous infusion and/or increasing the dose) of the analgesic therapy (five events *v* one event; $P = .08$).

A total of 12 blood transfusions were administered during 10 episodes of ACS. Two transfusions were administered during two different dexamethasone-treated episodes of ACS, whereas 10 transfusions, including two exchange transfusions, were given during eight episodes of placebo-treated patients ($P = .013$; Table 3). Clinical deterioration and a decline in hemoglobin concentration were the indication for 8 of the 10 transfusions in the placebo-treated group. The two dexamethasone-treated patients received a transfusion for a decline in hemoglobin concentration (from 8.7 g/dL to 5.3 g/dL and from 7.0 g/dL to

**Table 4. Clinical and Laboratory Characteristics of the Seven Patients Who Were Readmitted Within 72 Hours After Discharge**

| Patient No. | Randomization and No. of Doses Received | First Admission | | | Hours Elapsed Between Discharge and Readmission | Subsequent Admission | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Concomitant Pain | Hospital Stay (hr) | Chest Radiograph* | | Reason for Readmission | Concomitant Pain | Hospital Stay (hr) | Chest Radiograph† |
| 1 | Dexamethasone 4 doses | Chest, back | 36 | Same | 27 | VOC‡ | Back, abdomen | 65 | ND |
| 2 | Dexamethasone 4 doses | Abdomen, chest | 63 | Improved | 36 | Stroke | Head | 65 | ND |
| 3 | Dexamethasone 4 doses | Chest, extremity | 72 | Same | 15 | VOC | Back | 48 | ND |
| 4 | Dexamethasone 4 doses | Chest | 42 | Same | 56 | VOC | Arm | 88 | ND |
| 5 | Dexamethasone 2 doses | Chest, back | 19 | Worse | 58 | VOC | Hand | 105 | Normal |
| 6 | Dexamethasone 3 doses | None | 34 | Improved | 24 | ACS | None | 125 | New infiltrates |
| 7 | Placebo 4 doses | Extremity | 36 | Improved | 48 | Aplastic crisis | None | 33 | ND |

Abbreviations: VOC, vaso-occlusive pain crisis; ACS, acute chest syndrome; ND, not done; improved, partial or complete resolution of pulmonary infiltrates; same, no changes in pulmonary infiltrates; worse, extension of previous pulmonary infiltrates or new infiltrates.

*At the time of discharge, when compared with the admission chest radiograph.

†At the time of the second admission.

‡Developed ACS during the third day of hospital course.

5.7 g/dL, respectively). Their clinical course was otherwise stable.

*Laboratory and Imaging Results*

Comparison of steady state hemoglobin concentration and transcutaneous oxygen saturation levels with nadir values observed during the episode of ACS indicated that dexamethasone therapy did not prevent a significant decline in these measurements ($P = .07$ and $P = .79$, respectively).

Comparison of chest radiograph findings on admission and discharge disclosed no apparent impact of dexamethasone therapy on short-term progression or resolution of the pulmonary infiltrates. Five patients in the dexamethasone group and nine in the placebo group had a partial or complete resolution of their infiltrate by the time of discharge. Ten patients in the dexamethasone group and seven in the placebo group had no change in their pulmonary infiltrates, while four patients in the dexamethasone group and three patients in the placebo group had extension of the pulmonary infiltrates noted on admission. Five patients (two in the placebo-treated group) did not have a repeat chest radiograph at the time of discharge.

*Readmission*

All enrolled patients were evaluated for readmission to the hospital for 3 weeks after discharge. Seven patients (six of whom had received dexamethasone; Table 3; $P = .095$) were readmitted, each within 72 hours after initial discharge. Nevertheless, only one patient was readmitted with ACS ($P = 1.00$). The seven patients who were readmitted exhibited no apparent demographic, clinical, and/or laboratory characteristics that differed from the rest of the study population (Table 4).

