

A Short Burst of Oral Corticosteroid for Children with Acute Asthma: Is There an Impact on Immunity?

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Background: We wished to examine the impact of a short course of oral corticosteroids on the immune function of children with acute asthma and explore the mechanism of immune suppression, if any.

Methods: We conducted a prospective cohort study of children aged 3–17 years presenting with acute asthma to the emergency department. The exposure of interest was a short course of systemic corticosteroids. In emergency department, corticosteroid-treated and nonexposed children were immunized with 3 antigens, namely, a neoantigen (Bacteriophage ϕ X 174) and 2 recall antigens (diphtheria and tetanus). After 5 ± 1 weeks, children were reimmunized with Bacteriophage ϕ X 174. Antibody titers were measured 1, 2 (peak), and 5 weeks after the primary immunization, and 1 week (peak) after the secondary one.

Results: We enrolled 41 children, 27 treated with and 14 unexposed to oral corticosteroids. Corticosteroid-treated children displayed an 85% lower adjusted total (IgG and IgM) peak titers to the primary Bacteriophage immunization compared to controls [ratio of geometric means (95% confidence interval): 15% (5% to 43%)]. There were no group differences in the rise of diphtheria or tetanus antibodies. After the secondary Bacteriophage immunization, corticosteroid-treated patients showed no significant group difference in peak total titers [ratio of geometric means (95% confidence interval): 1.84% (0.66%, 5.10%)], amplification and absolute, and percent IgG titers as compared to unexposed children.

Conclusions: In children with acute asthma, a short course of oral corticosteroids may be associated with depressed immune response to a new antigen, with recovery within 6 weeks and no apparent impact on response to known antigens.

Introduction

NATIONAL AND INTERNATIONAL consensus guidelines on pediatric asthma recommend the use of systemic corticosteroids in the initial management of acute asthma unresponsive to inhaled bronchodilators.^{1,2} The efficacy of systemic corticosteroids in reducing both the risk and the duration of hospital admission in children with acute asthma has been clearly demonstrated.^{3,4} Yet, their safety profile continues to raise concerns among parents and physicians. Previous studies have confirmed an impact on bone metabolism and bone mineral density, but no sustained effect on adrenal function in children receiving up to 11 short courses per year.^{5,6} The possibility of severe immunosuppression was evoked by fatal varicella in an asthmatic child who re-

ceived a short course of oral corticosteroids during the incubation period and who has no demonstrable varicella antibody titers.⁷

Recent evidence suggests that even a short course of systemic corticosteroids may decrease cellular and humoral immunity in immunocompetent children. Indeed, nonspecific suppression of lymphocyte counts and immunoglobulins were documented within 2 weeks of initiating a short course of systemic corticosteroids.^{8–12} In previously vaccinated children, breakthrough varicella infection has been associated with a recent short course of systemic steroids.¹³ However, cohort studies have reported no apparent group differences in the antibody response to influenza vaccine between children with acute asthma treated and those not treated with oral corticosteroids.^{14,15} Two case-control

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studies yield conflicting conclusions about the relationship between oral corticosteroids and the risk of severe varicella, thus failing to elucidate the issue.^{16,17}

The objective was to evaluate the impact of a short course of systemic corticosteroids on the functional integrity of humoral immunity in children with acute asthma by quantifying the primary and secondary antibody responses to a neoantigen (ie, an antigen not previously encountered by the child) and the antibody response to recall (ie, known) antigens, administered concurrently with oral corticosteroids.

Materials and Methods

Study design and setting

We conducted a prospective cohort study of children who presented with acute asthma to the emergency department (ED) of a tertiary care pediatric hospital. The protocol was approved by the Scientific and the Institutional Review Boards of the Montreal Children's Hospital. The U.S. Food and Drug Administration and the Health Canada's Health Protection Branch specifically allowed the use of Bacteriophage ϕ X 174 for this protocol to assess the immune response under the U.S. Food and Drug Administration Investigational new drug number #5760. Informed consent was obtained from parents and assent was obtained from children aged 7 years and older.

Subjects

Children between 3 and 17 years of age were eligible if they presented during the study period with a clinical diagnosis of asthma,¹⁸ required at least 1 nebulization of albuterol, had a good understanding of English or French, and had received at least 4 diphtheria and tetanus immunizations. The decision to administer prednisone/prednisolone [usually 1 mg/kg (maximum: 50 mg) for 5 days] was left to the discretion of the ED physician in face of suboptimal response to bronchodilators.¹ Children prescribed oral corticosteroids constituted the exposed group; those not so prescribed served as controls. Patients were excluded if they had fever in the preceding 12 h; coexisting acute respiratory illness; recent exposure to varicella; other chronic lung or immunologic disease; intake of systemic corticosteroids or ≥ 50 g of dermatological corticosteroids in the preceding 28 days; admission to the intensive care unit; or recent (≤ 3 months) immunization with a diphtheria or tetanus-containing vaccine.

