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Inhaled Corticosteroids Use Before Hospitalization May Be Protective in Children With Direct Lung Injury

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Abstract

BACKGROUND: Systemic corticosteroid use in acute respiratory failure has yielded uncertain benefits, partially because of off-target side effects. Inhaled corticosteroids (ICSs) confer localized antiinflammatory benefits and may protect adults with direct lung injury (DLI) from developing respiratory failure. To our knowledge, this relationship has not been studied in children.

RESEARCH QUESTION: Do children with DLI who are prescribed ICSs before hospitalization have lower odds of progressing to respiratory failure?

STUDY DESIGN AND METHODS: This retrospective, single-center cohort identified children seeking treatment at the ED with DLI and medication records before hospitalization. The primary outcome was intubation; secondary outcomes included noninvasive respiratory support (NRS). We tested the association of ICSs with intubation and NRS, adjusting for confounders. We stratified analyses on history of asthma and performed a sensitivity analysis adjusting for systemic corticosteroid use to account for status asthmaticus.

RESULTS: Of 35,220 patients, 17,649 patients (50%) were prescribed ICSs. Intubation occurred in 169 patients (73 patients receiving ICSs) and NRS was used in 3,582 patients (1,336 patients

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Additional information: The e-Tables are available online under "Supplementary Data."

receiving ICS). ICS use was associated with lower intubation (adjusted OR, 0.46; 95% CI, 0.31–0.67) and NRS (aOR, 0.45; 95% CI, 0.40–0.49). The association between ICS and NRS differed according to history of asthma ($P = .04$ for interaction), with ICS exposure remaining protective only for patients with a history of asthma. Results held true in sensitivity analyses.

INTERPRETATION: ICS use prior to hospitalization may protect children with DLI from progressing to respiratory failure, with possible differential efficacy according to history of asthma.

Keywords

ARDS; direct lung injury; inhaled corticosteroids; intubation; noninvasive respiratory support; noninvasive ventilation; pediatric; respiratory failure

Respiratory illness is the most common reason for both hospitalization and ICU admission in children.[1,2] Treatment for direct lung injury (DLI) primarily is supportive.[3,4] Systemic corticosteroids may be used if DLI progresses to severe ARDS, with studies yielding mixed results.[5–11] Steroids have numerous antiinflammatory effects, such as decreasing extravasation of fluid through intracellular junctions and limiting pulmonary edema, inhibiting neutrophil adhesion to endothelial cells, exerting antiinflammatory effects via glucocorticoid receptors, and enhancing adrenergic receptors and effect.[5,6] Studies of systemic corticosteroids in ARDS have demonstrated benefits in oxygenation, lung mechanics, and hemodynamics, with conflicting results on mortality and clinically relevant outcomes resulting from potential off-target side effects and inconsistencies in timing of initiation.[7–12] Inhaled corticosteroids (ICSs) have a localized and direct site of action for DLI, with minimal systemic absorption. ICS use in DLI may be beneficial prophylactically and in preventing progression to respiratory failure because drug delivery in later and more severe illness may be variable and may be affected by pulmonary edema and $\dot{V}/\dot{Q}$ mismatch.

Studies in animal models suggest that ICSs can attenuate inflammation and can improve oxygenation, hemodynamics, and lung mechanics, particularly when ICSs are given before or early after lung injury.[13–17] Two retrospective studies in adults suggest that prior ICS use in patients at risk of ARDS may protect against progression to actual ARDS, and this was most evident in patients with DLI at presentation.[18–20] This was supported by a phase II feasibility trial comparing placebo with combination ICSs and inhaled beta-agonists (IBAs) in patients admitted to the hospital at risk of ARDS developing, demonstrating improved oxygenation and reduced risk of developing ARDS or requiring mechanical ventilation.[21] A phase III randomized control trial assessing whether the use of combination ICSs plus IBAs in adults admitted to the hospital with pneumonia and hypoxemia prevents progression to respiratory failure is ongoing (ClinicalTrials.gov Identifier: NCT04193878).[22,23]

However, in pediatrics, no studies evaluating if ICS use in children protects against all-cause DLI progressing to respiratory failure have been published to our knowledge. Children have a higher prevalence of DLI and respiratory illness than adults, and the epidemiologic features of infectious DLI are more likely to be viral in children than in adults.[2,24,25] Thus, it is not clear whether the benefits of early ICSs would translate to children with DLI. However, given the smaller airways and coexistence of asthma-like phenotypes in

pediatrics, it is plausible that ICSs would have greater efficacy specifically in children with DLI. Therefore, we aimed to determine if patients prescribed ICSs before DLI were less likely to progress to respiratory failure. We hypothesized that ICS exposure before hospitalization was associated with decreased progression to intubation and to use of noninvasive respiratory support (NRS).