The dexamethasone-treated patient readmitted because of a cerebrovascular accident (patient 2; Table 4) was a 6-year-old boy who developed left hemiparesis and headache 36 hours after discharge. During the previous admission, he had no dexamethasone-related complications (such as hypertension) known to contribute to stroke. However, he had received a blood transfusion because of a decline in hemoglobin concentration (from 7.0 to 5.7 g/dL). His posttransfusion hemoglobin concentration was 9.5 g/dL. On readmission, magnetic resonance imaging showed a cerebral infarct in the right middle cerebral artery distribution. Magnetic resonance angiography imaging and transcranial Doppler studies showed extensive large vessel disease. The patient experienced a near complete neurological recovery and remains on a chronic transfusion program without further sequelae.

*Other Complications*

No specific complications related to the use of dexamethasone (such as hypertension, psychosis, symptomatic osteonecrosis, gastrointestinal bleeding, hyperglycemia, or opportunistic infection) were observed during the study period or on follow-up in any of the 38 patients. All blood pressure values were within the age-related normal range for pediatric patients. A specific comparison of individual blood pressure measurements in each dexamethasone- or placebo-treated patient was not undertaken.

*Follow-up*

Twenty-four patients (12 in each group) returned for a follow-up outpatient clinic visit 7 days after discharge. All patients were free of symptoms. There were no statistically significant differences between the two groups when the results of follow-up chest radiographs were compared with the findings at discharge. Specifically, 10 patients in the dexamethasone group and nine in the placebo group had partial or complete resolution of pulmonary infiltrates between discharge and the follow-up visit. One patient in each group had no change, while

one patient in the dexamethasone group and two patients in the placebo group had extension of previous pulmonary infiltrates. The distribution of results in the two groups is similar ($P = .40$).

*Results of Stepwise Multiple Linear Regression Analysis*

Stepwise multiple regression analysis explored the relationship of age, gender, number of previous ACS episodes, presence or absence of concomitant pain, and type of treatment to the length of hospitalization. In order of importance, three variables entered the prediction equation: type of treatment, number of previous episodes, and gender. The multiple regression was significant at the $P = .002$ level with a multiple $R = .565$.

Results of this analysis indicated that irrespective of treatment group, the males tended to have a shorter hospitalization than did females, and those children with no previous ACS episodes tended to have a shorter hospital stay than those with one or more prior events. Patients' age and the presence of concomitant pain played no role in predicting response to dexamethasone as measured by length of hospital stay.

## DISCUSSION

The treatment of ACS has included hospitalization, supplemental oxygen, intravenous and/or oral antibiotics, analgesics, and simple or exchange transfusion.[2,18-21] However, no single therapeutic approach has previously been shown to be effective in ACS when tested by a randomized controlled trial. Although aggressive blood transfusion support has been widely used and is seemingly beneficial, there is no consensus on its indications or method of administration.[21]

To our knowledge, the use of glucocorticoids in patients with SCD and ACS has not been previously reported. However, steroids have been used to treat acute vaso-occlusive crises.[22,24] Griffin et al[22] studied the role of methylprednisolone (15 mg/kg) in patients with SCD and pain. Duration of analgesic therapy and hospital stay were significantly reduced in the steroid-treated group. However, an excess number of patients randomized to methylprednisolone were readmitted due to recurrence of pain. Concerns about administering such high doses of methylprednisolone and the possible ''rebound'' effect suggested the use of a lower dose of a longer acting glucocorticoid (eg, dexamethasone) in the current study. The dexamethasone dose and schedule used here was comparable to that previously used in infants and children with bacterial meningitis and croup.[25,26]

In this double-blind placebo-controlled trial, which assessed the efficacy of dexamethasone in children with mild to moderately severe ACS, treatment with dexamethasone reduced the length of hospitalization by about 40%. In our patients, adjuvant dexamethasone therapy appears to have prevented clinical deterioration and reduced the need for blood transfusion to treat the worsening anemia that often characterizes ACS.[4,5,7] Furthermore, dexamethasone therapy had a highly favorable impact on the duration of fever, oxygen requirement, and need for opioid analgesia.