Immunization protocol

At the index visit in the ED, children received Bacteriophage ϕ X 174 administered intravenously (2×10^9 plaque-forming units PFU/Kg of body weight) and an intramuscular injection of the tetanus-diphtheria vaccine (0.5 mL of d₂T₅, ie, 2 Lf units of diphtheria and 5 Lf units of tetanus toxoid; Aventis Pasteur, Toronto, Canada); a second Bacteriophage immunization took place 5 ± 1 weeks after enrollment (Fig. 1). Bacteriophage ϕ X 174 is recognized as a sensitive T cell-dependent neoantigen to quantify the primary and secondary antibody responses in patients with inherited and acquired immunodeficiency disorders.^{19–25} Antibody titers were measured 1, 2 (peak), and 5 weeks after the primary immunization, and 1 week (peak) after the secondary one.

Study endpoints

The clearance of Bacteriophage ϕ X 174 from the serum was determined 1 week after the initial immunization, by an agar overlay method.^{19,26} The primary antibody response was determined by the total (IgM and IgG) specific immunoglobulins measured at 14 ± 2 days and by the rise from baseline over the initial 14 days, after initial immunization. The secondary response was documented at 7 ± 2 days (peak) after the booster immunization by the: (a) total (IgM and IgG) Bacteriophage-specific antibodies,¹⁹ (b) specific IgG titer, (c) fold increase in titers between the peak primary and secondary response representing amplification, and (d) percent IgG antibodies [ratio of IgG/(IgG and IgM)].^{26,27} Total antibody titers to Bacteriophage ϕ X 174 were determined by a neutralizing assay and expressed as the rate of phage inactivated over time (K value, K_v).²⁷ Neutralizing antibodies resistant to 2-mercaptoethanol were considered to be IgG.²⁸ The serum samples were stored at -70°C until analysis at the University of Washington, Seattle. The results were interpreted by one of the authors (HO) blinded to the exposure status.¹⁹

IgG antibodies to tetanus and diphtheria were measured using antigen-specific enzyme-linked immunosorbent assay test (Scimedx Corp., Denville, NJ).²⁹ A normal booster response was operationally defined as a 10-fold or greater increase from baseline in antidiphtheria and antitetanus toxoid antibodies.³⁰ In a secondary analysis, we excluded patients with baseline values >1 IU/mL to minimize the underestimation of the titer increase due to the upper detection limit of the enzyme-linked immunosorbent assay (5 IU/mL). These assays were performed at the Montreal Children's Hospital and were interpreted by one of the authors (B.D.M.) blinded to the exposure status.

The severity of the index exacerbation in each patient was assessed by the intensity of treatment received in the ED, disposition, and, at the time of immunization, by the oxygen saturation and the Pediatric Respiratory Assessment Measurement, a validated 12-point asthma score.³¹ We evaluated asthma control over the previous month using the Asthma Quiz for Kidz,³² and health care services utilization in the preceding 12 months. Nasopharyngeal secretions were cultured for common respiratory viruses. We documented exposure to, and doses of, all glucocorticoid preparations in the 6 months before and 6 weeks after enrollment, including those dispensed by pharmacies, administered in hospital, and/or recorded in the patients' diaries.

Statistical analyses

With 36 patients enrolled in a 2:1 exposed:unexposed ratio and a 2-sided α of 0.05, the power for detecting a ratio of geometric means of 115%, equivalent to 0.2 standard deviation, in peak IgM and IgG antibodies following the second Bacteriophage immunization was 80%, assuming a coefficient of variation of 10%.³³ Exposed patients who received <3 doses of oral corticosteroids were excluded. Controls who subsequently received oral corticosteroids were analyzed until corticosteroid use.

All titers were log-transformed and tested for normality assumption. After analysis, titers were converted to non-logarithmic form and reported as geometric means with the 95% confidence interval (CI). Differences in proportion were