Study Design and Methods

Study Design and Setting

This was a single-center, retrospective, observational cohort study performed at the Children's Hospital of Philadelphia (CHOP). The CHOP Institutional Review Board approved this study (Identifier: 21–018485) and deemed it exempt from additional review or need for informed consent.

Study Population

Patients who sought treatment at the CHOP ED with DLI and reliable outpatient medication records were included in this study. We identified DLI by International Classification of Diseases, 10th Revision (ICD-10), codes for acute asthma, bronchiolitis, reactive airway disease, pneumonia, aspiration, pulmonary trauma or contusion, drowning, inhalational toxin, and acute respiratory failure (e-Table 1). Given the change from the International Classification of Diseases, Ninth Revision, to the ICD-10, we looked at patients who sought treatment from January 2015 through December 2020, restricting ourselves to the ICD-10. Patients were included if they had an outpatient encounter within the CHOP network up to 1 year before the ED visit, and therefore had an outpatient medication reconciliation completed. This was carried out to ensure reliable medication records before admission and to obtain as accurate classification of the main exposure (ICS use before hospitalization) as feasible. We excluded encounters where the DLI ICD-10 code was not the primary or admitting diagnosis. Patients with tracheostomies were excluded because they do not require intubation or NRS for escalation of respiratory support. We also excluded patients with limitations of care orders and patients who were transferred to the CHOP ED from an outside hospital ED.

Variables

Our exposure of interest was ICS use before presentation to the CHOP ED, which was identified based on the medication reconciliation from the most recent outpatient encounter (e-Table 1). Baseline characteristics collected included age, sex, race, ethnicity, Zip code, type of insurance, history of asthma, and number of outpatient medications prescribed. Zip code was used with the Internal Revenue Service's statistics of income from 2019 as a proxy for socioeconomic status, scored from 1 to 6.[26] Type of insurance was categorized as private, public (Medicare or Medicaid), self-pay, or unknown. History of asthma was determined based on outpatient IBA prescription on medication reconciliation or if the patient had an ICD-10 code indicating a history of asthma. Number of outpatient medications prescribed was used as a marker of medical complexity and was determined based on the medication reconciliation from the most recent outpatient encounter. Type of DLI was recorded; if patients were recorded as having more than one type of DLI in the ICD-10 codes from

that encounter (ie, aspiration and reactive airway disease), both were recorded. Exposure to systemic steroids within 48 h of ED presentation was recorded.

The primary outcome of interest was need for intubation. The secondary outcome was use of NRS, defined as high-flow nasal cannula, use of CPAP or bilevel positive airway pressure, or use of both. Secondary outcomes also included admission to the hospital, admission to the ICU, length of stay, and mortality.

Analysis

We estimated that 5% to 10% of the population would be taking ICSs and that 5% of patients would require mechanical ventilation based on the clinical studies from the adult population.[18,19] To detect an OR of 0.7, we needed approximately 20,000 to 40,000 patients at an α value of .05 to achieve 80% power.

We compared baseline characteristics between encounters with and without ICS exposure. Categoric data are presented as number and percent, and continuous variables are presented as median and interquartile range (IQR). Multivariable logistic regression was performed, adjusting for age, sex, race, ethnicity, type of insurance, Zip code-based socioeconomic status, medication reconciliation-based medical complexity, and history of asthma. These confounders were selected using a causal framework, with a Directed Acyclic Graph (DAG) (Fig 1). Given the “backdoor” relationship between ICS exposure and status asthmaticus on the DAG, we a priori planned to test for interaction and to stratify the adjusted analysis by history of asthma. In an effort to control for the potentially lower rates of progression to NRS or intubation more precisely, we also conducted a sensitivity analysis that adjusted for receipt of systemic steroids within 48 h of ED presentation as a proxy for status asthmaticus.[27] This sensitivity analysis also addresses the potential confounding resulting from systemic corticosteroids on the association between ICSs and the primary outcome because of overlapping mechanisms of action. An additional sensitivity analysis was performed that excluded high-flow nasal cannula from NRS, therefore only examining patients who received CPAP or bilevel positive airway pressure.

