Immunosuppressive Effects in Infants Treated With Corticosteroids for Infantile Hemangiomas

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Background: Infantile hemangiomas are the most common benign tumors of infancy. Up to 38% of hemangiomas require treatment with systemic medications because of complications. Corticosteroids have been the mainstay for treating such hemangiomas. However, prospective studies evaluating their immunosuppressive effects in infants with hemangiomas are lacking.

Observations: Sixteen patients who presented to the Birthmark and Vascular Anomalies Center at the Children’s Hospital of Wisconsin from November 1, 2006, through February 28, 2008, were enrolled in the study. A significant reduction in the numbers of all B- and T-lymphocyte subpopulations was observed after corticosteroid administration. CD19+ B lymphocytes and CD4+ T cells were significantly reduced by 8 weeks of corticosteroid therapy, whereas CD8+ T cells were reduced at week 16 compared with baseline. Immune function was also affected because 13 and 5 patients had protective diphtheria titers and tetanus titers, respectively, 3 months after discontinuation of corticosteroid therapy compared with baseline.

Conclusions: These results demonstrate that corticosteroids measurably affect both lymphocyte cell numbers and function in this patient population. Prophylaxis with the combination of trimethoprim and sulfamethoxazole should be considered in infants treated with corticosteroids for infantile hemangiomas. We also recommend that tetanus and diphtheria antibodies be checked in patients who receive oral corticosteroids during the immunization period and that additional immunization be administered if the titers are not protective after corticosteroid therapy.

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INFANTILE HEMANGIOMAS (IHS) are the most common tumors of childhood, occurring in as many as 10% of children by 1 year of age.1-3 Although most hemangiomas are self-limited, 10% to 38% of children with hemangiomas referred to tertiary care specialists require treatment because of complications, such as ulceration, bleeding, permanent disfigurement, obstruction of vision and airway, or high-output cardiac failure.3-6 Treatment of IHS is designed to control growth, minimize deformity, preserve function, and limit the amount of psychological and emotional stress on the patient and the parents. Systemic pharmacotherapy is most often used to treat large hemangiomas that present a surgical challenge or those causing functional or life-threatening problems. Hagstrom et al8 demonstrated that 12% of infants will require pharmacologic intervention and that hemangiomata size, segmental distribution, and location were statistically significant risk factors for complications and the need for therapy.6 Agents with activity in treating hemangiomas include oral and intraleisional corticosteroids,7,9 interferon alfa-2a,9 vinca alkaloids,8-11 and propranolol.12 Prospective data addressing the efficacy and safety of accepted pharmacologic interventions for the treatment of hemangiomas have not been generated, and available data are confounded by the lack of a consensus on treatment criteria, variable study design, and objective outcome measures.

Corticosteroids continue to be a standard therapy for the treatment of IHS with a high probability of life-threatening or functional complications.2,3,13 Now that physicians have additional pharmacologic options, it is important to begin to evaluate and quantify the toxicity of existing and new therapeutic interventions in these infants. Although corticosteroids are an effective therapy to control hemangioma growth, the adverse effects of systemic corticosteroid administration to infants have not been systematically evaluated in large numbers of patients. A small study14,15 re-
ported that infants receiving oral corticosteroids for hemangiomas have significant adrenal suppression and growth retardation. Although never objectively documented or quantified in this patient population, additional adverse effects, such as immune suppression, hypertension, bone demineralization, sleep disturbance, irritability, personality change, and gastrointestinal irritation, are presumed to occur. Additional compromise of the infant’s developing immune system by systemic corticosteroid therapy is a clinical concern as demonstrated by 3 case reports of life-threatening Pneumocystis carinii pneumonia (PCP) infections.

In this study, we prospectively analyzed the effects of systemic corticosteroid administration on lymphocyte cell numbers and the generation of immunoglobulin antibodies to regular childhood vaccinations in a group of infants treated for IHs. Corticosteroids had a profound yet reversible effect on immune function in this young patient population.