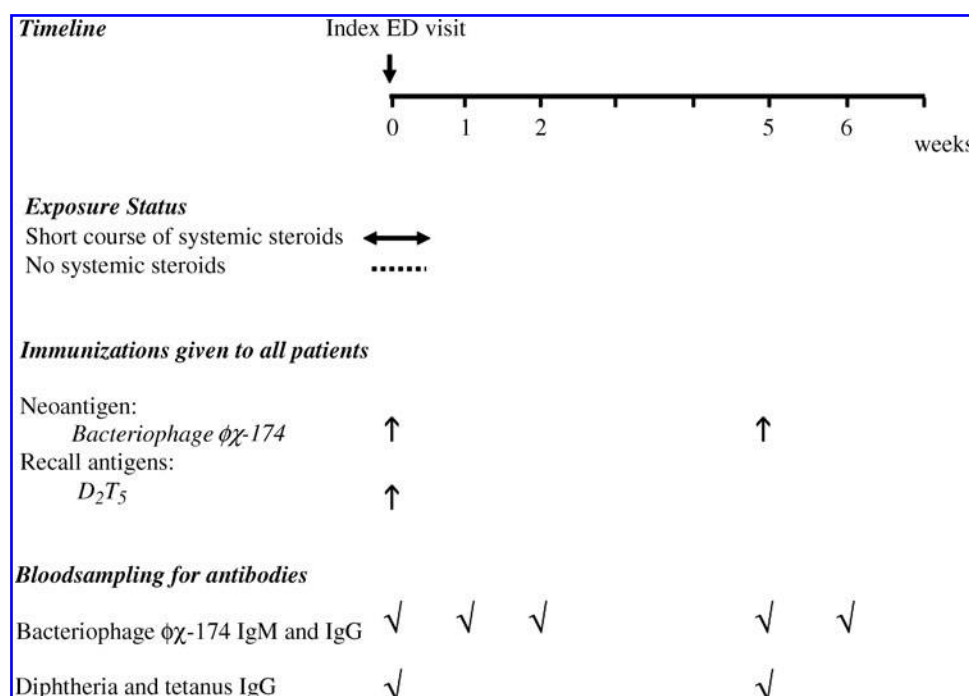


FIG. 1. The exposure was a 5-day course of oral corticosteroids. All exposed (double-headed arrows) and unexposed (dashed line) patients were immunized with Bacteriophage ϕ X 174 (arrow) and the tetanus-diphtheria (D_2T_5) vaccine (arrow) at the index visit, and re-immunized with bacteriophage (arrow) 5 ± 1 weeks later. Blood samples (check signs: ✓) for bacteriophage titers were collected at enrollment, at 7 ± 2 and 14 ± 2 days after the primary immunization, before and 7 ± 2 days after the secondary immunization; blood samples for diphtheria and tetanus were collected at enrollment and at the time of the second immunization.

examined with the chi-square test or Fisher's exact test, as appropriate. Group differences in continuous outcomes were adjusted using multivariate linear models using backward stepwise regression (entry: $P < 0.20$; exit: $P > 0.05$). Covariates that produced a 10% of greater change in treatment effect were deemed confounders and kept in the model. The titer rise from baseline following immunization was analyzed using repeated measures ANOVA.

Because of the expected confounding by indication where patients with severe exacerbations were more likely to receive oral corticosteroids, we used *propensity scores* to balance the baseline differences in the exposed and unexposed groups.³⁴ The propensity score, representing the child's baseline probability of receiving or not oral corticosteroids, was derived from a backward logistic regression. All models included the propensity score and were adjusted for confounders and the following candidate covariates: age, gender, race, lot, delay between immunizations, ED visits in the preceding year, viral infection, and inhaled corticosteroid use in the preceding 6 months, the preceding 72 h, and during the next 6 weeks. Unless otherwise specified, values are presented as median (interquartile range). Data were analyzed with SAS software, version 9.2 (SAS Institute, Cary, NC). A P value < 0.05 was indicative of statistical significance.

Results

Of the 466 children approached, 41 were not screened and 249 failed to meet the eligibility criteria, resulting in 176 eligible patients. Nonparticipants were comparable to participants in gender, race, and health care resource utilization in the preceding year, with the exception of younger age [8 (4,12) versus 13 (8,15) years, $P < 0.001$]. Forty-one patients were enrolled: 27 in the corticosteroid-exposed group and 14 in the control group. All patients' data were analyzed until

endpoint, with complete data obtained in 37 participants (Fig. 2).

As expected, children who received oral corticosteroids were sicker: they required more prolonged and intensive treatment with albuterol and a higher proportion required hospital admission than controls (Table 1). By the time they were immunized though, a median of 4.5 h (1.8, 17) after the initial dose of systemic corticosteroids, they displayed a degree of airway obstruction and oxygenation similar to controls. Inhaled corticosteroids were prescribed more frequently (81% versus 50%) in the oral corticosteroid group than in the control group, with 14 (52%) versus 4 (29%) patients received high doses ($\geq 800 \mu\text{g/day}$) of CFC-propelled beclomethasone or equivalent. Respiratory viruses were isolated in 2 (exposed) of the 25 patients in whom an adequate nasopharyngeal aspirate was obtained: one was positive for the respiratory syncytial virus and another harbored both an adenovirus and rhinovirus; both children were asymptomatic within 48 h of enrollment. The propensity score model, which included age, ethnic group, PRAM score, and use of inhaled corticosteroids in the preceding 72 h, removed all baseline group differences.

All children appropriately cleared Bacteriophage within 7 days. Eight patients (32%) in the corticosteroid-exposed group compared to 2 (14%, $P = 0.3$) in the unexposed group displayed an unadjusted peak primary response at 2 weeks below 2 standard deviations of the reference values, that is, in the range observed with immune deficiency. Similarly 7 (29%) exposed children versus 2 (15%) unexposed children displayed an abnormally low peak total (IgG and IgM) titers 1 week following the secondary immunization (Fig. 3A). After adjustment for propensity score, corticosteroids exposure, and age, the 2-week peak titers to primary Bacteriophage immunization remained significantly lower in the corticosteroid-exposed group than in controls with a ratio of geometric means of 15% (95% CI: 5%, 43%) (Fig. 3B).

