Published in final edited form as:

Pediatr Crit Care Med. 2018 November ; 19(11): e585–e594. doi:10.1097/PCC.0000000000001695.

Inflammatory and Comorbid Features of Children Admitted to a Pediatric Intensive Care Unit for Status Asthmaticus

Jocelyn R. Grunwell, MD, PhD^{1,2}, Curtis Travers, MPH¹, and Anne M. Fitzpatrick, PhD^{1,2}

¹Emory University School of Medicine, Department of Pediatrics, Atlanta, GA

²Children's Healthcare of Atlanta at Egleston, Atlanta, GA

Abstract

Objective—To determine risk factors associated with admission to a pediatric intensive care unit (PICU) with or without endotracheal intubation for an asthma exacerbation. We hypothesized that children with critical and near-fatal asthma would have distinguishing clinical features but varying degrees of asthma severity and measures of type 2 inflammation.

Design—Retrospective analysis of prospectively collected data of children with asthma recruited into outpatient asthma clinical research studies at Emory University between 2004 and 2015.

Setting—Large, free-standing academic quaternary care children's hospital in Atlanta, Georgia.

Patients—Children 6 to 18 years of age with physician-diagnosed and confirmed asthma.

Interventions—None.

Measurements and Main Results—A total of 579 children were analyzed with 170 (29.4%) children being admitted to the PICU for an asthma exacerbation in their lifetime. Of these 170 children with a history of critical asthma, 24.1% were classified as having mild-to-moderate asthma, and 83/170 children (48.8%) had been intubated and experienced near-fatal asthma. Multiple logistic regression was used to identify risk factors associated with increased odds of PICU admission with or without endotracheal intubation. Hospitalization within the prior 12-months of survey (odds ratio (OR): 8.19, 95% confidence interval (CI): 4.83–13.89), a history of pneumonia (OR: 2.56, 95% CI: 1.52–4.29), having a designation of increased chronic asthma severity on high-dose inhaled corticosteroids (OR: 2.76, 95% CI: 1.62–4.70), having a father with asthma (OR: 2.15, 95% CI: 1.23–3.76), living in a region with a higher burden of poverty (OR:

Correspondence: jgrunwe@emory.edu; Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta at Egleston, Division of Critical Care Medicine, 1405 Clifton Road NE, Atlanta, GA 30322; phone 404-785-1600; fax 404-785-6233.

Copyright form disclosure: Drs. Grunwell and Fitzpatrick received support for article research from the National Institutes of Health. Mr. Travers has disclosed that he does not have any potential conflicts of interest.

Authors' contributions: JG and AF conceived and developed the study. JG drafted the manuscript. CT helped to develop the study, conducted statistical analyses, and helped to interpret the data. JG, CT, and AF edited the manuscript. All authors read and approved the manuscript.

Article Tweet: Identification of inflammatory and comorbid factors associated with critical and near-fatal asthma in a well-defined cohort of children.

Conflict of Interest Statement:

The authors have no conflicts of interest to disclose.

1.28, 95% CI: 1.02–1.61), and being of black race (OR: 2.01, 95% CI: 1.05–3.84) were all associated with increased odds of PICU admission with or without intubation.

Conclusions—Our findings suggest that there are factors associated with critical and near-fatal asthma, distinct from the chronic asthma severity designations, that should be the focus of future investigation.

Keywords

asthma; endotracheal intubation; pediatric intensive care unit; pneumonia

INTRODUCTION

Over six million children less than 18 years of age are currently diagnosed with asthma and most of these children are poorly controlled despite therapy attempts (1). Asthma exacerbation is therefore the leading medical emergency in children, with critical asthma responsible for up to 20% of all admissions to pediatric intensive care units (PICU) (2–4). Some children with critical asthma require endotracheal intubation and mechanical ventilation, a condition termed near-fatal asthma (5). Although current National Institutes of Health/National Heart, Lung, and Blood Institute guidelines propose criteria for asthma severity based on symptoms and medication responses, these guidelines do not delineate features of critical or near-fatal asthma (6). Indeed, many children classified as having intermittent or mild persistent asthma are hospitalized with critical and/or near-fatal asthma exacerbations (7).

Attempts at characterizing critical asthma phenotypes have been limited by incomplete characterization of clinical features including lung function, medication use, and inflammatory biomarkers. Therefore, it is unclear what features are associated with critical asthma in children, and whether these features can be identified in children in outpatient settings. Characterization of the molecular and cellular patterns of airway inflammation in children with asthma are not routine. Whereas some investigators have found increased allergic eosinophilic airway responses characterized by type 2 inflammatory cytokines IL-4, IL-5, and IL-13 (8, 9), others have discovered neutrophilic, mixed neutrophil-eosinophil, and paucigranular patterns of airway inflammation (10, 11). High numbers of airway neutrophils are associated with type 1 inflammation characterized by infection-fighting cytokines IL-2 and IFN- γ that are resistant to corticosteroid therapy (11–13). To address this knowledge gap, we compared the characteristics of children with critical and near-fatal asthma to children without critical asthma in a large dataset of well-phenotyped children with asthma. We hypothesized that children with critical and near-fatal asthma would have distinguishing clinical features but varying degrees of asthma severity and measures of type 2 inflammation. We further hypothesized that a subset of children with critical and near-fatal asthma would have associated frequent pulmonary infections.