### METHODS

#### EXPERIMENTAL DESIGN

Institutional review board approval was obtained before initiation of the study. Patients presenting to the Birthmark and Vascular Anomalies Center at the Children’s Hospital of Wisconsin from November 1, 2006, through February 28, 2008, were prospectively enrolled in the study. Inclusion criteria included infants younger than 6 months with complicated IHs that required treatment with oral corticosteroids. These infants were otherwise healthy and had no prior exposure to corticosteroids or other systemic medication used to treat IHs. Eligible patients were enrolled before initiation of therapy and were required to participate in normal childhood vaccination regimens, including diphtheria and tetanus toxoids and acellular pertussis. All parents and guardians signed informed consent.

Demographic and clinical data were collected on each patient, including the following: (1) biographic and demographic information, including birth date, age, sex, and location of lesion; (2) standard measurements, including weight, length, and blood pressure; (3) starting dose and duration of corticosteroid therapy; and (4) visit data, including subjective parental reports regarding intercurrent infections, irritability, increase in appetite, and gastric complaints (reflux symptoms) (Table 1).

Enrolled patients received prednisolone sodium phosphate suspensions (15 mg/5 mL) administered by mouth every morning at a starting daily dose of 2.5 mg/kg. Patients were evaluated at a minimum of every 4 weeks while undergoing therapy and at 3 months after completion of therapy. Response to therapy was assessed by interval change in the size of the hemangioma using the soft tape measurement technique by the treating pediatric dermatologist (B.A.D.) at 8 weeks of corticosteroid therapy. Complete response was defined as no residual hemangioma, partial response as a greater than 30% decrease in the size of the hemangioma, stable disease as a less than 30% increase, and progressive disease as a greater than 30% growth in the size of the hemangioma. Prednisolone dosing was increased to 3.0 mg/kg if the tumor size increased by 10% or more or if there was worsening of functional impairment. Prednisolone was reduced by 20% per month if the functional impairment improved, the ulceration healed, or there was stabilization or regression of the size of the IH (partial response). Height, weight, head circumference, vital signs (including blood pressure), intercurrent infections, and adverse effects (symptoms of gastrointestinal reflux, irritability, and increased appetite) were monitored and recorded every 2 months after initiation of therapy. Hypertension was defined as a systolic blood pressure of greater than the 95th percentile for age. Height, weight, and head circumference were recorded and plotted for age on the growth curve at 8-week intervals. Growth retardation was defined as a 20-point decrease in percentile at a specific age. Complete blood cell count with automated differential, enumeration of lymphocyte subpopulations, and tetanus and diphtheria titers were measured at study entry (before therapy), every 2 months while receiving therapy, and 3 months after therapy.

### ASSESSMENT OF IMMUNOLOGIC STATUS

Flow cytometry (BD FACSCalibur; BD Biosciences, San Jose, California) was performed on heparinized whole peripheral blood specimens to assess the membrane phenotype of lymphocytes in a Clinical Laboratory Improvement Amendments–approved diagnostic laboratory. Briefly, 100 µL of whole peripheral blood was stained with antibodies conjugated to 4-color antibody combinations. Four-color analysis was performed with the following antibodies (and clones): CD3 fluorescein isothiocyanate (SK7) (BD Biosciences), CD4 phycoerythrin (SK3) (BD Biosciences), CD19 allophycocyanin (SHJ25C1) (BD Biosciences), and CD56 allophycocyanin (N901; Beckman Coulter Inc, Brea, California), with the 2 antibody combinations of CD3/CD4/CD8/CD19 and CD3/CD16/CD56/CD55. Stained peripheral blood samples underwent red blood cell lysis (FACSLyse; BD Biosciences) and were then washed twice in a phosphate-buffered saline and 0.1% sodium azide combination. Data acquisition and analysis were performed using Cell Quest Pro software (BD Biosciences). Nonviable cells and debris were excluded, and lymphocytes were identified based on forward and side scatter properties (Figure 1). Absolute values were calculated using the product white blood cell count times the percentage of lymphocytes determined from a standard hematology analyzer (Cell-Dyne 3000; Abbott Laboratories, Abbott Park, Illinois) and flow cytometry to identify the lymphocyte subset percentages. Results were compared with baseline values and values of age-matched control patients. Antibody titers for tetanus and diphtheria were determined from whole blood by clinical reference laboratories (Specialty Laboratories, Valencia, California) at baseline, 2-month intervals during corticosteroid treatment, and 3 months after the completion of corticosteroid therapy. Patients were considered immunized if they had specific IgG titers higher than 0.150 IU/mL and higher than 0.099 IU/mL for tetanus and diphtheria, respectively (Specialty Laboratories). Enrolled patients received their vaccinations following the schedule outlined by the American Academy of Pediatrics (4 doses appropriately
Veriﬁcation of all immunizations and dates was obtained from the primary care physicians via telephone.