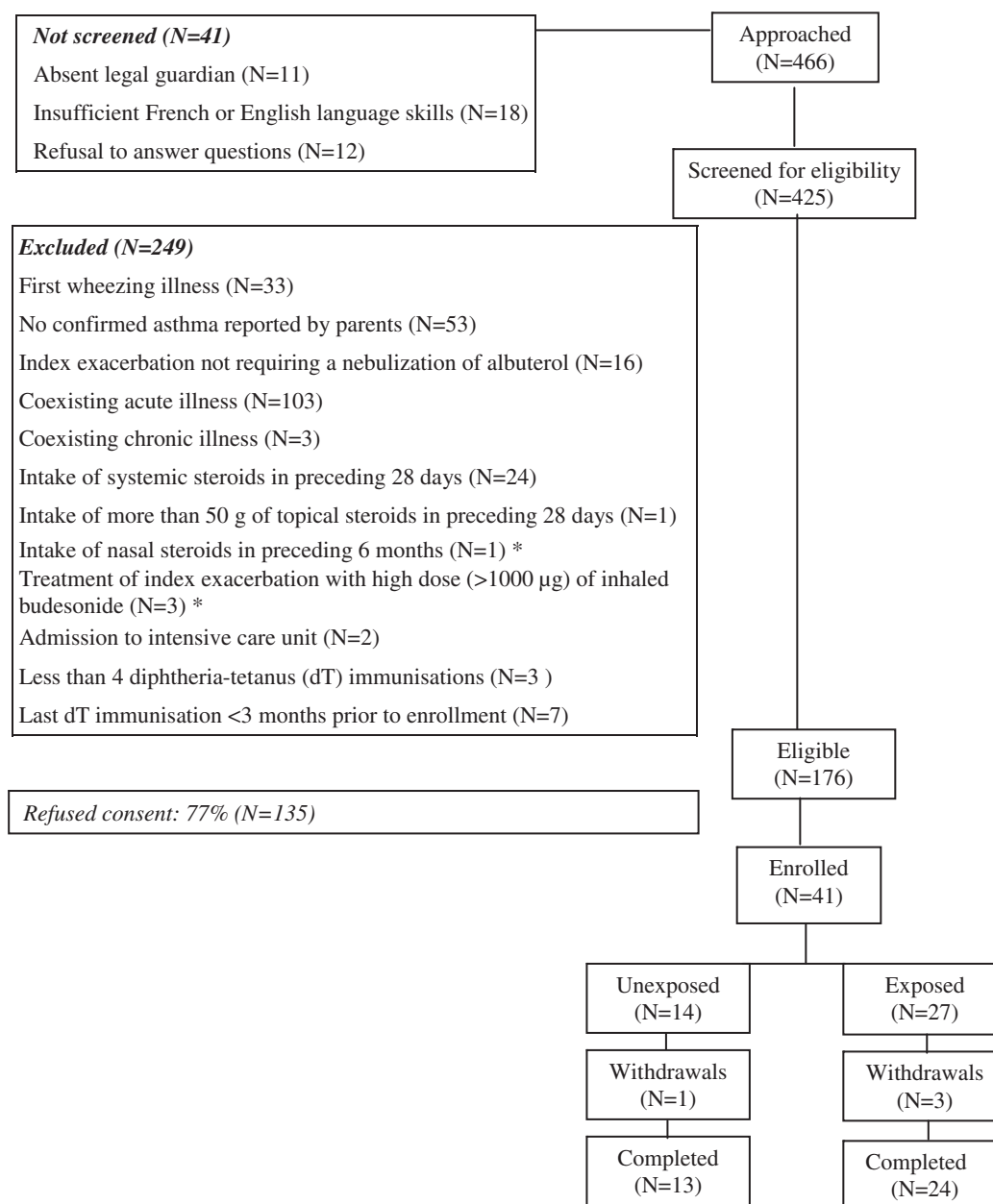


FIG. 2. This figure depicts the patient selection. To maximize generalizability of findings, 2 exclusion criteria identified by an asterisk (*), namely, intake of nasal corticosteroids in the preceding 6 months and use of 1000 mcg/day or more of beclomethasone dipropionate or equivalent for the treatment of the index exacerbation, were dropped after approaching the first 50 patients. The participation rate was 24%. Of the 41 patients enrolled, 1 child in the control group was withdrawn after receiving oral corticosteroids after the index visit and 3 exposed subjects were removed: 1 failed to complete the course of corticosteroids, 1 had a vagal reaction during the primary Bacteriophage injection, and 1 presented with pneumonia and acute asthma at the time of the second immunization. Complete data were obtained from 37 participants.

One week postsecondary immunization, however, there was no statistically significant group difference in the peak total (IgG and IgM) titers, after adjustment for propensity score and peak titers after primary immunization (Fig. 3B). There was also no significant group difference in the other markers of the response to the secondary immunization, that is, total and percent IgG titers, and amplification, with most values in the expected range of normal in both groups¹⁹ (Table 2). Of note, no markers of acute asthma severity appeared as significant predictor of peak im-

mune response following both the first and secondary immunization.

There was no overall group difference in the rise in antibodies to diphtheria or tetanus, although there was a trend toward more exposed patients with a questionable response to tetanus antigen (Table 3). No group differences were observed when excluding patients with high baseline values for change in diphtheria and tetanus.