We performed a subgroup analysis examining only patients admitted to the hospital to assess better whether an effect in patients with more severe acute illness is present. We also performed a subgroup analysis based on history of chronic lung disease (CLD), determined by ICD-10 codes for CLD or bronchopulmonary dysplasia. The ICD-10 code needed to be from that patient encounter, but was not necessarily the primary or admitting code. Analyses were performed using STATA software (StataCorp).

Results

Description of the Cohort

Of the 38,838 encounters of patients seeking treatment in the ED with DLI by ICD-10 codes and with a prior CHOP outpatient encounter within the previous year, 35,220 patient encounters were included (Fig 2). Of these, 17,649 patients (50.1%) had ICSs prescribed on the outpatient medication reconciliation and were considered exposed to ICSs, with 17,571 patients (49.9%) not exposed to ICSs before hospitalization. The median time from

prior outpatient encounter to ED presentation was 38 days (IQR, 9–100 days). The baseline characteristics are shown in Table 1. The ICS-exposed group were older, were prescribed more outpatient medications, and were more likely to have a prior history of asthma. Only 295 ICS-exposed patients did not have a history of asthma. Patients with ICS exposure and no history of asthma trended toward being younger (median age, 3.9 years [IQR, 2.0–8.7 years] vs 6.4 years [IQR, 3.7–10.4 years]) and were more likely to have CLD (3.4% with CLD vs. 1.7% without CLD), compared to patients with ICS exposure and a history of asthma. When looking at types of DLI, more patients in the ICS-exposed group presented with status asthmaticus, whereas patients without ICS exposure were more likely to present with bronchiolitis, reactive airway disease, or pneumonia (e-Table 2). The percentage of patients receiving systemic steroids within 48 h of ED presentation was similar to the percentage of patients with status asthmaticus on presentation between groups (e-Table 2).

Of patients seeking treatment in the ED, 38.9% were admitted to the hospital and 7.4% were admitted to the ICU during the hospitalization (Table 2). Frequencies of hospital and ICU admission were lower in ICS-exposed patients compared with non-ICS-exposed patients (hospital admission rates of 36.3% vs. 41.6% and ICU rates of 6.3% and 8.6%, respectively). Length of stay was similar between groups. Death was rare, occurring in 13 patients (< 0.1%; six patients in the ICS-exposed group and seven patients in the non-ICS-exposed group).

Association Between ICS Exposure and Respiratory Failure

Intubation occurred in 169 patients: 73 patients receiving ICSs and 96 patients not receiving ICSs (Table 2). ICS exposure was associated with nonsignificantly lower odds of intubation (unadjusted OR, 0.76; 95% CI, 0.56–1.03) (Table 3). After adjusting for confounders, ICS was associated with a lower rate of intubation (adjusted OR [aOR], 0.46; 95% CI, 0.31–0.67) (Table 3). When stratified by history of asthma ($P = .87$ for interaction), the association between ICS exposure and intubation remained significant for patients with a history of asthma (aOR, 0.49; 95% CI, 0.33–0.72), but not for patients without a history of asthma (aOR, 0.38; 95% CI, 0.05–2.8), albeit with a comparable effect size.

NRS was used in 3,582 patients: 1,336 patients receiving ICSs and 2,245 patients not receiving ICSs (Table 2). ICS exposure was associated with lower odds of escalation to NRS (unadjusted OR, 0.56; 95% CI, 0.52–0.60) (Table 3). This remained significant after adjusting for confounders, with ICS exposure associated with lower frequency of NRS use (aOR, 0.45; 95% CI, 0.40–0.49). When stratified by history of asthma ($P = .04$ for interaction), ICS exposure remained protective for patients with a history of asthma (aOR, 0.41; 95% CI, 0.37–0.46), but not for patients without a history of asthma (aOR, 0.89; 95% CI, 0.61–1.30), who showed a substantially attenuated effect size.