METHODS

We conducted a retrospective analysis of children 6 to 18 years of age with physician-diagnosed asthma recruited into outpatient asthma clinical research studies at Emory

University between January 01, 2004 and December 31, 2015. Children with any historical admission to a PICU with or without need for endotracheal intubation for status asthmaticus were compared to children without a prior PICU admission. Admission criteria were consistent for the duration of the study period and included: 1) need for a third continuous nebulized albuterol treatment, and/or 2) need for non-invasive respiratory support delivered by high-flow nasal-cannula or bi-level positive airway pressure, and/or 3) need to deliver an 80%/20% heliox mixture, and/or 4) need to deliver greater than or equal to 50% fraction-inspired oxygen by Venturi mask or positive pressure ventilation strategies. Hospitalization or emergency department use within the 12-months prior to study enrollment were used to define healthcare use.

Participants

All children who underwent standardized characterization in research protocols were eligible for inclusion (14, 15). These protocols were approved by Emory University's Institutional Review Board. Written informed consent was obtained from the legal guardians of each child, and verbal and written assent were obtained from the participating child for the original study for which data were acquired.

Eligible children had never smoked, had physician-diagnosed asthma along with a history of 12% relative change in forced expiratory volume in one second (**FEV₁**) after bronchodilator administration. Children were classified as having severe asthma according to the American Thoracic Society workshop criteria (16). This definition assumes that comorbid conditions have been treated or addressed and that the child is adherent with prescribed asthma treatment. Thresholds for high-dose inhaled corticosteroids (**ICS**) were defined as an inhaled fluticasone equivalent >800 mcg if ≥ 12 years or >400 mcg if <12 years of age. Original study exclusion criteria included birth prior to 35 weeks gestation, a history of developmental delay, or an asthma exacerbation treated with systemic corticosteroid within the 4 weeks prior to study enrollment. Children with steroid-exposure were excluded to obtain true baseline spirometry, laboratory, and symptomatology data not confounded by their recent asthma exacerbation. Chronic neurologically impaired children were excluded from the study due to limitations in participation in spirometry testing. All children were stable at the time of characterization with no signs of acute respiratory illness. Children with an acute worsening of asthma control were treated and reassessed later.

Characterization procedures

Participants underwent a battery of standardized phenotypic characterization procedures that included questionnaires, serum immunoglobulin E (**IgE**) and complete blood count with differential, allergy skin prick testing, and bronchial responsiveness to methacholine as previously described (17, 18). Spirometry was performed with a portable spirometer (KoKo® Legend, Ferraris, Louisville, CO). The best of three forced vital capacity (**FVC**) maneuvers was interpreted according to population reference standards (19). Exhaled nitric oxide (NIOX, Aerocrine, Solna, Sweden) was quantified using online methods (15). Aeroallergen sensitization was defined as a positive skin prick test with wheal ≥ 3 mm and flare ≥ 10 mm in diameter or a specific aeroallergen IgE test > 0.35 kU/L. Community (i.e., ZIP code) characteristics were obtained from Tables S101 (Age and Sex), S1501

(Educational Attainment), and DP03 (Selected Economic Characteristics) of the 2010–2014 American Community Survey 5-year estimates, available at www.factfinder.census.gov (20).

Statistical analyses

Descriptive statistics were calculated for all variables of interest. Frequencies were calculated for categorical variables and reported as percentages. Means and standard deviations or medians and interquartile ranges were calculated for continuous variables, where appropriate. Normality of the data was determined by Shapiro tests and visual inspection of histograms. Comparisons between intubated, PICU never intubated, and never PICU were performed using chi-square, ANOVA, and Kruskal-Wallis tests, where appropriate. *Post-hoc* tests between PICU admitted vs. Never PICU, Intubated vs. Never PICU, and Intubated vs. PICU Never Intubated were performed, and multiple comparisons were controlled for using Bonferroni corrections; *p*-values were assessed at $\alpha = 0.05/3 = 0.017$. Variables with multiple, mutually exclusive responses were tested with a single chi-square test. Variables with multiple, non-mutually exclusive responses were tested with individual chi-square tests assessing for the presence versus absence of each response. Multiple logistic regression models were used to identify primary factors associated with PICU admissions (21). Candidate variables showed univariate associations of $p < 0.05$ and forward selection was used to select the final model. Due to the concern of older patients having a longer period to have had a PICU admission, an indicator variable for age 12 years was forced into the final model. Only unique children were included in the dataset precluding the issue of coding for recurrent admissions. The same modeling strategy was used for the multinomial logistic regression model with the 3-category outcome of Intubated, PICU Not Intubated, and Never PICU. Odds ratios were calculated for both PICU groups versus Never PICU. Ordinal models were tested but did not meet the proportional odds assumption. Statistical analyses were performed with SAS Version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