No patient experienced serious health events. Following immunizations, 18% of patients experienced an adverse

TABLE 1. CHARACTERISTICS OF PARTICIPANTS

	Oral steroid, n = 27	No oral steroid, n = 14	P value
Demographics			
Gender (male), median (25%, 75%)	10 (37%)	6 (43%)	0.72
Age (years), median (25%, 75%)	13 (8, 16)	11.5 (7, 14)	0.42
Race, n (%)			
Caucasian	18 (67%)	10 (71%)	0.89
Black	6 (22%)	2 (15%)	
Others	3 (11%)	2 (14%)	
Number of prior diphtheria-tetanus immunizations, median (25%, 75%)	5 (5, 5)	5 (5, 5)	0.66
Asthma morbidity			
Asthma Quiz for Kidz score ^a in past 7 days, median (25%, 75%)	4 (2, 4)	2 (2, 4)	0.48
Acute care visits in past 12 months, median (25%, 75%)	1 (0, 3)	2 (1, 3)	0.30
One or more hospital admissions for asthma, n (%)	n = 27 9 (33%)	n = 11 3 (27%)	1.00
Medication in previous 6 months	n = 26	n = 14	
Inhaled corticosteroids, n (%) ^b	9 (35%)	2 (14%)	0.27
Short course of systemic corticosteroids, n (%) ^c	9 (35%)	3 (21%)	0.48
Inhaled corticosteroids in 72 h before immunization, n (%) ^d	9 (35%)	4 (29%)	0.70
Treatment of the index exacerbation			
Duration of active treatment (hours), median (25%, 75%)	5 (3, 17)	2 (2, 2.3)	0.005
# of albuterol treatments, median (25%, 75%)	4.5 (3, 13)	2 (1, 3)	0.002
# of anticholinergic treatments, median (25%, 75%)	0 (0, 3)	0 (0, 0)	0.06
Systemic corticosteroids, n (%)	27 (100%)	0 (0%)	—
Daily dose (mg of prednisone), median (25%, 75%)	50 (40, 50)	—	—
Daily dose/kg (mg of prednisone), median (25%, 75%) ^e	0.9 (0.7, 1.1)	—	—
Cumulative number of days, median (25%, 75%) ^f	5 (4, 6)	—	—
Status at time of immunization			
Delay since triage (hours), median (25%, 75%)	5.0 (3, 17)	2.3 (2.1, 2.8)	0.005
Pediatric respiratory assessment measure, median (25%, 75%) ^g	2 (1, 4)	2.5 (2, 4)	0.27
Oxygen saturation, n (%)			
≥95%	21 (78%)	8 (57%)	0.25
92%–94%	5 (18%)	6 (43%)	
<92%	1 (4%)	0 (0%)	
Disposition			
Hospital admission, n (%)	10 (37%)	0 (0%)	0.009
Discharge medications			
Inhaled corticosteroids, n (%)	n = 26 21 (81%)	n = 14 7 (50%)	0.04
Daily dose (μg), median (25%, 75%)	n = 21 988 (800, 1000)	n = 7 833 (200, 1200)	0.57
Duration (days), median (25%, 75%)	21 (13, 41)	15 (4, 31)	0.33
Nasal corticosteroids, n (%)	n = 26 2 (8%)	n = 14 1 (7%)	1.00
Topical corticosteroids, n (%)	1 (4%)	1 (7%)	1.00

Values are reported as number (percentage) of children or median (25%, 75%).

^aA validated self-assessment measure of asthma control on a score of 0 (best) to 6 (worst), based on the number of indicators of poor control.²⁹

^bPercentage of children with ≥1 prescription served by the pharmacy in the past 6 months. The cumulative or daily dose of inhaled corticosteroids could only be estimated for the small fraction of patients with ≥2 prescriptions and hence was not reported.

^cPercentage of children with ≥1 prescription served by the pharmacy in the past 6 months. No child received more than 1 short course of systemic corticosteroids.

