Glucocorticoids and Hospital Length of Stay for Children with Anaphylaxis: A Retrospective Study

Kenneth A. Michelson, MD, Michael C. Monuteaux, ScD, and Mark I. Neuman, MD, MPH

Objective To evaluate whether glucocorticoid administration is associated with improved outcomes in children with anaphylaxis.

Study design We included children from the Pediatric Health Information System database who were diagnosed with anaphylaxis at 35 US children's hospitals between 2009 and 2013. Patients were stratified by disposition from the emergency department (ED), either hospitalized or discharged. We evaluated the association between glucocorticoid administration and prolonged length of stay (LOS), defined as hospital stay ≥2 days, and subsequent epinephrine administration among hospitalized children. Among discharged children, we assessed the association between glucocorticoid administration and ED revisits within 3 days. Analyses were adjusted for illness severity using ordering of laboratory tests, medications, oxygen, intravenous fluids, and admission to the intensive care unit.

Results Among 5203 children hospitalized with anaphylaxis, 424 (8.2%) had prolonged LOS. Glucocorticoid administration was inversely associated with prolonged LOS (aOR, 0.61; 95% CI, 0.41-0.93) and with subsequent epinephrine use (aOR, 0.63; 95% CI, 0.43-0.84) among hospitalized children. Glucocorticoid administration was not associated with the odds of a 3-day revisit (aOR, 1.01; 95% CI, 0.50-2.05) among discharged patients.

Conclusion The use of glucocorticoids was inversely associated with prolonged LOS among children hospitalized with anaphylaxis, but was not associated with 3-day ED revisits among discharged children. These findings support the use of glucocorticoids in children hospitalized with anaphylaxis. *(J Pediatr 2015;167:719-24)*.

The incidence of anaphylaxis has been increasing worldwide, accounting for more than 2800 annual pediatric hospitalizations in the US.[1-5] Although most cases of anaphylaxis resolve after initial treatment, up to 20% of patients have protracted symptoms or a biphasic reaction, a delayed recrudescence of illness occurring hours after improvement of the initial symptoms.[6-13]

Glucocorticoids are often used as initial therapy for allergic reactions and anaphylaxis, and are postulated to act as preventive therapy for protracted or biphasic anaphylaxis (PBA).[14-19] Glucocorticoids are increasingly being used in the US and were used in at least one-half of patients evaluated in an emergency department (ED) in 2004.[14,20] Guidelines in the US, United Kingdom, and Europe recommend glucocorticoids as second-line agents for the treatment of anaphylaxis after the use of epinephrine, and all note the paucity of evidence supporting this recommendation.[17,19,21] However, even with short courses, the use of glucocorticoids may be associated with adverse effects including mood changes, rebound atopic dermatitis, and osteoporosis.[22-24] There are no clinical trials assessing glucocorticoid efficacy for prevention of PBA.[7,25]

Glucocorticoids are administered to 50-97% of individuals with anaphylaxis, despite a lack of compelling evidence supporting their use.[7,8,10,11,14,26] This wide variability in usage combined with the paucity of high quality data speak to the need for further studies evaluating whether there is any benefit to glucocorticoid therapy in anaphylaxis. We conducted a retrospective study of more than 10 000 children with anaphylaxis to evaluate whether glucocorticoid administration is associated with prolonged length of stay (LOS), a potential surrogate marker of PBA.

Methods

Patients were drawn from the Pediatric Health Information System (PHIS) database (Children's Hospital Association, Overland Park, Kansas). The PHIS database contains clinical and billing data from 44 not-for-profit, tertiary care children's hospitals. The data collection, validation, and safeguarding procedures are ensured through a joint effort between the Children's Hospital Association and participating hospitals, and have been described previously.[27-29] We included data

ED	Emergency department
ICU	Intensive care unit
LOS	Length of stay
PBA	Protracted or biphasic anaphylaxis
PHIS	Pediatric Health Information System

From the Division of Emergency Medicine, Boston Children's Hospital, Boston, MA

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from 35 hospitals with complete data reporting for hospitalized and ED patients. The Institutional Review Board at Boston Children's Hospital approved the study.