Numerous observers have suggested that recurrent and severe episodes of ACS may result in permanent lung disease.[9-12,17,27,28] Therefore, by shortening the duration of symptomatic ACS and reducing the accompanying inflammatory process, dexamethasone therapy may diminish or prevent irreversible injury to the pulmonary parenchyma.

Although the number of children in each subgroup was too small to provide definitive conclusions, in a stepwise multiple regression analysis, males and patients with fewer prior ACS episodes appeared to have a particularly favorable response to dexamethasone. Lung damage caused by previous episodes of ACS might have adversely influenced the response to dexamethasone. Additionally, young males have been shown to have a smaller peripheral airway diameter than females[29,30] so might therefore have benefitted more from the antiinflammatory properties of glucocorticoids.

The specific mechanisms by which dexamethasone may be beneficial during ACS are unclear. Because many of the signs and symptoms of painful vaso-occlusive crisis (and perhaps of intrapulmonary sickling as well) resemble those seen in states of inflammation, the salutary effects of dexamethasone noted here may have resulted from inhibition of the inflammatory response that accompanies tissue ischemia/infarction. Cytokines (eg, interleukins, tumor necrosis factor, prostaglandins, etc) released during infection and episodes of ischemia have been shown to play a pivotal role in inflammatory reactions within the lung.[31] Glucocorticoids inhibit the production of cytokines and alter arachidonic acid metabolism.[32-34] The clinical significance of these antiinflammatory pharmacologic properties have been well demonstrated in bacterial meningitis.[25] This mechanism may also explain the dramatic effect of dexamethasone on the resolution of fever in our patients.

There is increasing evidence that fat embolism resulting from bone marrow infarction may play a cardinal role in the pathophysiology of ACS.[16,17,35] Although we did not investigate our patients for fat embolism, it is of interest that glucocorticoids are often used in the prevention of pulmonary fat embolism after orthopedic trauma.[36,37] The precise mechanisms for the damaging effects of pulmonary fat embolism in ACS are not well understood. In a recent study, Styles et al[38] reported a 140-fold increase in levels of plasma phospholipase $A_2$ in patients with SCD and ACS compared with controls. Phospholipase $A_2$ and free fatty acids are known to cause bronchoconstriction and increase pulmonary vascular permeability, mucus secretion, and leukocyte chemotaxis.[39-43] Dexamethasone is a potent inhibitor of phospholipase $A_2$,[39,44,45] so perhaps its beneficial effects in ACS are mediated by blocking the liberation of free fatty acids and preventing their damaging effects on the lungs.

There were no significant differences in the clinical course or duration of hospital stay between our placebo-treated group and patients who were eligible, but not enrolled (Table 1). However, the average hospital stay in placebo-treated patients was shorter than in most previous reports of ACS.[4,5,8,17] There are several explanations for this observation. First, patients with severe ACS were excluded from the study. Such patients usually require exchange transfusion, intensive care, and prolonged hospitalization. Second, most reported series of ACS include patients admitted initially with ACS, as well as those who develop ACS while hospitalized for other reasons. Our cohort of study patients included only those with ACS diagnosed on admission. Not surprisingly, such patients have shorter hospital-

izations than those whose ACS develops while already hospitalized.[4] Third, it has been reported that older patients with multiple prior events of ACS have longer hospitalizations.[3,7,46] Thus, the younger age (mean, 6.7 years) and fewer prior episodes of ACS (median, 2 previous events) may explain the relatively brief hospital stay of the placebo-treated group.

Although no complications of dexamethasone therapy were observed in our patients, caution must be exercised when using glucocorticoids in patients with sickle cell anemia, as such individuals are predisposed to develop avascular necrosis of the hip and shoulder. However, when extremely high glucocorticoid doses are used for prolonged periods in children without SCD, avascular necrosis has rarely been reported.[46,47]

Patient 2 (Table 4) had a stroke within 48 hours after discharge. During his hospital admission, he received a simple packed red blood cell transfusion. Strokes have been described after simple or exchange transfusion resulting in a posttransfusion hemoglobin concentration over 12 g/dL.[48,49] However, this was not the case in our patient. Furthermore, ACS appears to be an independent significant risk factor for stroke in patients with sickle cell anemia.[50] Although our patient had neither hypertension nor other obvious complications of corticosteroids, we cannot definitively exclude the possibility that dexamethasone might have played a role in this event.