The results were unchanged qualitatively in the sensitivity analysis when adjusting for receipt of systemic corticosteroids within 48 h of presentation (e-Table 3). The results also were similar in the sensitivity analysis that excluded high-flow nasal cannula as NRS (e-Table 4).

Subgroup Analysis

Subgroup analysis was performed for the 13,703 patient encounters requiring admission to the hospital from the ED. Our results were unchanged qualitatively, with ICS exposure associated with lower odds of intubation (aOR, 0.55; 95% 0.38–0.81) and NRS (aOR, 0.53; 95% CI, 0.48, 0.59) (e-Table 5). When stratified by history of asthma, we saw qualitatively unchanged trends in ICS compared with the entire cohort.

CLD was diagnosed by ICD-10 code in 481 patient encounters. Subgroup analysis was performed for patients with and without a history of CLD (e-Table 6) and suggested a protective association between ICS exposure and escalation to intubation (aOR, 0.39; 95% CI, 0.27–0.55) and NRS (aOR, 0.35; 95% CI, 0.32–0.38) in patients without CLD. In patients with a history of CLD, these protective associations did not reach statistical significance (intubation: aOR, 0.43 [95% CI, 0.12–1.54]; NRS: aOR, 0.66 [95% CI, 0.43–1.00]).

Discussion

In this large, single-center, retrospective study, we found that ICS exposure before hospitalization was associated with decreased escalation to intubation and NRS in pediatric patients seeking treatment in the ED with DLI. When stratified by history of asthma, this association was seen only for patients with a history of asthma. For patients without a history of asthma, point estimates suggested a possible protective effect of ICS exposure, but did not reach statistical significance.

This study is the first to our knowledge to assess ICS exposure before hospitalization and progression to respiratory failure in all-cause pediatric DLI. Our work is consistent with the literature on adults. Festic et al[18] published a secondary analysis on the multicenter Lung Injury Prediction Score cohort of approximately 5,100 patients, which looked at patients admitted to the hospital with risk factors for progression to ARDS. Festic et al's[18] data showed protection with ICS that was most pronounced with DLI in unadjusted analysis (4% vs 11% progression to lung injury), but was not significant after propensity matching. This study raised concerns for type II error with overmatching and included matching for COPD and asthma in its adjusted analysis. Mangi et al[19] retrospectively looked at adult patients admitted to a single hospital system with a risk factor for ARDS. Similar to Festic et al's results, Mangi et al's unadjusted analysis showed a significant benefit from ICSs, yet the adjusted analysis (which also adjusted for asthma and COPD) was nonsignificant. A prospective feasibility trial was performed in adult patients at risk of ARDS with acute hypoxemia, excluding patients with indications for ICS and IBA use, such as asthma and COPD.[21] The trial showed statistically significant improvement in oxygenation (measured by oxygen saturation/FIO2 ratios) in patients who received combined ICS and IBA therapy and demonstrated that early administration of medication for at-risk patients is feasible and safe. A larger phase III randomized control trial is underway in adults to assess if early combination ICS and IBA therapy in adults admitted with pneumonia and hypoxemia prevents progression to respiratory failure (ClinicalTrials.gov Identifier: NCT04193878); it also excludes patients with conditions requiring ICS or IBA therapy.[22,23]

Patients with a history of asthma are more likely to present with status asthmaticus, and pediatric patients frequently are prescribed ICSs because of a history of persistent asthma. We anticipated this “backdoor” connection between ICS exposure, history of asthma, and status asthmaticus in the causal model (Fig 1). Although asthma is an unavoidable limitation in pediatric observational studies looking at ICSs and DLI, we addressed this by adjusting for and stratifying our analysis based on a personal history of asthma and performing a sensitivity analysis adjusting for systemic steroid use to account for status asthmaticus. We tested this assumption by looking for an interaction between ICS use and personal history of asthma. The interaction term was significant for escalation to NRS, but not for intubation. The lack of interaction significance with escalation to intubation suggests the possibility of a real protective effect of ICSs in DLI, regardless of a history of asthma. However, the rarity of intubation and the retrospective nature of our study precludes stronger conclusions. The significant interaction with escalation to NRS suggests that patients with chronic inflammatory disease, such as asthma, may be more likely to experience clinical benefits from early ICS exposure with all-cause DLI than patients without a history of asthma. Although adult cohort studies adjusted for history of asthma and COPD, our DAG and results suggest that this may not have addressed the interaction between ICS exposure before hospitalization, personal history of asthma or COPD, and acute status asthmaticus or COPD exacerbation adequately. We believe our approach of both adjustment and stratification better addresses the relationship among asthma, ICSs, and respiratory failure. COPD is rare in pediatric patients, with only 18 encounters in the cohort of 35,220 patients having an ICD-10 code for COPD, and thus we did not adjust for or stratify by COPD in our study.