We included children aged 1 month to 18 years presenting to an ED with a primary diagnosis of anaphylaxis (*International Classification of Diseases, Ninth Revision* codes 995.0, 995.6, and 995.60-995.69) between January 1, 2009, and September 30, 2013. We excluded children with a previous ED visit within 3 days for a primary or secondary diagnosis of anaphylaxis, as well as those with missing data regarding hospitalization.

Primary Exposure

Patients were considered to have received a glucocorticoid if they received 1 or more doses of dexamethasone, methylprednisolone, prednisolone, or prednisone intravenously or orally on the day of presentation.

Outcomes

The primary outcome among hospitalized patients was prolonged LOS, defined as stay of ≥2 days. A secondary outcome among hospitalized children was the use of parenteral epinephrine beyond the first hospital day. Among discharged patients, the outcome was a revisit to the ED for a diagnosis of allergic reaction (All Patient Refined Diagnosis Related Group, version 24 code of 811) within 3 days of the initial visit, regardless of whether or not the second visit resulted in hospitalization.

Covariates

Potential confounders were markers of severity and were determined a priori based on their potential to both influence the decision to use glucocorticoids and to prolong LOS.[29,30] We included only potential confounders that were highly likely to be determined concurrently with or before the decision to administer glucocorticoids, to avoid inadvertently including mediators or colliders in the model.

Potential confounders included demographic characteristics, such as age, sex, race (white, black, Asian, or other), and insurance status (public, private, or other). We also included asthma codiagnosis, defined as a secondary diagnosis of asthma during their anaphylaxis visit, and history of asthma, defined as a visit in the previous 24 months with an associated asthma diagnosis code (*International Classification of Diseases, Ninth Revision* code 493.xx).[31] Patients were also classified based on the presence of a complex chronic condition using a previously reported classification method.[32] To account for differences in illness severity, we also adjusted our analysis for the use of medications administered during the initial hospital day, including bronchodilators (albuterol, levalbuterol, or salbutamol), inhaled epinephrine or racepinephrine, parenteral epinephrine, H1 blockers (diphenhydramine, cetirizine, or hydroxyzine), H2 blockers (ranitidine, cimetidine, nizatadine, or famotidine), and administration of intravenous fluids.[10,17,29,30] We also adjusted our analysis for other markers of severity, including performance of a venous or arterial blood gas analysis, chemistry profile, intubation, central venous cannulation, or admission to an intensive care unit (ICU).[33]

The screen for confounders was performed separately for hospitalized and discharged children, resulting in a different list of variables for inclusion in multivariate models.

Statistical Analyses

Multivariate logistic regression was used to assess the association between glucocorticoid use and prolonged LOS, adjusting for covariates identified as potential confounders that were associated with glucocorticoid administration on univariate testing ($P < .20$). Because our data were abstracted from several hospitals, the assumption of independent observations might not hold. To accommodate these data, our regression model used clustered sandwich SE estimates, which allow for intrahospital correlation, relaxing the assumption that observations from the same hospital are independent.

To assess for the impact of possible prehospital glucocorticoid administration, we repeated the analysis after excluding patients transferred to the PHIS participating institution. We also repeated the analysis after excluding patients admitted to an ICU, to evaluate a subpopulation of children with nonsevere anaphylaxis.

We evaluated the association between glucocorticoid administration and use of parenteral epinephrine after the first hospital day, adjusting for the same covariates. We then restricted the analysis to the subgroup of patients who had received epinephrine on the first hospital day. We also evaluated the association between glucocorticoid administration and the odds of an ED revisit within 3 days among discharged patients.

Finally, we repeated all analyses by excluding medications and interventions that could mediate the association between glucocorticoid administration and prolonged LOS (for hospitalized children) or 3-day ED revisits (for discharged children).

Hospital-Level Analyses. At the hospital level, we assessed the association between the proportion of hospitalized patients receiving glucocorticoids and prolonged LOS using the Spearman rank correlation coefficient. All statistical tests were 2-sided and performed using Stata 13.1 (StataCorp, College Station, Texas), and the α level was set at 0.05.

Prolonged LOS as a Measure of PBA. We reviewed the electronic medical record at our institution to evaluate the extent to which prolonged LOS represented PBA (defined in the medical record audit by any persistent skin/mucosal, gastrointestinal, respiratory, or cardiovascular symptoms lasting longer than 6 hours from presentation, or evidence of any worsening of allergic symptoms after initial improvement).[9]