There were 580 total children identified in the database; however, 1 patient was missing ICU information and 579 were included for the analysis. Of these children, 170 (29.4%) had been admitted to a PICU, excluding the neonatal period, for asthma in their lifetime. Of these 170 children with a history of critical asthma, 83/170 children (48.8%) had been intubated and experienced near-fatal asthma. The proportion of children with mild-to-moderate asthma in the Never PICU patients was 235/409 (57.6%) versus 24/87 (27.6%) and 17/83 (20.5%) in the PICU never intubated versus intubated groups, respectively ($p < 0.001$) (Table 1). Children 12 years of age and older were more likely to have been intubated compared with children under 12 years of age (Table 1). Black children predominated in our asthma cohort (58.0% vs. 29.9% white and 12.1% other) and are overrepresented compared to the racial demographics of the Metro Atlanta, Georgia region (55.4% white, 32.4% black, 12.2% other). Intubated children were more likely to be black race than those not admitted to the PICU (80.7% vs 52.3%, Table 1, $p < 0.001$) (Table 1). Children from socioeconomically disadvantaged communities were more likely to have been hospitalized in a PICU compared with children never hospitalized in a PICU (Table 1).

Clinical associations with PICU admission and endotracheal intubation

Children admitted to a PICU had more frequent episodes of weekly and daily wheezing and weekly and daily night awakenings than children never in the PICU (Table 2). A history of pneumonia, gastroesophageal reflux disease, exposure to secondary indoor smoking, and a father with a history of asthma were all associated with a higher frequency of ICU admissions. There were no triggers of asthma exacerbations that were significantly different amongst groups after multiple comparisons (Table 2). There were no significant differences between the children who had a history of intubation compared with the children admitted to the PICU and never intubated (Table 2).

Medication, healthcare use, and lung function

As expected, children with a history of intubation (79.5%) or a PICU admission without intubation (72.4%) were more likely to use high dose ICS compared with 42.4% of children never admitted to a PICU ($p < 0.001$) (Table 3). Likewise, children with a history of intubation (56.8%) or a history of PICU admission (48.3%) were more likely to use daily β -agonist medication (32.8%, $p < 0.001$). Combinations of medications such as ICS along with a long-acting β -agonist (LABA) and Montelukast or the use of Omalizumab were more commonly used in children intubated and/or in the PICU compared with children never in a PICU. Children with an intubation or PICU history were more likely to have been hospitalized or visited an Emergency Department in the previous year compared to children never in the PICU (Table 3). Finally, children with a PICU history were more likely to have lower FEV₁, regardless of intubation history, compared with children with asthma never admitted to a PICU (Table 3).

Type 2 inflammatory markers by PICU admission and endotracheal intubation

Children with a PICU admission history who were intubated were more likely to have a higher absolute eosinophil count than children never admitted to a PICU (Table 4). There was no difference in the number of aeroallergen skin prick responses or serum IgE levels. The median exhaled nitric oxide level was higher in children with a history of PICU admission without intubation or a history of PICU admission with intubation compared to children without PICU admission.

Multiple variable associations of PICU admission and endotracheal intubation

We used multiple logistic regression to estimate the odds of being admitted to the PICU (Table 5 and eTable 1). Age was forced into the model as older children have a longer window of opportunity to be admitted to the PICU for an asthma exacerbation. We found that being admitted to the hospital for an asthma exacerbation in the 12 months prior to data collection was associated with increased odds of ever having been admitted to a PICU (odds ratio: 8.19, 95% CI: 4.83 – 13.89, $p < 0.001$) (Table 5). Having a history of pneumonia was also correlated with increased odds of having had a PICU admission for an asthma exacerbation (odds ratio: 2.56, 95% CI: 1.52 – 4.29, $p < 0.001$) (Table 5). Other factors related to increased odds of PICU admission for asthma included black race (odds ratio: 2.01, 95% CI: 1.05 – 3.84, $p = 0.034$), living in an area with a higher percentage of the residents having income below the poverty line (odds ratio: 1.28, 95% CI: 1.02 – 1.61, $p =$

0.037), having a father with a history of asthma (odds ratio: 2.15, 95% CI: 1.23 – 3.76, $p = 0.007$), or having a history of severe asthma or high corticosteroid use (odds ratio: 2.76, 95% CI: 1.62 – 4.70, $p < 0.001$) (Table 5). We performed a sensitivity analysis with the model excluding severe asthma/high inhaled corticosteroid use with similar odds ratios for the significant variables with the addition of the medication combination consisting of an inhaled corticosteroid + a long-acting beta-agonist + Montelukast with an odds of 1.97 (95% CI: 1.21 – 3.22, $p = 0.007$) and a protective effect of monocytes with an odds of 0.88 (95% CI: 0.78 – 0.99, $p = 0.028$) (eTable 2). The odds ratios for being admitted to a PICU with or without endotracheal intubation compared to never being admitted are shown in Figure 1.

DISCUSSION

This study describes the clinical, lung function, inflammatory, and comorbid characteristics of critical and near-fatal asthma in a well-phenotyped cohort of children. We used multiple logistic regression to analyze the characteristics associated with increased odds of experiencing critical or near-fatal asthma. Hospitalization within the prior 12 months for an asthma exacerbation was the factor most highly associated with increased odds of a PICU admission, a result consistent with a retrospective review of over 26,000 children ages 2 to 17 years from a pan-Canadian administrative database (22). Other significant factors associated with increased odds of PICU admission included having a history of pneumonia, having a designation of increased chronic asthma severity on high-dose inhaled corticosteroids, having a paternal history of asthma, living in a region with a higher burden of poverty, and being of non-Caucasian race. Designation of asthma severity is driven by chronic symptom severity and prescribed dose of inhaled corticosteroids, and admission to a PICU for critical or near-fatal asthma likely drives prescription practice. Therefore, it is not surprising that the critical and near-fatal groups have the highest symptom and medication burden.