Although the cohort included a higher percentage of patients receiving ICSs before hospitalization than anticipated, we observed a less frequent primary outcome of intubation. The higher use of ICSs before hospitalization likely was the result of selecting patients with recent outpatient medication reconciliations at a CHOP-affiliated facility, which potentially biased our population toward a more medically complex cohort. Furthermore, rates of childhood asthma in Philadelphia are more than double the national average.[28] The lower rate of intubation likely was because we studied patients seeking treatment in the ED, rather than patients admitted to the hospital, because one mechanism of ICS protection may be reduced admission rates. Furthermore, many of the patients demonstrated status asthmaticus, which has a lower intubation rate than other forms of DLI.[27] Our secondary outcomes included NRS use, which was a more common occurrence. Despite this, we detected a statistically significant difference in both intubation and NRS in the entire cohort. In our subgroup analysis, the protective association between ICS exposure and escalation to intubation and NRS was significant only in those without CLD; although the point estimates trended similarly in those with CLD, they were not statistically significant. This likely was a result of being underpowered to detect statistical significance, because only 481 patients had a diagnosis of CLD.

This study has several limitations. First, it was a retrospective, single-center study. Despite biological plausibility, no prior clinical pediatric studies have been published; we wished to determine the potential clinical relevance and to approximate effect sizes of ICS exposure on progression to respiratory failure. Our study was limited to a single-center cohort because we required reliable medication records from before hospitalization and included patients

seeking treatment early in the illness trajectory who were not necessarily hospitalized. Hospital admission and ICU databases may be biased toward patients later in the disease course, whereas we specifically hypothesized that ICS exposure would protect against this progression. Although we included only patients with reliable outpatient medication reconciliation, our study remains limited by adherence and not knowing whether patients were taking ICSs at the time of presentation to the ED. Furthermore, in comparing patients with and without ICS exposure before hospitalization, numerous confounders were present. We addressed this by creating a DAG and adjusting for confounders with a multivariable logistic regression model; however, certain confounders, such as medical complexity, were difficult to quantify. We used the number of outpatient medications prescribed as a proxy for medical complexity. Our study also is limited by immortal time bias, although the mortality rate in the cohort was low (< 0.1%) and the subgroup analysis looking at admitted patient encounters was consistent with the results from the entire cohort. Additionally, with a large number of patients demonstrating status asthmaticus and many receiving systemic corticosteroids, we likely have not disentangled fully the associations among ICS exposure before hospitalization, acute use of systemic corticosteroid therapy, and progression to respiratory failure. Excluding patients with status asthmaticus would have decreased our sample size dramatically, rendering the study underpowered to assess any meaningful relationship. Instead, we addressed this by stratifying based on history of asthma and by performing a sensitivity analysis adjusting for receipt of systemic corticosteroids. These analyses provide additional nuance to our findings, but the possibility of residual confounding remains. Furthermore, with the point estimates favoring protection against intubation and NRS in patients both with and without a history of asthma, as well as the relative paucity of side effects of ICSs, our findings support further work investigating the use of ICSs in pediatric DLI.

Despite these limitations, our data are congruent with adult studies and animal models showing potential protection of early ICS use in DLI from progression to respiratory failure. Our study was a large cohort study with granular medication and outcome data. Although multicenter observational studies should be performed to validate our findings, the limitations and biases from the “backdoor” connection among ICSs, history of asthma, and status asthmaticus likely will persist. A feasibility trial that tests the efficacy of ICSs in pediatric patients seeking treatment in the ED with DLI without status asthmaticus, stratified by history of asthma, is warranted to elucidate further if an acute role of ICSs in preventing progression to respiratory failure exists.