Although the readmission rate among dexamethasone-treated patients was not significantly higher ($P = .095$) than placebo-treated patients, individuals randomized to dexamethasone therapy were more likely to be readmitted with sickle cell-related complications. When all vaso-occlusive-related hospital readmissions were taken into consideration, the hospital stay length between the two groups became insignificant. Yet, dexamethasone therapy still played a key role in improving the overall well-being of the patients by preventing clinical deterioration, decreasing the need for oxygen therapy, red blood cell transfusions, opioid therapy, and the resolution of fever. There is no clear explanation for this phenomenon. It can be hypothesized that because the time between the reappearance of their symptoms and the last dose of study drug is similar to the plasma half-life of dexamethasone (24 hours), the exacerbation of the symptoms might have represented a ''rebound'' effect. In addition, there are three case reports of glucocorticoids precipitating vaso-occlusive crises and or bone marrow fat necrosis. However, the relationship between the development of the event and the administration of glucocorticoid appears to be only temporal, not causal.[16,51] To our knowledge, there is no physiologic or pharmacologic explanation for this phenomenon.

Dexamethasone is the first therapeutic intervention shown to benefit children with ACS in a randomized, double-blind placebo-controlled trial. ACS in children differs appreciably in its clinical features from the disease in adults.[3] Because the study did not include older adolescents and/or adults, severely affected patients, or patients who developed ACS while in the hospital for another reason, further study of dexamethasone is warranted in patients with ACS and SCD.

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## REFERENCES

1. Buchanan GR: Newer concepts in the management of sickle cell disease. Focus and Opinion: Pediatrics 1:100, 1995

2. Vichinsky EP: Comprehensive care in sickle cell disease: Its impact on morbidity and mortality. Semin Hematol 28:220, 1991

3. Vichinsky EP, Styles LA, Colangelo LH, EC Wright, Castro O, Nikerson B, Disease Cooperative Study of Sickle Cell: Acute Chest Syndrome in sickle cell disease: Clinical presentation and course. Blood 89:1787, 1997

4. Sprinkle RH, Cole T, Smith S, Buchanan GR: Acute chest syndrome in children with sickle cell disease. A retrospective analysis of 100 hospitalized cases. Am J Pediatr Hematol Oncol 8:105, 1986

5. Poncz M, Kane E, Gill M: Acute chest syndrome in sickle cell disease: Etiology and clinical correlates. J Pediatr 107:861, 1985

6. Castro O, Brambilla DJ, Thorington B, Reindorf CA, Scott RB, Gillette P, Vera JC, Levy PS: The acute chest syndrome in sickle cell disease: Incidence and risk factors. Blood 84:643, 1994

7. Koren A, Wald I, Halevi R, Ben Ami M: Acute chest syndrome in children with sickle cell anemia. Pediatr Hematol Oncol 7:99, 1990

8. Davies SC, Win AA, Luce PJ, Riordan JF, Brozovic M: Acute chest syndrome in sickle cell disease. Lancet 1:36, 1984

9. De Ceulaer K, McMullen KW, Maude GH, Keatinge R, Serjeant GR: Pneumonia in young children with homozygous sickle cell disease: Risk and clinical features. Eur J Pediatr 144:255, 1985

10. Miller GJ, Serjeant GR: An assessment of lung volumes and gas transfer in sickle-cell anemia. Thorax 26:309, 1971

11. Bowen EF, Crowston JG, De Ceulaer K, Serjeant GR: Peak expiratory flow rate and acute chest syndrome in homozygous sickle cell disease. Arch Dis Child 66:330, 1991