There was, however, a sizeable percentage of children in our cohort defined as having mild or moderate asthma with critical asthma (27.6%) and near-fatal asthma (20.5%) (Table 1). By contrast, of the children categorized as having severe asthma, 42.4%, had never been admitted to a PICU for an exacerbation. The mismatch between chronic asthma severity stratification and the tendency of some children with mild asthma to present with critical and near-fatal asthma has been reported in both children and adults (23, 24). Similar to our findings, Carroll and colleagues noted that features associated with recurrent PICU admissions for severe asthma exacerbations were associated with a child being overweight, receiving public insurance, and not being Caucasian (23). Multiple PICU admissions and/or intubations were not assessed as part of the original study, and therefore we cannot analyze risk factors for recurrent critical and near-fatal asthma.

Although critical and near-fatal asthma are associated with asthma severity, we believe that critical and near-fatal asthma are distinct phenotypes. Characterization of this distinct phenotype is necessary not only to design interventions to prevent the occurrence of critical and near-fatal asthma, but to identify a subgroup of children for which current therapies inadequately treat their asthma. These children may have distinct pathobiological mechanisms that would respond to alternative therapies.

The frequency of invasive mechanical ventilation has been reported to range from 10 – 12% in a retrospective review of Pediatric Health information System (PHIS) administrative database from 2004 – 2008, that included our institution (25). The frequency of invasive mechanical ventilation in our cohort (83/409, 20%) is not the true incidence of near-fatal asthma at our center as there is selection bias for children recruited from high-risk asthma and allergy clinics who are likely more motivated to participate in a research study following near-fatal asthma. Likewise, only a small percentage of children admitted to our PICU with asthma are invasively mechanically ventilated compared to the enriched frequency of 83/170 (48.8%) of children reported in this cohort. In addition, children over 12 years of age are more likely to have been intubated due to the increased chance the longer the child has carried a diagnosis of asthma.

Early childhood lower respiratory viral infections, such as human rhinovirus and respiratory syncytial virus, are implicated in the development of childhood asthma and with severe, sudden-onset asthma exacerbations (26, 27). Complex interactions between the genetic predisposition, environmental factors, and infectious agent contribute to a dysregulated immune response, allergic sensitization and airway colonization/infection with pathogenic bacteria. We note that pneumonia was a factor associated with increased odds of PICU admission with or without intubation. It is unclear whether early-life lower respiratory infections with injury to the airway epithelium create a proinflammatory environment in which asthma develops, or whether children who wheeze with lower respiratory infections have a genetic predisposition to develop asthma and the wheezing is a marker of this susceptibility (28, 29). Asthma exacerbations are often triggered by upper respiratory infections (URI); however, we did not find any association with URI and a history of PICU admission.

It is known that school age children with severe asthma often have multiple allergies and a predominance of eosinophils (12). By contrast, preschool age children with recurrent wheeze are predominantly characterized by bacterial infection and neutrophil predominance (12). Our study focused on school-age children, and while we saw an increase in circulating eosinophil percentage in children with critical and near-fatal asthma in univariate analysis, this factor was not significant in the final multiple variable model. We also noted higher levels of FeNO in children with critical and near-fatal asthma compared with children with no prior PICU admission in univariate analysis; however, there was no association with serum IgE levels or allergen skin prick sensitization tests. In addition, we did not see an association with atopic dermatitis and allergies in our patient cohort. Exhaled nitric oxide is a marker for eosinophilic asthma that is typically suppressed by corticosteroid therapy indicating that children in our cohort may be either corticosteroid non-adherent or refractory to corticosteroid therapy.

Autopsy findings from children with fatal asthma have noted two distinct inflammatory findings; children with mucus-plugging and eosinophilic pulmonary infiltration who present with a gradual onset of respiratory failure and those children with a neutrophil-predominant pulmonary infiltration without mucus-plugging of the distal airways who present with a severe asphyxia onset of respiratory symptoms (30, 31). Molecular phenotyping has shown that a mixed Th1 and Th2 phenotype is present in children with a severe asthma phenotype

(32), yet no such phenotyping has been undertaken in a critical asthma patient cohort. The lack of information on the airway environment and the inflammatory cells populating the critical asthmatic's airway either during an acute exacerbation or during convalescence hinders phenotyping of patients and prevents hypothesis driven mechanistic studies and drug development that could lead to the discovery of novel therapeutic targets.

We employed a multiple variable regression analysis to our cohort of children; however, application of a non-hierarchical cluster analysis, like that undertaken by the Severe Asthma Research Program (SARP), may yield valuable insight into novel phenotypes of children with critical and near-fatal asthma (14, 24, 33–36). While the description of children with critical and near-fatal asthma is robust and comprehensive, we did not endotype children with critical or near-fatal asthma nor did we sample or assess Th1 or Th2 airway inflammation. Cluster analysis and endotyping strategies will likely be more informative in the development of biologically plausible hypotheses and pharmacological targets to prevent and intervene during a critical or near-fatal asthma exacerbation. For example, the association between a pneumonia history and critical asthma exacerbations warrants investigation into use of immunomodulatory anti-infectives, such as azithromycin, as a strategy to prevent and treat acute critical asthma exacerbations.