Interpretation

In this large retrospective study, ICS use before hospitalization was associated with one-half the odds of escalation to intubation and NRS in pediatric patients seeking treatment in the ED with DLI. The protective effect seems to be strongest in patients with a history of asthma. Future studies should explore whether a role exists for early prophylactic ICS use in pediatric DLI without status asthmaticus, stratified by history of asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

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Data Sharing:

Limited de-identified data that support the findings of this study are available on reasonable request.

ABBREVIATIONS:

aOR	adjusted OR
CHOP	Children's Hospital of Philadelphia
CLD	chronic lung disease
DAG	directed acyclic graph
DLI	direct lung injury
ICD-10	International Classification of Diseases, 10th Revision
ICS	inhaled corticosteroid
IBA	inhaled beta-agonist
IQR	interquartile range
NRS	noninvasive respiratory support

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Take-home Points

Study Question:

Do children presenting to the emergency department with all-cause direct lung injury who are prescribed inhaled corticosteroids prior to hospitalization have lower odds of progressing to respiratory failure?

Results:

Children prescribed inhaled corticosteroids prior to hospitalization were half as likely to be intubated or to be escalated to noninvasive respiratory support. When stratified by personal history of asthma, this protective effect was only statistically significant for children with a history of asthma.

Interpretation:

Inhaled corticosteroid use prior to hospital presentation may protect children with all-cause direct lung injury, particularly those with a history of asthma, from progressing to respiratory failure.

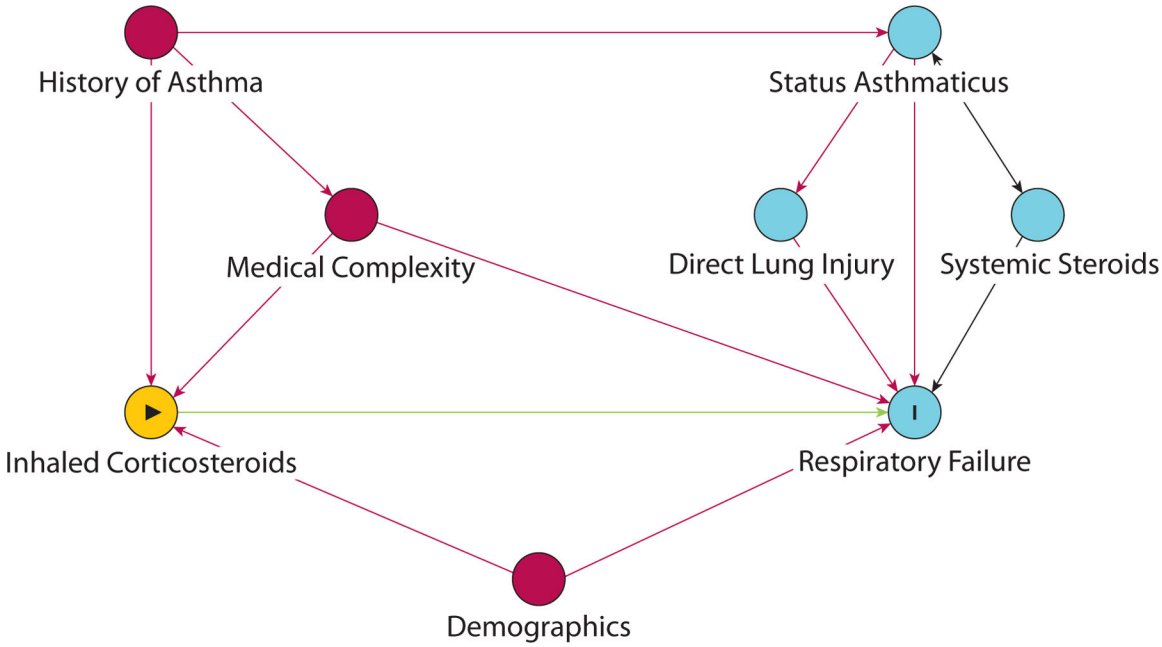

Figure 1 –.

Diagram showing a directed acyclic path for our hypothesis. Demographics include age, sex, race, Hispanic or Latino ethnicity, insurance, and Zip code-based socioeconomic status. The circle with a triangle represents the exposure and the circle with an I represents outcome.