STATISTICAL ANALYSIS

Descriptive statistical analysis was performed on the data collected using 1-way analysis of variance to calculate descriptive statistics, conﬁdence intervals, and t tests. The Bonferroni multiple comparison test was used to compare mean differences of CD4, CD8, CD19, and CD56 cell counts at baseline; at weeks 8, 16, and 24 of therapy; and 3 months after therapy.

RESULTS

Seventeen patients met the study eligibility criteria and were enrolled in the study (Table 2). One patient withdrew consent for the study, leaving 16 patients available for analysis. The demographics of our patient population were similar to previously published reports. There were 3 boys and 13 girls, with a mean age of 2.9 months (median age, 2.7 months; age range, 1.6–6.2 months) at enrollment. All the patients were white. The
RESPONSE TO THERAPY

Eight of the 16 patients (50%) had a partial response (>30% decrease in hemangioma size) to therapy, whereas the other 50% of patients had stabilization (≤30% increase to >30% decrease in hemangioma size) of disease after 8 weeks of corticosteroid therapy. The mean duration of corticosteroid therapy was 22 weeks (range, 8–32 weeks). The dosage of corticosteroids was adjusted, depending on the interval response of the hemangioma to therapy, but continued during the proliferative phase of the hemangioma. Therapy was discontinued if there was no evidence of regrowth with tapering of corticosteroids. Therapy remained significantly depressed at all therapy time points despite reductions in corticosteroid dose over time. In contrast, the numbers of natural killer (CD56+) cells were not significantly affected by corticosteroid treatment (Table 3 and Figure 2). Numbers of all lymphocyte subpopulations normalized within 3 months of stopping corticosteroid therapy (Table 3 and Figure 2). These results demonstrate a significant yet reversible effect on lymphocyte cell numbers in patients with hemangiomas treated with corticosteroids.

RESPONSE TO VACCINATION

We next determined the impact of corticosteroid therapy on immune function in this population. None of the study patients had repeated or serious infectious complications (defined as requiring intravenous antibiotics or hospitalization) while receiving corticosteroid therapy. An accepted measure of in vivo immune function is antibody generation to foreign antigens.23 Infants and young children are routinely immunized to prevent serious communicable diseases, such as diphtheria and tetanus. Appropriate response to vaccine administration requires that the coordinated interaction between T and B lymphocytes and the normal protective levels of IgG antibodies have been determined for the population.24

At baseline, diphtheria and tetanus titers were available for 14 of the 16 enrolled patients. Protective antibody titers for diphtheria (>0.099 IU/mL) and tetanus (>0.15 IU/mL) were found in 8 and 12 patients, respectively, of the 14 evaluated at baseline. All patients had received at least 1 acellular pertussis vaccination before study entry. However, baseline values were certainly influenced by maternal IgG25,26 because the mean age of patients at the time of enrollment was 2.9 months. To best assess response to a series of immunizations while receiving corticosteroid therapy, antibody titers to tetanus and diphtheria were measured 3 months after completion of prenisolone therapy. All 16 patients received at least 3 acellular pertussis immunizations, and all patients received all scheduled immunizations while receiving study therapy. Only 5 of the 16 fully immunized patients had protective tetanus titers, whereas 13 patients had protective diphtheria titers 3 months after discontinuation of corticosteroid therapy. These results demonstrate that corticosteroids measurably affect both lymphocyte cell counts and function in this patient population.