Conclusions

Although fatal asthma is rare, critical and near-fatal asthma are common. An in-depth individualized assessment, including endotyping, is needed to personalize the pediatric intensivists and pulmonologists approach to asthma care and prevent life-threatening outcomes. Our findings suggest that there are factors associated with critical and near-fatal asthma, distinct from the chronic asthma severity designations, that should be the focus of future investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We acknowledge the Emory+Children's Pediatric Research Biostatistics Core for help with statistical analysis. This work was supported in part by R01 NR013700, the National Center for Advancing Translational Sciences of the National Institutes of Health (award no. UL1 TR000454) to Dr. Anne Fitzpatrick, and the Atlanta Pediatric Scholars Program grant K12 HD072245 to Dr. Jocelyn Grunwell.

Abbreviations

FEV₁	Forced expiratory volume in one second
FVC	Forced vital capacity
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL	Interleukin

References

1. National Health Interview Survey (NHIS). Data: 2016 Lifetime Asthma, Current Asthma, Asthma Attacks among those with Current Asthma. 2016. [cited 12 May 2018]Available from: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2016_SHS_Table_C-1.pdf
2. Bohn D, Kissoon N. Acute asthma. *Pediatr Crit Care Med*. 2001; 2(2):151–163. [PubMed: 12797875]
3. Hartman ME, Linde-Zwirble WT, Angus DC, et al. Trends in admissions for pediatric status asthmaticus in New Jersey over a 15-year period. *Pediatrics*. 2010; 126(4):e904–911. [PubMed: 20876177]
4. Biagini Myers JM, Simmons JM, Kercksmar CM, et al. Heterogeneity in asthma care in a statewide collaborative: the Ohio Pediatric Asthma Repository. *Pediatrics*. 2015; 135(2):271–279. [PubMed: 25601985]
5. Newth CJ, Meert KL, Clark AE, et al. Fatal and near-fatal asthma in children: the critical care perspective. *J Pediatr*. 2012; 161(2):214–221. e213. [PubMed: 22494876]
6. Guidelines for the Diagnosis and Management of Asthma (EPR-3). 2007. [cited 29 Apr 2018]Available from: <https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma>
7. Carroll CL, Schramm CM, Zucker AR. Severe exacerbations in children with mild asthma: characterizing a pediatric phenotype. *J Asthma*. 2008; 45(6):513–517. [PubMed: 18612906]
8. Dunican EM, Fahy JV. The Role of Type 2 Inflammation in the Pathogenesis of Asthma Exacerbations. *Ann Am Thorac Soc*. 2015; 12(Suppl 2):S144–149. [PubMed: 26595730]
9. Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. *Nat Rev Immunol*. 2015; 15(1):57–65. [PubMed: 25534623]
10. Hastie AT, Moore WC, Meyers DA, et al. Analyses of asthma severity phenotypes and inflammatory proteins in subjects stratified by sputum granulocytes. *J Allergy Clin Immunol*. 2010; 125(5):1028–1036. e1013. [PubMed: 20398920]
11. Moore WC, Hastie AT, Li X, et al. Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis. *J Allergy Clin Immunol*. 2014; 133(6):1557–1563. e1555. [PubMed: 24332216]
12. Guiddir T, Saint-Pierre P, Purenne-Denis E, et al. Neutrophilic Steroid-Refractory Recurrent Wheeze and Eosinophilic Steroid-Refractory Asthma in Children. *J Allergy Clin Immunol Pract*. 2017; 5(5):1351–1361. e1352. [PubMed: 28363401]
13. Eller MCN, Vergani KP, Saraiva-Romanholo BM, et al. Can inflammatory markers in induced sputum be used to detect phenotypes and endotypes of pediatric severe therapy-resistant asthma? *Pediatr Pulmonol*. 2018
14. Fitzpatrick AM, Teague WG. Severe Asthma in Children: Insights from the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *Pediatr Allergy Immunol Pulmonol*. 2010; 23(2):131–138. [PubMed: 21761006]
15. Fitzpatrick AM, Teague WG, Meyers DA, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol*. 2011; 127(2):382–389. e381–313. [PubMed: 21195471]
16. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014; 43(2):343–373. [PubMed: 24337046]
17. Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol*. 2007; 119(2):405–413. [PubMed: 17291857]
18. Fitzpatrick AM, Gaston BM, Erzurum SC, et al. Features of severe asthma in school-age children: Atopy and increased exhaled nitric oxide. *J Allergy Clin Immunol*. 2006; 118(6):1218–1225. [PubMed: 17157650]
19. Wang X, Dockery DW, Wypij D, et al. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol*. 1993; 15(2):75–88. [PubMed: 8474788]