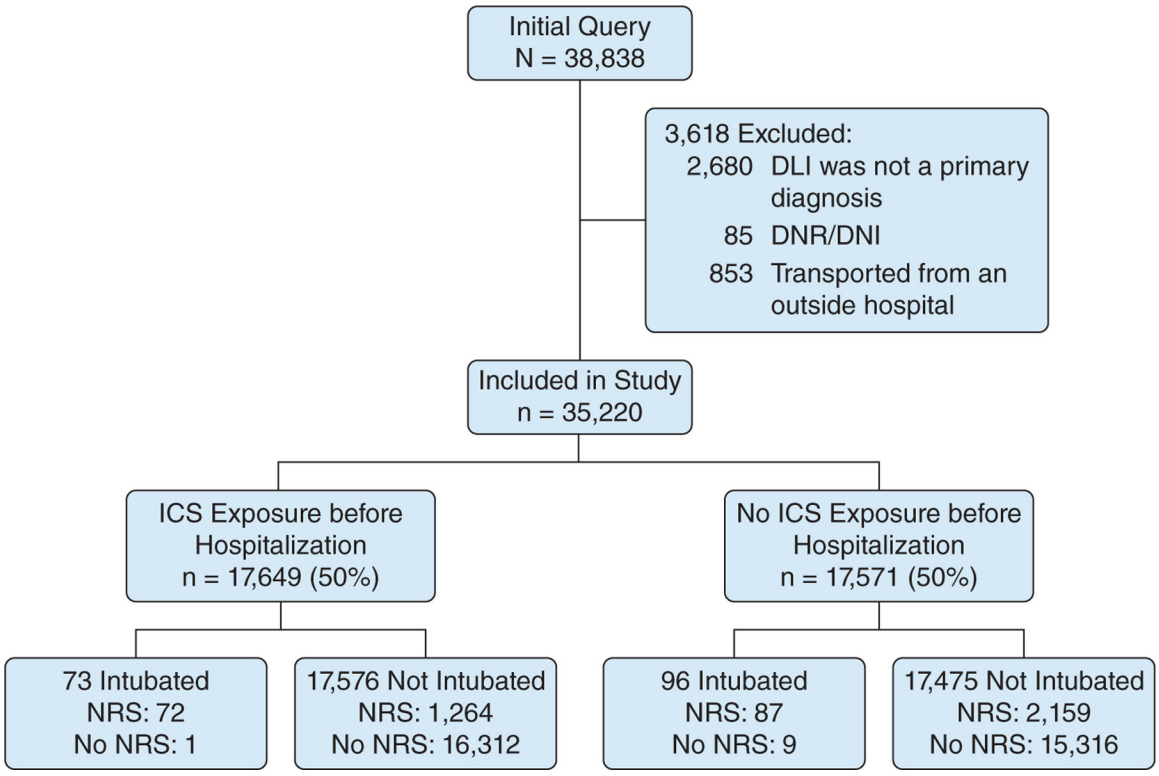

Figure 2 –.

Study flow diagram showing patients included in study. Intubation and NRS use are nonexclusive, meaning that a patient may require NRS before or after being intubated. DLI = direct lung injury; ICS = inhaled corticosteroid; NRS = noninvasive respiratory support. DNR/DNI indicate limitation of care orders (do not resuscitate and do not intubate, respectively).

TABLE 1]

Baseline Characteristics by Encounter, Based on Exposure

Characteristic	Total (N = 35,220)	ICS	
		Yes (n = 17,649)	No (n = 17,571)
Age, y			
< 2	9,771 (28)	1,609 (9)	8,162 (46)
2-< 8	15,655 (44)	9,125 (52)	6,530 (37)
8-< 12	5,220 (15)	3,774 (21)	1,446 (8)
12-< 16	2,754 (8)	1,964 (11)	790 (4)
> 16	1,820 (5)	1,177 (7)	643 (4)
Sex			
Female	14,941 (42)	7,531 (43)	7,410 (42)
Male	20,279 (58)	10,118 (57)	10,161 (58)
Race			
White	5,306 (15)	2,066 (12)	3,240 (18)
Black	24,765 (70)	13,372 (76)	11,393 (65)
Asian	1,070 (3)	347 (2)	723 (4)
American Indian	20 (< 1)	9 (< 1)	11 (< 1)
Pacific Islander/Hawaiian	29 (< 1)	19 (< 1)	10 (< 1)
Multiple	1,183 (3)	585 (3)	598 (3)
Unknown	2,847 (8)	1,251 (7)	1,596 (9)
Hispanic/Latino			
No	31,981 (91)	16,054 (91)	15,927 (91)
Yes	3,175 (9)	1,572 (9)	1,603 (9)
Unknown	64 (< 1)	23 (< 1)	41 (< 1)
Insurance			
Private	9,348 (27)	4,257 (24)	5,091 (29)
Public	25,495 (72)	13,175 (75)	12,320 (70)
Self-pay	371 (1)	211 (1)	160 (1)
Unknown	6 (5)	6 (< 1)	0
SES weighted score			