12. Powars D, Weidman JA, Odom-Maryon T, Nilan JC, Johnson C: Sickle cell chronic lung disease: Prior morbidity and the risk of pulmonary failure. Medicine 67:66, 1988

13. Shulman ST, Bartlett J, Clyde WA, Ayoub EM: The unusual severity of *Mycoplasma* pneumonia in children with sickle cell disease. N Engl J Med 287:164, 1972

14. Miller ST, Hammerschlag MR, Chirgwin K, Rao SP, Roblin P, Gellin M, Stilerman T, Schachter J, Cassell G: Role of *Chlamydia pneumoniae* in acute chest syndrome of sickle cell disease. J Pediatr 118:30, 1991

15. Gelfand MJ, Daya SA, Rucknagel DL, Kalinyak KA, Paltiel HJ: Simultaneous occurrence of rib infarction and pulmonary infiltrates in sickle cell disease patients with acute chest syndrome. J Nucl Med 34:614, 1993

16. Johnson K, Stastny JF, Rucknagel DL: Fat embolism syndrome associated with asthma and sickle cell beta$^+$-thalassemia. Am J Hematol 46:354, 1994

17. Vichinsky E, Williams R, Das M, Earles AN, Lewis N, Alder A, McQuitty J: Pulmonary fat embolism: A distinct cause of severe acute chest syndrome in sickle cell anemia. Blood 83:3107, 1994

18. Hassell KL, Eckman JR, Lane PA: Acute multiorgan failure syndrome: A potentially catastrophic complication of severe sickle cell pain episodes. Am J Med 96:155, 1994

19. Lanzkowsky P, Shende A, Karayalcin G, Kim YJ, Aballi AJ: Partial exchange transfusion in sickle cell anemia. Am J Dis Child 132:1206, 1978

20. Pearson HA, Diamond LK: The critically ill child: Sickle cell disease crises and their management. Pediatrics 48:629, 1971

21. Wayne AS, Kevy SV, Nathan DG: Transfusion management of sickle cell disease. Blood 81:1109, 1993

22. Griffin TC, McIntire D, Buchanan GR: High-dose intravenous methylprednisolone therapy for pain in children and adolescents with sickle cell disease. N Engl J Med 330:733, 1994

23. Falleta JM, Woods GM, Verter JI, Buchanan GR, Pegelow CH, Iyer RV, Miller ST, Holbrook CT, Kinney TR, Vichinsky E, Becton DL, Wang W, Johnstone HS: Discontinuing penicillin prophylaxis in children with sickle cell anemia. J Pediatr 127:685, 1995

24. Isaacs WA, Effiong CE, Ayeni O: Steroid in the prevention of painful episodes in sickle-cell disease. Lancet 1:570, 1972

25. Odio CM, Faingezicht I, Paris M, Nassar M, Baltodano A, Rogers J, Saez-Llorens X, Olsen KD, McCracken GH Jr: The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. N Engl J Med 324:1525, 1991

26. Cruz MN, Stewart G, Rosenberg N: Use of dexamethasone in the outpatient management of acute laryngotracheitis. Pediatrics 96:220, 1995

27. Haynes J, Kirkpatrick MB: The acute chest syndrome of sickle cell disease. Am J Med Sci 305:326, 1993

28. Weil JV, Castro O, Malik AB, Rodgers G, Bonds DR, Jacobs TP: Pathogenesis of lung disease in sickle hemoglobinopathies. Am Rev Resp Dis 148:249, 1993

29. Mead J: Dysanapsis in normal lungs assessed by the relationship between maximal flow, static recoil, and vital capacity. Am Rev Resp Dis 121:339, 1980

30. Hibbert ME, Couriel JM, Landau LI: Changes in lung, and chest wall function in boys and girls between 8 and 12 yr. J Appl Physiol 57:304, 1984

31. Luster AD: Chemokines-chemotactic cytokines that mediate inflammation. N Engl J Med 338:436, 1998

32. Henderson WR: Lipid-derived and other chemical mediators of inflammation in the lung. J Allergy Clin Immunol 79:543, 1987