20. U.S. Census Bureau American. Community Survey. 2010–2014. [cited 2018 29 Apr] Available from: <https://www.census.gov/programs-surveys/acs.html>
21. Lang T. Documenting research in scientific articles: Guidelines for authors: 3. Reporting multivariate analyses. *Chest*. 2007; 131(2):628–632. [PubMed: 17296672]
22. Tse SM, Samson C. Time to Asthma-Related Readmission in Children Admitted to the ICU for Asthma. *Pediatr Crit Care Med*. 2017; 18(12):1099–1105. [PubMed: 28922266]
23. Carroll CL, Uygungil B, Zucker AR, et al. Identifying an at-risk population of children with recurrent near-fatal asthma exacerbations. *J Asthma*. 2010; 47(4):460–464. [PubMed: 20528602]
24. Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations. *Am J Respir Crit Care Med*. 2017; 195(3):302–313. [PubMed: 27556234]
25. Bratton SL, Newth CJ, Zuppa AF, et al. Critical care for pediatric asthma: wide care variability and challenges for study. *Pediatr Crit Care Med*. 2012; 13(4):407–414. [PubMed: 22067984]
26. Bacharier LB, Cohen R, Schweiger T, et al. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. *J Allergy Clin Immunol*. 2012; 130(1):91–100. e103. [PubMed: 22444510]
27. Zomer-Kooijker K, van der Ent CK, Ermers MJ, et al. Increased risk of wheeze and decreased lung function after respiratory syncytial virus infection. *PLoS One*. 2014; 9(1):e87162. [PubMed: 24498037]
28. Beigelman A, Bacharier LB. The role of early life viral bronchiolitis in the inception of asthma. *Curr Opin Allergy Clin Immunol*. 2013; 13(2):211–216. [PubMed: 23385289]
29. Beigelman A, Bacharier LB. Early-life respiratory infections and asthma development: role in disease pathogenesis and potential targets for disease prevention. *Curr Opin Allergy Clin Immunol*. 2016; 16(2):172–178. [PubMed: 26854761]
30. Carroll N, Carello S, Cooke C, et al. Airway structure and inflammatory cells in fatal attacks of asthma. *Eur Respir J*. 1996; 9(4):709–715. [PubMed: 8726935]
31. Sur S, Crotty TB, Kephart GM, et al. Sudden-onset fatal asthma. A distinct entity with few eosinophils and relatively more neutrophils in the airway submucosa? *Am Rev Respir Dis*. 1993; 148(3):713–719. [PubMed: 8368644]
32. Fitzpatrick AM, Higgins M, Holguin F, et al. The molecular phenotype of severe asthma in children. *J Allergy Clin Immunol*. 2010; 125(4):851–857. e818. [PubMed: 20371397]
33. Fitzpatrick AM. Severe Asthma in Children: Lessons Learned and Future Directions. *J Allergy Clin Immunol Pract*. 2016; 4(1):11–19. quiz 20–11. [PubMed: 26772923]
34. Fitzpatrick AM, Moore WC. Severe Asthma Phenotypes - How Should They Guide Evaluation and Treatment? *J Allergy Clin Immunol Pract*. 2017; 5(4):901–908. [PubMed: 28689840]
35. Moore WC, Fitzpatrick AM, Li X, et al. Clinical heterogeneity in the severe asthma research program. *Ann Am Thorac Soc*. 2013; 10(Suppl):S118–124. [PubMed: 24313761]
36. Teague WG, Phillips BR, Fahy JV, et al. Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age. *J Allergy Clin Immunol Pract*. 2018; 6(2):545–554. e544. [PubMed: 28866107]

Figure 1.

A forest plot of adjusted odds ratios from a multiple logistic regression model for risk factors associated with pediatric intensive care unit (PICU) admission with or without endotracheal intubation compared to Never PICU admission as the reference. The adjusted odds ratios for being admitted to the PICU, but not intubated (black squares) and admitted to the PICU and intubated (grey squares) and whiskers depicting the 95% confidence intervals are shown with never in the PICU acting as the reference.

Table 1

Demographics of the participants by PICU admission and endotracheal intubation

Characteristic, n (%)	Never PICU <i>n</i> = 409	PICU Admission <i>n</i> = 170		<i>p</i> -value
		Never Intubated <i>n</i> = 87	Intubated <i>n</i> = 83	
Asthma Severity ^a				
Mild to moderate	235 (57.6%)	24 (27.6%)	17 (20.5%)	< 0.001 ^{*A}
Severe	173 (42.4%)	63 (72.4%)	66 (79.5%)	
Age, yr, median (IQR)	10 (8 – 13)	12 (9 – 14)	12 (9 – 14)	0.015 [*]
range	5 – 18	6 – 18	6 – 18	
Adolescents (12–18 years)				
n (column %, row %)	167 (40.8%, 65.2%)	47 (54.0%, 18.3%)	42 (50.6%, 16.4%)	0.036 [*]
Children (6–11 years)				
n (column %, row %)	242 (59.2%, 74.9%)	40 (46.0%, 14.5%)	41 (49.4%, 12.7%)	
Sex, <i>n</i> = 579				
Female	177 (43.3%)	38 (43.7%)	27 (32.5%)	0.181
Male	232 (56.7%)	49 (56.3%)	56 (67.5%)	
Race				
Black	214 (52.3%)	55 (63.2%)	67 (80.7%)	< 0.001 ^{*A}
White	144 (35.2%)	21 (24.1%)	8 (9.6%)	
Other	51 (12.5%)	11 (12.6%)	8 (9.6%)	
Ethnicity				
Hispanic	26 (6.4%)	10 (11.5%)	4 (4.8%)	0.165
Non-Hispanic	383 (93.6%)	77 (88.5%)	79 (95.2%)	
Body mass Index				
Normal	220 (54.5%)	40 (45.6%)	39 (47.6%)	0.487
Overweight	81 (20.1%)	18 (20.7%)	18 (22.0%)	
Obese	103 (25.5%)	29 (33.3%)	25 (30.5%)	
Population by zip code, median (SD)	34,314 (17,479)	31,915 (15,341)	35,577 (15,236)	0.223
Percent by zip code, median (IQR)				
Unemployed	10.5 (8.1 – 15.3)	12.6 (8.4 – 15.8)	15.0 (9.0 – 19.9)	< 0.001 ^{*A}
Bachelor's degree	29.1 (20.3 – 42.2)	24.4 (17.5 – 37.4)	21.8 (16.8 – 31.5)	0.001 ^{*A}
Below poverty	19.5 (13.9 – 25.6)	21.8 (13.8 – 30.1)	25.2 (21.8 – 36.6)	< 0.001 ^{*A}