Infantile hemangiomas are benign tumors composed of proliferating endothelial cells that become clinically evident within the first months of life. They are common tumors, with an estimated prevalence of approximately 3% to 10% in white infants. Recent data suggest that there is an increasing incidence related to the increasing rate of low-birth-weight infants in the United States.27 Systemic pharmacotherapy is used to treat large lesions, lesions that present a surgical challenge, or those that cause functional or life-threatening problems. Despite the numbers of infants affected and the severity of potential

Table 2. Patient Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Demographics and Characteristic</th>
<th>No. (%) of 16 Patients</th>
</tr>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (81)</td>
</tr>
<tr>
<td>White race</td>
<td>16 (100)</td>
</tr>
<tr>
<td><strong>Age at enrollment, mo</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.9</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.7 (1.6-6.2)</td>
</tr>
<tr>
<td><strong>Starting daily corticosteroid dose</strong></td>
<td>2.5</td>
</tr>
<tr>
<td>(prednisone, 15 mg/5 mL), mg/kg</td>
<td></td>
</tr>
<tr>
<td><strong>Length of therapy, mean (range), wk</strong></td>
<td>22 (8-32)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemangioma location</th>
<th>No. (%) of 16 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyelid (upper and lower)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Nose (bridge, sidewalls, tip)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Arm</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Glabella</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Cheek</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Anterior aspect of the neck</td>
<td>1 (6)</td>
</tr>
</tbody>
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*Data are number (percentage) of patients unless otherwise indicated.*
complications, we lack uniform guidelines for the therapy, and there are no Food and Drug Administration–approved agents for treatment of IHs. Data evaluating efficacy and safety of accepted pharmacologic interventions for the treatment of hemangiomas are lacking, and consensus on treatment criteria and objective outcome

Table 3. Absolute Lymphocyte Counts in Study Patients Compared With Age-Matched Normal Values

<table>
<thead>
<tr>
<th>Lymphocyte Subpopulation</th>
<th>Baseline (n=15; Mean Age, 3 mo)</th>
<th>Week 8 (n=16; Mean Age, 5 mo)</th>
<th>Week 16 (n=15; Mean Age, 7 mo)</th>
<th>Week 24 (n=11; Mean Age, 8 mo)</th>
<th>3 Months After Therapy (n=16; Mean Age, 13 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>Patients 3076 Controls 2500</td>
<td>Patients 751 Controls 2500</td>
<td>Patients 668 Controls 2800</td>
<td>Patients 995 Controls 2800</td>
<td>Patients 2331 Controls 2300</td>
</tr>
<tr>
<td>CD8</td>
<td>Patients 1389 Controls 1000</td>
<td>Patients 678 Controls 1000</td>
<td>Patients 382 Controls 1300</td>
<td>Patients 758 Controls 1100</td>
<td>Patients 1052 Controls 1100</td>
</tr>
<tr>
<td>CD19</td>
<td>Patients 1389 Controls 1300</td>
<td>Patients 622 Controls 1300</td>
<td>Patients 382 Controls 1300</td>
<td>Patients 308 Controls 1300</td>
<td>Patients 1176 Controls 1400</td>
</tr>
<tr>
<td>CD56</td>
<td>Patients 259 Controls 300</td>
<td>Patients 321 Controls 300</td>
<td>Patients 272 Controls 300</td>
<td>Patients 381 Controls 300</td>
<td>Patients 323 Controls 400</td>
</tr>
</tbody>
</table>

*aReference values adapted from Comans-Bitter et al.19

Figure 2. Quantitative immune analysis. Asterisk indicates P<.001; †, P=.001-.01.
measures do not exist for data that are available. As new options for therapy, such as propranolol, are introduced, we must methodically evaluate potential adverse effects of new and existing agents to determine which intervention is safest and most effective for infants with complicated hemangiomas.

Systemic glucocorticoids are a standard treatment for hemangiomas, lymphocytic cancers, and many disorders of inflammation. The broad efficacy of glucocorticoids is believed to result from the pleiotropic effects of the glucocorticoid receptor on multiple signaling pathways. These broad actions, however, likely contribute to the adverse effects of prolonged glucocorticoid administration, including growth retardation, hypertension, inhibition of wound repair, osteoporosis, metabolic abnormalities, and immunosuppression.