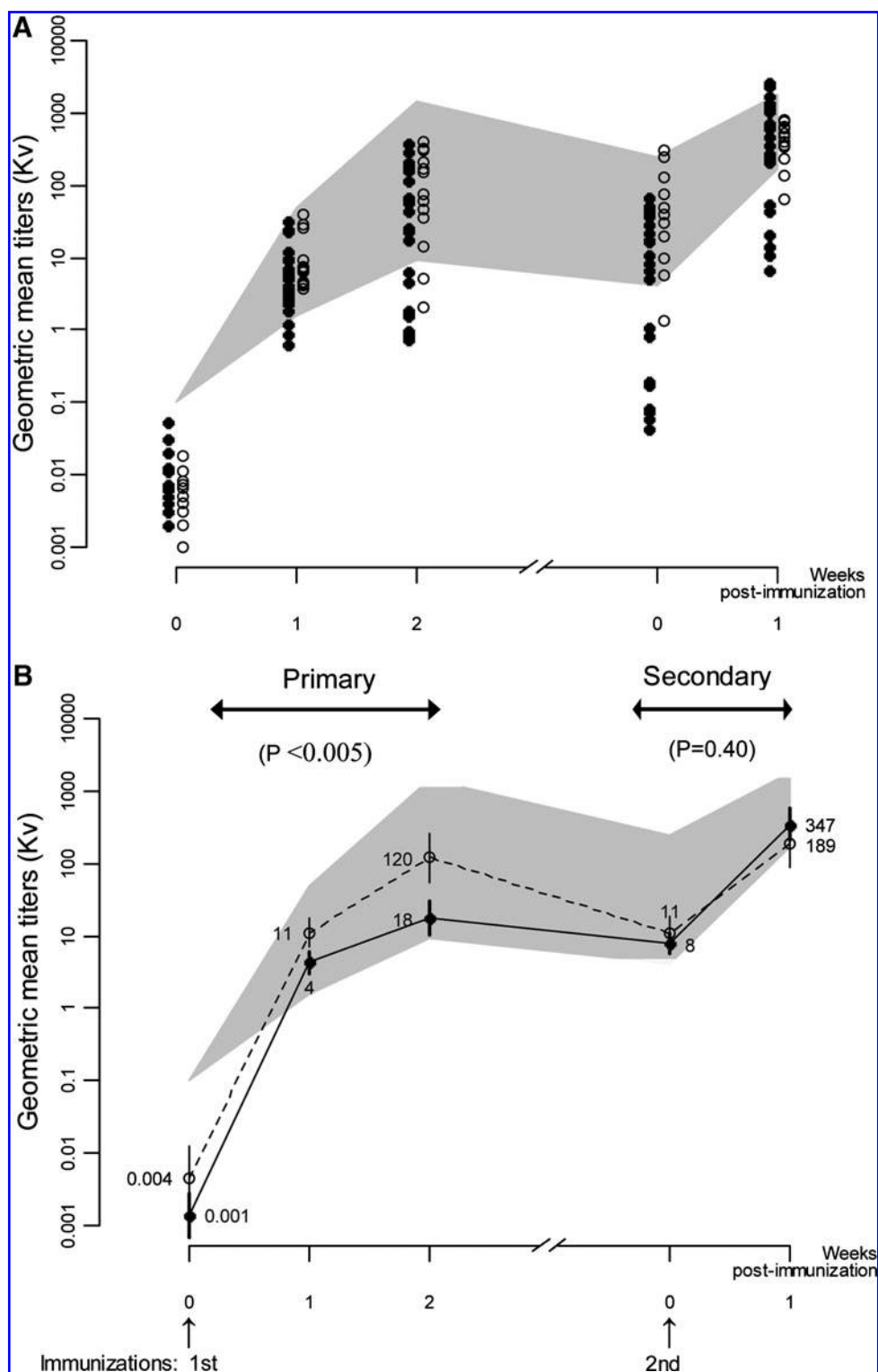
^dPercentage of children with intake of inhaled corticosteroids as reported by parents.

^eBecause of the maximum daily dose of 50 mg, the median (25%, 75%) daily dose/kg for children who weighed ≥50 kg was 0.8 (0.5, 0.9) mg; for those <50 kg, 1.2 (1.1, 1.2) mg. The dose of dexamethasone used in a single patient was converted to prednisone-equivalent using the conversion factor of 0.66.

^fAll patients but 4 patients received 1 course of oral corticosteroids. Between the 2 immunizations, 3 received a second course at 10, 17, and 34 days, respectively; a fourth received 2 additional courses (at 25, 42 days).

^gA validated 12-point pediatric asthma severity score based on oxygen saturation, suprasternal retractions, air entry, wheezing, and scalene retraction (0 = normal, 12 = most severe).²⁸

FIG. 3. The total (IgG and IgM) Bacteriophage-specific antibodies following primary and secondary immunizations (arrows) are presented for children exposed to oral corticosteroids (solid circle) and not exposed (open circle). Titers are expressed as the first-order rate constant of phage inactivation (K value, Kv) derived by a standard formula. Vertical lines represent 95% confidence interval around the adjusted mean values. The shaded area represents the 95% confidence interval for the reference values.¹⁹ In (A), the crude individual observations are displayed. In (B), the mean-adjusted antibody titers are displayed for children exposed to oral corticosteroids (solid circle, solid line) and not exposed (open circle, dashed line). Compared to the unexposed group, the corticosteroid-exposed group displayed a significant lower rise in antibody titers to the peak primary response at 2 weeks ($P < 0.005$), with no group difference in the rise to the peak secondary response at 1 week postsecondary immunization ($P = 0.4$).



event; an exposed adolescent with fear of needles displayed a vasovagal reaction following the Bacteriophage injection, 5 (4 exposed and 1 unexposed) had an injection-site reaction and 1 exposed, a local reaction to the tourniquet.

Discussion

In this challenging protocol, we immunized acutely ill asthmatic children with a neoantigen (Bacteriophage ϕ X 174)

and 2 recall (diphtheria-tetanus) protein antigens. Children exposed to oral corticosteroids displayed a significantly lower peak antibody response following the primary immunization with Bacteriophage ϕ X 174. However, the comparable bacteriophage-specific titers following the second immunization in children exposed to oral corticosteroids and those not exposed support the absence of a sustained immunosuppression. The similar and normal response to recall antigens (d_2T_5) supports an adequate memory response to

TABLE 2. SECONDARY IMMUNE RESPONSE TO BACTERIOPHAGE ϕ X 174

	Oral steroid, n = 24	No oral steroid, n = 13	Ratio of geometric means (95% CI)	Mean group difference (95% CI)
Total IgG and IgM, geometric mean (95% CI)	347 (209, 578)	189 (89, 403)	1.84% (0.66%, 5.10%) ^a	—
IgG, geometric mean (95% CI)	49 (25, 99)	27 (9, 80)	1.84% (0.40%, 8.54%) ^b	—
Adequate amplification, % (95% CI) ^c	78% (49%, 106%)	56% (24%, 89%)	—	22% (−26%, 69%) ^d
Ratio of IgG/(IgG + IgM), % (95% CI)	26% (16%, 35%)	19% (9%, 29%)	—	7% (−8%, 22%) ^e

All titers are expressed as the rate of phage inactivated over time (K value, Kv).