^aAmerican Thoracic Society Criteria^{*}Indicates difference between Never PICU and PICU Admission

[^] Indicates difference between Never PICU and Intubated

[#] Indicates difference between Never Intubated and Intubated

Bonferoni corrections used

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Clinical characteristics by PICU admission and endotracheal intubation

Characteristic, n (%)	Never PICU n = 409	PICU Admission n = 170		p-value
		Never Intubated n = 87	Intubated n = 83	
Wheezing Symptoms (n = 575)				
Never	148 (36.2%)	19 (21.8%)	20 (23.5%)	0.009 ^{*A}
Once per month	105 (25.7%)	20 (23.0%)	12 (15.2%)	
Weekly, < 2/week	69 (16.9%)	20 (23.0%)	18 (22.8%)	
Weekly, < 1/day	50 (12.2%)	14 (16.1%)	16 (20.3%)	
Daily	37 (9.1%)	14 (16.1%)	13 (16.5%)	
Night Waking Symptoms (n = 575)				
Never	200 (48.9%)	30 (34.5%)	28 (35.4%)	< 0.001 ^{*A}
Once per month	75 (18.3%)	16 (18.4%)	9 (11.4%)	
Weekly, < 2/week	58 (14.2%)	18 (20.7%)	10 (12.7%)	
Weekly, < 1/day	44 (10.8%)	11 (12.6%)	8 (10.1%)	
Daily	32 (7.8%)	12 (13.8%)	24 (30.4%)	
Medical History				
Allergies (n = 577)	340 (83.1%)	75 (86.2%)	74 (91.4%)	0.156
Eczema (n = 577)	242 (59.2%)	49 (56.3%)	51 (63.0%)	0.680
Nasal polyps (n = 576)	25 (6.1%)	5 (5.8%)	6 (7.4%)	0.890
Sinusitis (n = 575)	115 (28.2%)	32 (36.8%)	29 (35.8%)	0.161
Pneumonia (n = 571)	153 (37.9%)	58 (67.4%)	56 (69.1%)	< 0.001 ^{*A}
GERD ^a (n = 551)	80 (20.7%)	21 (25.0%)	33 (41.3%)	0.001 ^{*A}
Family Asthma History				
Father (n = 549)	83 (21.3%)	28 (33.7%)	30 (39.5%)	0.001 ^{*A}
Mother (n = 564)	155 (38.9%)	29 (34.5%)	35 (43.2%)	0.519
Sibling (n = 534)	213 (56.1%)	40 (48.8%)	42 (58.3%)	0.414
Indoor Exposures				
Second-hand smoke (n = 574)	54 (13.3%)	18 (20.7%)	20 (24.7%)	0.017 ^{*A}
Cat (n = 570)	60 (14.8%)	10 (11.8%)	6 (7.5%)	0.192
Dog (n = 568)	151 (37.6%)	23 (26.7%)	27 (33.8%)	0.155
Triggers				
Upper respiratory infection (n = 576)	376 (92.2%)	86 (98.9%)	77 (95.1%)	0.058
Daily Activities (n = 574)	114 (28.1%)	34 (39.1%)	31 (38.3%)	0.044 [*]
Pets (n = 562)	275 (69.3%)	61 (70.9%)	50 (63.3%)	0.514
Sports (n = 573)	345 (85.2%)	71 (81.6%)	65 (80.3%)	0.441

^a Gastroesophageal reflux disease

* Indicates difference between Never PICU and PICU Admission

^ Indicates difference between Never PICU and Intubated

Indicates difference between Never Intubated and Intubated

Bonferoni corrections used

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3

Medication use, health care use, and lung function by PICU admission and endotracheal intubation