33. Wallner BP, Mattaliano RJ, Hession C, Cate RL, Tizard R, Sinclair LK, Foeller C, Chow EP, Browning JL, Ramachandran KL, Pepinsky RB: Cloning and expression of human lipocortin: A phospholipase $A_2$ inhibitor with potential anti-inflammatory activity. Nature 320:77, 1986

34. Schleimer RP: Effects of glucocorticoids on inflammatory cells relevant to their therapeutic applications in asthma. Am Rev Resp Dis 141:S59, 1990 (suppl)

35. Shapiro MP, Hayes JA: Fat embolism in sickle cell disease. Arch Intern Med 144:181, 1984

36. Schonfeld SA, Ploysongsang Y, DiLisio R, Crissman JD, Miller E, Hammerschmidt DE, Jacob HS: Fat embolism prophylaxis with corticosteroids. Ann Intern Med 99:438, 1983

37. Alho A: Fat embolism syndrome: Etiology, pathogenesis and treatment. Acta Chir Scand 499:75, 1980

38. Styles L, Schalkwijk C, Vichinsky E, Lubin BH, Kuypers FA: Dramatically increased phospholipase $A_2$ in sickle cell disease associated with acute chest syndrome (ACS). Blood 84:219, 1994 (suppl 1)

39. Tocker JE, Durham SK, Welton AF, Selig WM: Phospholipase $A_2$-induced pulmonary and hemodynamic responses in the guinea pig. Effects of enzyme inhibitors and mediators agonists. Am Rev Resp Dis 142:1193, 1990

40. Vadas P, Browing J, Edelson J, Pruzanski W: Extracellular phospholipase $A_2$ expression and inflammation. The relationship with associated disease states. J Lipid Mediat 8:1, 1993

41. Edelson JD, Vadas P, Villar J, Mullen JBM, Pruzanski W: Acute lung injury induced by phospholipase $A_2$: Structural and functional changes. Am Rev Resp Dis 143:1102, 1991

42. Pereira GR, Fox WW, Stanley CA, Baker L, Schwartz JG: Decreased oxygenation and hyperlipidemia during intravenous fat infusions in premature infants. Pediatrics 66:26, 1980

43. Peltier LF: The toxic properties of neutral and free fatty acids. Surgery 40:665, 1956

44. Vadas P, Stefanski E, Pruzanski W: Potential therapeutic efficacy of inhibitors of human phospholipase $A_2$ in septic shock. Agents Actions 19:194, 1986

45. van den Bosh H, Schalkwijk C, Pfeilschifter J, Marki F: The induction of cellular group II phospholipase $A_2$ by cytokines and its prevention by dexamethasone. Adv Exp Med Biol 318:1, 1992

46. Miller J III: Prolonged used of large intravenous steroid pulses in the rheumatic diseases of children. Pediatrics 65:989, 1980

47. Bernini JC, Carrillo JM, Buchanan GR: High dose intravenous methylprednisolone therapy for patients with Diamond-Blackfan anemia refractory to conventional doses of steroids. J Pediatr 127:654, 1995

48. Fort DW, Rogers ZR, Buchanan GR: Cerebral infarction following partial exchange transfusion in three children with sickle cell anemia. Proceeding of the Sixteenth Annual Meeting of the National Sickle Cell Disease Program, Mobile, AL, March 24-26, 1991, p 50

49. Rackoff WR, Ohene-Frempong K, Month S, Scott P, Neahring B, Cohen AR: Neurologic events after partial exchange transfusion for priapism in sickle cell disease. J Pediatr 120:882, 1992

50. Ohene-Fempong K, Weiner JS, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH, Gill FM: Cerebrovascular accidents in sickle cell disease: Rates and risk factors. Blood 91:288, 1998

51. Gladman DD, Bombardier C: Sickle cell crisis following intraarticular steroid therapy for rheumatoid arthritis. Arthritis Rheum 30: 1065, 1987