^aAdjusted for propensity score and peak primary response in total IgG and IgM ($R^2 = 0.57$).

^bAdjusted for propensity score, age, delay between immunizations, and peak primary response in total IgG and IgM ($R^2 = 0.69$).

^cGreater than a 2-fold increase in peak titers following the second immunization, as compared to following the first immunization.

^dAdjusted for propensity score, lot, heart rate, cumulative dose of inhaled glucocorticoids during the study, and peak primary response in total IgG and IgM ($R^2 = 0.39$).

^eAdjusted for propensity score, lot, number of courses of steroids in the preceding 12 months, and daily dose of inhaled glucocorticoids during the study ($R^2 = 0.49$).

CI, confidence interval.

known antigens, even when exposure occurred during a burst of oral corticosteroids. The findings suggest a transient immune suppression occurring in some children who are concomitantly exposed to a new antigen and systemic corticosteroids during an asthma exacerbation, with recovery within 6 weeks.

The depressed antibody response to the primary Bacteriophage immunization is in line with the previously reported nonspecific suppression of serum immunoglobulins 2 weeks after systemic corticosteroids in normal volunteers and adults with acute asthma.^{9,11,12} A normal response involves the recognition, uptake, and processing of the antigen by B cells, presentation of the antigen to effector T cells, and stimulation of antigen-specific B cells to proliferate and be-

come IgM-secreting and/or memory B cells. Several hypotheses may thus explain the observed depression. First, it may be due to increased catabolism and decreased synthesis of immunoglobulins.⁹ Second, the findings may be mediated by a specific steroid-induced suppression of T helper cells whose function is to induce B cells to develop into antibody-secreting memory B cells and plasma cells,³⁵ explaining the suppression of the primary response with a normal secondary response.³⁶ Finally, as per Kurashima and colleagues' observation, naïve T helper cells appear more sensitive to corticosteroids than memory T-cells.³⁷ This would account for the selective suppression of the primary response to a neoantigen (Bacteriophage) in presence of normal response to recall diphtheria and tetanus antigens.

TABLE 3. IMMUNE RESPONSE TO RECALL PROTEIN ANTIGENS

	Oral steroid, n = 26	No oral steroid, n = 14	Ratio of geometric means (95% CI)	P value
Diphtheria	n = 23	n = 13		
Magnitude of response				
% adequate (>10-fold increase)	8 (35%)	4 (31%)		1.00 ^a
% questionable (3–10-fold increase)	8 (35%)	5 (38%)		
% abnormal (<3-fold increase)	7 (30%)	4 (31%)		
Fold increase in titers (geometric mean, 95% CI)				
All patients ^b	5.9 (3.2, 11.0) n = 17	6.8 (2.8, 16.7) n = 9	87% (25%, 299%)	0.82
Excluding patients with high baseline values ^c	10.1 (5.6, 18.2) n = 24	11.3 (4.7, 27.4) n = 13	89% (27%, 295%)	0.85
Tetanus				
Magnitude of response				
% adequate (>10-fold increase)	12 (50%)	7 (54%)		0.07 ^b
% questionable (3–10-fold increase)	9 (38%)	1 (8%)		
% abnormal (<3-fold increase)	3 (13%)	5 (38%)		
Fold increase in titers (geometric mean, 95% CI)				
All patients ^d	10.7 (4.6, 24.9) n = 16	8.7 (2.3, 32.1) n = 8	123% (20%, 770%)	0.82
Excluding patients with high baseline values ^e	20.7 (11.1, 38.7)	41.9 (15.5, 113.7)	50% (13%, 191%)	0.29

^aP value for Fisher's exact test.

^bAdjusted for propensity score, cumulative dose of inhaled glucocorticoids during the study ($R^2 = 0.07$).

^cAdjusted for propensity score, cumulative dose of inhaled glucocorticoids during the study ($R^2 = 0.13$).

^dAdjusted for propensity score, delay between the immunizations ($R^2 = 0.13$).

^eAdjusted for propensity score ($R^2 = 0.10$).

The peak titers following the second immunization is the most sensitive measure of a sustained immunodeficiency to a neoantigen as it directly documents the integrity of humoral immunity and indirectly that of T-cell function. A normal response implies expansion of memory B cells, isotype switching to IgG resulting in the amplification of titers; these processes are T cell dependent.^{26,27} In this study, a 5-day course of oral corticosteroids has no prolonged impact on humoral immunity as the exposed group displayed no statistically significant difference in titers, memory, amplification, and IgG isotype conversion to the control group. Our findings concur with 2 controlled studies examining the impact of oral corticosteroids on antigen-specific antibodies in children with acute asthma, where there were no group differences in antibody titers to an injection of influenza vaccine in the ED.^{14,15} In these studies, though, the proportion of children naïve to the antigen (ie, with low prevaccination titers) was small, precluding any firm conclusion regarding the response to a new antigen but supporting our findings of an adequate response to recall antigens (diphtheria and tetanus).