Many have documented the suppressive effects of corticosteroids on immune function in adults and children with a variety of diseases. However, there have been no prospective studies to date that have evaluated the effects of systemic corticosteroid administration in infants at the dose and duration used for IHs. In this prospective study, we demonstrate that prednisolone has a profound yet reversible effect on cellular and humoral immunity in this young patient population.

The frequency and severity of complications from corticosteroid therapy have been correlated with the use of potent systemic corticosteroids, higher dose and longer duration of treatment, and a younger age at the time of treatment. The current practice in treating IHs uses prednisolone starting at high doses (2–3 mg/kg daily), followed by dose modification based on clinical assessment of disease response. Most patients require at least 2 months of corticosteroid therapy for treatment of a complicated hemangioma, and up to 21 months of therapy have been reported in the literature. Patients in this study were treated for a mean of 22 weeks (5½ months). Complications in our patients included immune suppression (16 of 16), hypertension (2 of 16), irritability and sleep disturbances (10 of 16), hyperphagia and weight gain (12 of 16), and disturbances in linear growth (10 of 16). Most effects were seen at higher prednisolone doses, with reduced severity and frequency occurring during corticosteroid taper and complete resolution after therapy ended. Our results are consistent with other reports that demonstrated a dose-dependent effect of corticosteroids on linear growth and adrenal suppression, hypertension, irritability, and gastric irritation in patients treated for hemangiomas. Sadan and Wolach reported growth retardation as one of the adverse effects of corticosteroid therapy and noted that “catch-up” growth was evident within a few months of stopping therapy and bone age became consistent with chronologic age. Similar catch-up growth was also reported by Lomenick et al in their retrospective study of 13 infants treated with glucocorticoids for hemangiomas. In contrast, Boon et al found that adverse effects were minor and transient, and no serious long-term complications occurred in their patients with hemangiomas treated with corticosteroids. This study was retrospective and relied on a questionnaire sent to the families of children treated during a 14-year period, possibly leading to recall bias, particularly as it related to frequency and severity of adverse effects experienced during or shortly after therapy.

The adverse effects of glucocorticoids on immune parameters have been demonstrated in pediatric and adult patients diagnosed as having a variety of inflammatory diseases. Glucocorticoid therapy in these patients was associated with both cellular and humoral immunosuppression, resulting in increased numbers of infections. In our patients, the numbers of CD4+ T cells and B cells were the most sensitive to corticosteroid treatment, whereas CD8+ T cells and natural killer cells were affected to a lesser degree. Similar reductions in lymphocyte counts were found in patients with asthma treated with oral corticosteroids and possibly reflect increased sensitivity of CD4+ T-cell and B-cell populations to the lytic effects of corticosteroids.

The absolute CD4+ T-lymphocyte count has been correlated with risk of many types of infections, including PCP. In fact, corticosteroid use has been shown to be the most significant risk factor for the development of PCP in patients without AIDS. Patients in our study had mean CD4+ T-lymphocyte counts that were reduced to 30% and 25% of age-matched controls by 8 and 16 weeks of corticosteroid therapy, respectively. Low CD4+ T-cell counts were seen at all time points despite significant reduction in corticosteroid dose during the duration of treatment. Although this study was not powered to assess infection risk, the extent and duration of reduced CD4+ T-cell counts observed in our patient population have been shown to increase the risk for serious infection, including PCP in other populations. There are at least 3 case reports of life-threatening PCP infection and 1 death from PCP in infants treated with oral corticosteroids for complicated hemangiomas. The PCP prophylaxis has been shown to have a clinical benefit and to be cost-effective in the human immunodeficiency virus population with CD4+ T-cell counts less than 200/µL. In a meta-analysis conducted to examine PCP prophylaxis with the combination of trimethoprim and sulfamethoxazole, the investigators found a 91% reduction in PCP with prophylaxis and a reduction in mortality from PCP. In this analysis, 50% of the patients were children with systemic illnesses and/or multiple immunosuppressive agents, and no severe adverse effects were reported in the children. The incidence of severe adverse event with trimethoprim-sulfamethoxazole prophylaxis was 7.4 to 8.4 per 1000 children.