Characteristic, n (%)	Never PICU n = 409	PICU Admission n = 170		p-value
		Never Intubated n = 87	Intubated n = 83	
Inhaled Corticosteroids (n = 578)				
None	96 (23.5%)	7 (8.1%)	4 (4.8%)	
Low to moderate dose	139 (34.1%)	17 (19.5%)	13 (15.7%)	< 0.001 ^{*^}
High dose	173 (42.4%)	63 (72.4%)	66 (79.5%)	
Daily β -agonist use, μ g/day (n = 577)	134 (32.8%)	42 (48.3%)	46 (56.8%)	< 0.001 ^{*^}
Controller Medications				
None	63 (15.4%)	1 (1.2%)	1 (1.2%)	< 0.001 ^{*^}
Montelukast only	14 (3.4%)	1 (1.2%)	0 (0.0%)	0.182
ICS only	61 (14.9%)	5 (5.8%)	5 (6.0%)	0.011 [*]
ICS + LABA or Montelukast	101 (24.7%)	18 (20.7%)	14 (16.9%)	0.261
ICS + LABA + Montelukast	124 (30.3%)	45 (51.7%)	47 (56.6%)	< 0.001 ^{*^}
Omalizumab	10 (2.4%)	5 (5.8%)	6 (7.2%)	0.041 [*]
Oral corticosteroids	20 (4.9%)	9 (10.3%)	8 (9.6%)	0.072
Other combination	16 (3.9%)	3 (3.5%)	2 (2.4%)	0.939
Hospitalized in previous year (n = 578)	52 (12.8%)	54 (62.1%)	53 (63.9%)	< 0.001 ^{*^}
ED visits in previous year (n = 577)	174 (42.8%)	68 (78.2%)	62 (74.7%)	< 0.001 ^{*^}
Baseline spirometry, mean (SD)				
FVC	102.2 (14.6)	99.6 (19.2)	98.6 (16.5)	0.094
FEV1	92.0 (16.4)	85.1 (21.2)	85.2 (18.0)	<0.001 ^{*^}
FEV1/FVC	90.4 (11.7)	84.6 (12.0)	86.6 (12.1)	<0.001 ^{*^}

* Indicates difference between Never PICU and PICU Admission

[^] Indicates difference between Never PICU and Intubated[#] Indicates difference between Never Intubated and Intubated

Bonferroni corrections used

Table 4

Type 2 Inflammatory markers by PICU admission and endotracheal intubation

Characteristic, n (%)	Never PICU n = 409	PICU Admission n = 170		p-value
		Never Intubated n = 87	Intubated n = 83	
WBC Count, median (IQR)	6.2 (5.1 – 7.8)	6.1 (5.3 – 7.9)	5.9 (4.9 – 7.4)	0.406
Neutrophils	2852 (2048 – 4031)	2926 (2075 – 4234)	2632 (1861 – 3887)	0.527
Lymphocytes	2392 (2016 – 2892)	2436 (2034 – 2789)	2196 (1898 – 2698)	0.248
Monocytes	448 (340 – 567)	454 (342 – 573)	392 (252 – 483)	0.003 [^] #
Eosinophils	278 (150 – 468)	351 (160 – 575)	384 (218 – 576)	0.017 ^{*^}
Basophils	30 (17 – 51)	31 (22 – 53)	28 (19 – 45)	0.749
Leukocyte Blood %, mean (SD)				
Neutrophils	46.8 (13.1)	47.1 (13.5)	46.3 (14.9)	0.942
Lymphocytes	39.7 (1.3)	38.5 (10.4)	39.7 (12.1)	0.772
Monocytes, median (IQR)	7.0 (5.8 – 8.4)	6.9 (5.7 – 9.0)	6.1 (4.8 – 7.8)	0.014 [^]
Eosinophils, median (IQR)	4.0 (2.0 – 7.0)	5.7 (2.4 – 8.8)	6.0 (3.7 – 9.9)	<0.001 ^{*^}
Basophils, median (IQR)	0.5 (0.3 – 0.9)	0.5 (0.3 – 1.0)	0.5 (0.3 – 0.7)	0.768
Serum IgE, median (IQR) <i>range</i>	327 (100 – 776) 1 – 8566	485 (125 – 914) 12 – 7438	315 (95 – 1268) 1 – 6892	0.280
Number of aeroallergen skin prick responses, median (IQR) <i>range</i>	3 (1 – 7) 0 – 12	4 (2 – 7) 0 – 12	4 (2 – 8) 0 – 12	0.095
Exhaled nitric oxide median (IQR), <i>range</i>	22 (11 – 44) 1 – 260	31 (15 – 53) 4 – 269	33 (19 – 65) 5 – 177	<0.001 ^{*^}

* Indicates difference between Never PICU and PICU Admission

[^] Indicates difference between Never PICU and Intubated

Indicates difference between Never Intubated and Intubated

Bonferroni corrections used

Table 5

Multiple Logistic Regression Model of PICU Admission. (N = 488)

Characteristic	PICU Admission		
	Odds Ratio	95% CI	p-value
Age (12 years)	2.31	1.39 – 3.86	0.001
Race			
White	Reference	-	
Black	2.01	1.05 – 3.84	0.034
Other	1.30	0.53 – 3.20	0.568
% Below Poverty Line in Zip Code (per 10 units)	1.28	1.02 – 1.61	0.037
Pneumonia	2.56	1.52 – 4.29	<0.001
Severe Asthma/High Dose ICS	2.76	1.62 – 4.70	<0.001
Father Asthma	2.15	1.23 – 3.76	0.007
Hospitalized in Past 12 months of survey	8.19	4.83 – 13.89	<0.001