The initial impetus for the study was generated by case reports of severe or fatal varicella in immunocompetent patients receiving systemic corticosteroids.^{7,38} While Patel and collaborators concluded to the absence of relationship between corticosteroid exposure and severe varicella,¹⁶ Dowell and colleagues reported a strong association (odds ratio: 178, 95% CI: 59, 541).¹⁷ Of interest, the latter group identified the time proximity (ie, within 14 days) between corticosteroid intake and onset of the rash as a major determinant of the increased risk of severe infection, lending support to our findings.¹⁷ The lack of a close time proximity between exposure and infection would also explain the similar 12-month rate of infections in children previously exposed or not to oral corticosteroids.³⁹ Our findings complement the accrued evidence, suggesting that a short course of oral corticosteroids may transiently blunt the primary humoral response to, and perhaps augment the severity of, a concurrent infection occurring in close time proximity with one another.

Yet, despite widespread use of oral corticosteroids for treating acute childhood asthma,⁴⁰ the rate of severe infections remains rare. This may be explained by an increased risk possibly restricted to infectious agents to which the child is naïve; the decreasing number of varicella-susceptible children since implementation of the vaccine⁴¹; the minimal impact of a transient decrease in immunoglobulins in presence of intact cellular immunity—which acts as primary defense against viruses; and a narrow window of vulnerability. Before prescribing systemic steroids, though, it would appear prudent to systematically enquire about recent exposure to new antigens in live vaccines (eg, as the measles-mumps-rubella) or contagious diseases (eg, measles, varicella, and hepatitis).⁴² If systemic corticosteroids are deemed necessary despite a recent varicella exposure, susceptibility to varicella (by history or laboratory testing) should be assessed and preventive strategies implemented. Vaccination with varicella should be recommended for all susceptible asthmatic children.

The results must be interpreted in light of the following limitations. In the absence of an effective substitute for oral corticosteroids, the study could not ethically be conducted as a randomized, controlled trial. Due to the demanding pro-

ocol, only a quarter of eligible subjects were enrolled, raising the issue of selection bias. As parents hesitated to subject young children to repeated injections, the participants were generally older than nonparticipants. Moreover, the groups differ at baseline in age, asthma severity, inhaled corticosteroids, and possibly in other unknown characteristics. Although exposed children were younger, most depressed responses were observed in older subjects. Although not previously reported and despite propensity score, we cannot exclude the possibility that the lower primary response may be caused in part by greater asthma severity in the corticosteroid-exposed group. However, the absence of depressed immunoglobulin titers in patients with acute severe asthma not treated with corticosteroids and the similar suppression in patients with acute asthma and in healthy volunteers receiving corticosteroids suggest that the effect is independent of asthma severity.^{9,11–13} Exposed children received inhaled corticosteroids more often and in higher doses than controls. Yet, the growing literature documenting normal cellular⁴³ and humoral immunity^{12,35,44} despite high doses of inhaled corticosteroids supports the absence of an association with the immune response. Although systemic corticosteroids were administered in an open-label fashion, objective measurements of antibody titers interpreted by authors blinded to the exposure reasonably argue against observer bias. Our small sample size provided insufficient power to identify small group differences, thus preventing firm conclusions on the adequacy of the secondary response or patient characteristics that may modulate the observed risk. Having examined T cell-dependent protein antigens, our results may not apply to polysaccharide or non-T cell-mediated antigens. The immunosuppressive properties of other corticosteroid (such as dexamethasone) were not assessed. Finally, Bacteriophage ϕ X 174 provided only an indirect assessment of cellular immunity, which remains the first line of defense of viral infections, including protection against severe varicella infections.⁴⁵

Because of contraindications to immunization with coexisting fever or pneumonia, 41% of children were excluded. Consequently, the results apply primarily to afebrile children receiving a 5-day course of oral prednisolone in the treatment of an asthma exacerbation.

Our results support the possibility of a transient immune suppression when systemic steroids are administered while the child is mounting a primary immune response to a new antigen, with no sustained immunosuppression. The results deserve confirmation with specific attention to clarifying the timing and duration of the period of increased vulnerability and the characteristics of children at increased risk.

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Contributions

Francine M. Ducharme conceived the protocol, secured funding, coordinated the acquisition of data, monitored the quality and analysis of the data, interpreted the results, and wrote the article. Sandy Resendes coordinated the data collection and management. Xun Zhang analyzed the data with the assistance of Marilyse Julien; Hans Ochs provided the bacteriophage, supervised the analysis of bacteriophage-specific antibodies, and interpreted the data; Bruce Mazer assisted in the protocol conception, supervised the analysis of diphtheria & tetanus-specific titers, and interpreted the data. All authors approved the final version. Francine Ducharme had full access to all the data and takes responsibility for the integrity of data and the accuracy of data analysis.

Author Disclosure Statement

None of the authors have any conflict to declare as it relates to this article.

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