Immune function as measured by generation of specific immunoglobulin to acellular pertussis vaccination was also impaired in our study patients. Twelve of 14 patients had protective tetanus titers at baseline, whereas only 5 of 16 had protective titers 3 months after completion of corticosteroids. Although baseline values were likely influenced by maternal immunoglobulin, results from this study suggest that corticosteroid administration significantly impaired antigen-specific immunoglobulin generation in our patients. Unlike lymphocyte cell numbers that
quickly recovered after discontinuation of corticosteroid therapy, the low numbers of patients with protective tetanus titers at 3 months after therapy suggest a more sustained effect of corticosteroids on antibody generation. Corticosteroids are known to affect T- and B-lymphocyte activation in vitro.42 In these studies, T-cell response to antigen stimulation was more sensitive to corticosteroids than were responses to mitogens.42,43 Corticosteroids were shown to impair immunity to a specific antigen in a population of patients undergoing cardiac surgery through effects on antigen presentation and T-cell activation.44 We are unable to determine the mechanism(s) by which corticosteroids interfere with antigen-specific immunity in this population. However, future studies will include the enumeration of CD27 and CD70 cells as markers of B- and T-memory lymphocytes, respectively, to begin to elucidate this mechanism.

In contrast to the inhibitory effect of corticosteroids on tetanus immunity, 13 of the 16 patients had protective titers to diphtheria 3 months after completing corticosteroid treatment. It is unclear why there is a discrepancy in the numbers of patients with protective titers for tetanus (5 of 16) vs diphtheria (13 of 16) in this population. Whether this reflects a mechanistic difference of antibody production to these 2 antigens in children or a differential sensitivity of diphtheria and tetanus antigen-specific immunity to corticosteroids is currently unknown. Alternatively, this difference may reflect a simple quantitative difference between the definition of protective titers (diphtheria, >0.099 IU/mL; tetanus, >0.15 IU/mL) to the 2 antigens. To address this latter possibility, we evaluated absolute titers for patients with a nonprotective response to tetanus and compared them with titers for the group who responded well to diphtheria. We would expect the values in both groups to be similar if the discrepancy in protective titers were simply owing to differences in the quantitative definition of protection. The 11 patients who did not generate a protective antibody response to tetanus had a mean titer of 0.065 IU/mL, whereas the 13 patients who responded well to diphtheria had a mean titer of 0.747 IU/mL. These results suggest real differences in the mechanism of antibody production and/or corticosteroid sensitivity of this process in response to the 2 different antigens within this population.

Our study results have practical implications for the care of patients with hemangiomas undergoing medical treatment. Given the extent of lymphocyte depletion and compromised ability to respond to immunization, we would recommend that for all patients who received oral corticosteroids during the immunization period, antibodies for tetanus and diphtheria be checked after corticosteroid therapy and that additional immunization be considered if the titers are not protective at that time. In addition, one should consider PCP prophylaxis with trimethoprim-sulfamethoxazole in this population, especially if corticosteroid treatment persists for 2 or more months, a recommendation that has also been suggested by others.10-13,40 Furthermore, other drugs currently being used to treat hemangiomas, including vincristine sulfate46 and β-blockers,47 have known immunosuppressive effects, suggesting that studies evaluating their efficacy should include immune monitoring to assess for this potential toxic effect. Finally, although the focus of this study was immune compromise by corticosteroids, our patients experienced other serious complications, including hypertension (2 of 16), irritability and sleep disturbances (10 of 16), hyperphagia and weight gain (12 of 16), and disturbances in linear growth (10 of 16). These results demonstrate that the effects of corticosteroids are wide ranging and that physicians caring for these patients must have a monitoring plan that accounts for potential serious risks.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kelly, Drolet, and Grossman. Acquisition of data: Juern and Schauer. Analysis and interpretation of data: Kelly, Juern, Schauer, Grossman, and Drolet. Drafting of the manuscript: Juern and Schauer. Critical revision of the manuscript for important intellectual content: Kelly, Grossman, and Drolet. Administrative, technical, and material support: Juern, Kelly, Schauer, and Drolet. Study supervision: Kelly and Drolet.

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REFERENCES