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Characteristic	Total (N = 35,220)	ICS	
		Yes (n = 17,649)	No (n = 17,571)
1.0–1.8	6,960 (20)	3,778 (21)	3,182 (18)
1.81–2.2	14,719 (42)	7,725 (44)	6,994 (40)
2.21–2.6	6,527 (19)	3,083 (17)	3,444 (20)
2.61–3.0	3,848 (11)	1,735 (10)	2,113 (12)
3.01–4.0	3,106 (9)	1,300 (7)	1,806 (10)
4.0–6.0	60 (< 1)	28 (< 1)	32 (< 1)
Outpatient medications			
0–2	8,228 (23)	442 (3)	7,786 (44)
3–5	11,440 (32)	4,773 (27)	6,667 (38)
6–8	7,932 (23)	5,919 (34)	2,013 (11)
9–11	4,144 (12)	3,574 (20)	570 (3)
12–14	1,817 (5)	1,584 (9)	233 (1)
15–19	1,151 (3)	939 (5)	212 (1)
≤ 20	508 (1)	418 (2)	90 (1)
History of asthma			
Yes	25,346 (72)	17,354 (98)	7,992 (45)
No	9,874 (28)	295 (2)	9,579 (55)

Data are presented as No. (%). Age and number of outpatient medications were stratified into groups. ICS = inhaled corticosteroids; SES = socioeconomic status.

TABLE 2]

Primary and Secondary Outcomes by Exposure

Variable	Total (N = 35,220)	ICS	
		Yes (n = 17,649)	No (n = 17,571)
Intubation			
Yes	169 (0.5)	73 (0.4)	96 (0.5)
No	35,051 (99.5)	17,576 (99.6)	17,475 (99.5)
NRS			
Yes	3,582 (10.2)	1,336 (7.6)	2,246 (12.8)
No	31,638 (89.8)	16,313 (92.4)	15,325 (87.2)
Admission			
Discharged from ED	21,517 (61.1)	11,247 (63.7)	10,270 (58.4)
Hospital admission	13,703 (38.9)	6,402 (36.3)	7,301 (41.6)
ICU admission	2,609 (7.4)	1,105 (6.3)	1,504 (8.6)
Length of stay, h			
Hospital	35.2 (20.3–63.6)	35.0 (20.4–60.1)	35.5 (20.2–64.9)
ICU	56.0 (32.0–114.7)	62.0 (34.5–133.9)	51.8 (30.5–103.6)
Death			
Yes	13 (< 0.1)	6 (< 0.1)	7 (< 0.1)
No	35,207 (> 99.9)	17,643 (> 99.9)	17,564 (> 99.9)

Data are presented as No. (%) or median (interquartile range). ICS = inhaled corticosteroids; NRS = noninvasive respiratory support.

TABLE 3]

Unadjusted and Adjusted ORs With 95% CIs

	Unadjusted		Adjusted		
Variable	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	***P* Value (for Interaction)**
Intubation					
All	0.76 (0.56–1.03)	.072	0.46 (0.31–0.67)	< .001	.874
History of asthma	…	…	0.49 (0.33–0.72)	< .001	…
No history of asthma	…	…	0.38 (0.05–2.80)	.340	…
NRS					
All	0.56 (0.52–0.60)	< .001	0.45 (0.40–0.49)	< .001	.040
History of asthma	…	…	0.41 (0.37–0.46)	< .001	…
No history of asthma	…	…	0.89 (0.61–1.30)	.534	…

The multivariable regression model is adjusted for age, sex, race, ethnicity, insurance type, Zip code-based socioeconomic status, medical complexity, and history of asthma. For stratification based on history of asthma, the interaction *P* value is shown. NRS = noninvasive respiratory support.