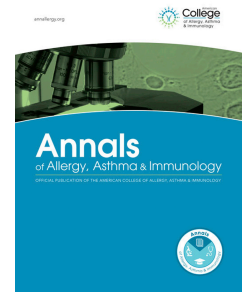


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Development of a Pediatric Asthma Predictive Index for Hospitalization

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Abbreviations: Asthma predictive index for hospitalization (APIH), emergency department (ED), oxygen saturation (SpO₂), respiratory rate (RR), inhaled corticosteroids (ICS), inhaled anti-inflammatory inhalers (IAI), short acting beta agonist (SABA), Pediatric Respiratory Assessment Measure (PRAM), Pulmonary Index Score (PIS), Pediatric Asthma Severity Score (PASS),

Respiratory rate, Accessory muscle use, and Decreased breath sounds (RAD) score,
Fluorescence enzyme immunoassay (FEIA), Clinical prediction rule (CPR)

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1 Introduction

2 Asthma is the third leading cause of hospitalization among children in the United States.¹
3 Currently 6.2 million children in the U.S. have asthma.¹ In 2014, the number of emergency
4 department (ED) visits for asthma exacerbation in children less than 15 years old was
5 approximately 820,000.² Recently, the total estimated cost of asthma to society was \$82 billion.³
6 There is currently no standard protocol for asthma admissions in the ED. This often leads to wide
7 variation in management and disparities in care.⁴

8
9 Several asthma severity scores including PRAM, PIS, PASS, and RAD have been created to
10 evaluate exacerbation severity and attempt to standardize clinician treatment. However, these
11 asthma severity scores are often insufficient to be used for hospitalization decisions.^{5,6} In
12 addition, most asthma severity scores used in the ED are only based on clinical findings of the
13 patient.⁷⁻¹⁰ Few have incorporated other factors such as epidemiology, co-existing atopy, and
14 medication adherence into the decision tree for asthma hospitalization. A comprehensive clinical
15 prediction model could guide clinicians in their admission decision. We initially sought to
16 identify the risk factors associated with asthma hospitalization. Using the identified risk factors,
17 we developed and internally validated a pediatric asthma predictive index for hospitalization
18 (APIH).

20 Methods

21 Study population

22 Data was collected from Kaiser Permanente Southern California members from March 4, 2014 to
23 March 4, 2015 who were diagnosed with asthma exacerbation in the emergency department. This

is a retrospective case control study of 12,066 pediatric patients between 5 to 18 years old. Inclusion criteria for diagnosis of asthma consists of participants who meet at least one of the following criteria: any hospital discharge, ED visit, or outpatient diagnosis ICD-9 code of asthma or at least 2 dispensing records for an inhaled steroid or bronchodilator. We excluded children with any chronic respiratory disease other than asthma. In addition, we excluded participants who had duplicate entries in the electronic medical record, only stayed in urgent care, or went to an ED or hospital outside of the Kaiser health system. ED visits or hospitalizations separated by more than 7 days were regarded as independent visits. The study protocol was approved by Kaiser Permanente Southern California IRB #10795.

Potential Risk factors

We examined epidemiologic factors including age, gender, ethnicity, and insurance status. Coexisting atopy, family history of atopy, and prior asthma emergency visits or hospitalizations were also investigated. History of pneumonia was captured with ICD 9 and 10 codes. We assessed use of medications with number of inhaled corticosteroid medications, short acting beta agonists, and oral steroids. Clinical findings at presentation to the ED included respiratory rate (RR) and oxygen saturation (SpO₂). ~~In addition, we assessed environmental sensitization with fluorescence enzyme immunoassay (FEIA, Immucap© Specific IgE). Allergens tested included: grasses, weeds, trees, molds, dust mites, cats, dogs, and cockroaches.~~

Main outcome

The primary outcome was hospitalization for asthma exacerbation. Risk factors were compared between patients hospitalized for asthma and those discharged from the ED. The risk factors that

had the highest association with asthma hospitalization were used to create a clinical prediction model. Clinical prediction rules (CPR) are important for children especially for diagnoses that can lead to poor outcomes and have higher diagnostic ambiguity since there are more communication difficulties with children.¹¹⁻¹³ We chose to use risk factors on presentation to the ED to create a clinical prediction model that is comprehensive, practical, and assistive for the physician.

Statistical analysis

All statistical analyses were performed in SAS Enterprise Guide version 9.3. Univariate logistic regression model was used to determine the individual association between each potential predictor and asthma hospitalization in the whole cohort. The potential predictors that were significantly associated with asthma hospitalization with $p < 0.05$ were retained as candidates for the predictive model. We then utilized multivariate analysis to further determine the best predictor variables for hospitalization.

To establish the predictive model for asthma hospitalization, the patients were randomly assigned to either trial dataset for model building or validation dataset for model confirmation. The trial dataset included 60% of the cohort and the validation data included 40% of the cohort. Demographics of the trial and validation cohorts were similar. Stepwise logistic regression was applied to the trial dataset to build the predictive model which incorporated all significant predictors resulted from multivariate logistic regression. This predictive model was confirmed by the validation dataset. Logistic regression with best set selection was performed to obtain the predictive model with the four most significant predictors to facilitate efficiency in decision

making. We then internally validated the hospitalization prediction index. C-index was measured to assess the discrimination power or future performance of our clinical prediction rule. A c-index of 1 is perfect discrimination and a c-index ≥ 0.7 is a favorable model.

Results

Figure 1 flow diagram details the patients meeting the inclusion criteria. A total of 12,066 patients were included in the study. Baseline characteristics of the patients are presented in Table 1. The median age was 10 years for emergency department discharge and 9 years for hospitalization. Overall, there were more males who had asthma exacerbations and more males who were hospitalized (64% each). The patient population had a wide variation in race and ethnicity with the majority being Hispanic. Approximately one third in both groups had Medicaid insurance. 867 ED asthma patients (7.2%) were hospitalized.

Univariable Analysis

Results of the univariate analysis are demonstrated in Table 2. Several variables were significantly associated with hospitalization, including: O2 saturation $<94\%$ (OR: 5.0, 95% CI 4.3, 6), RR >31 (OR 4.7, 95% CI 4, 5.5), past history of pneumonia (OR 3.4, 95% CI 3, 4), food allergy (OR 1.95, 95% CI 1.5, 2.5), and atopic dermatitis (OR 1.36, 95% CI 1.2, 1.6). In addition, family history of atopy (asthma, allergic rhinitis, or atopic dermatitis) correlated with hospitalization with asthma being the most significant (OR 1.85, 95% CI 1.6, 2.1). Uncontrolled asthma as evidenced by ≥ 6 SABA canisters dispensed in the prior 12 months (OR 1.5, 95% CI 1.1, 2), prior ED visit in past 12 months (OR 1.8, 95% CI 1.6, 2.1), and prior hospitalization in past 12 months (OR 2.7, 95% CI 2.2, 3.3) were also significantly linked with hospitalization.

FEIA (Immunocap ©) evaluation for atopic sensitization was also associated with asthma hospitalization (OR 1.45, 95% CI 1.2, 1.7). Of interest, oral corticosteroids dispensing in the prior 12 months did not correlate with hospitalization. Presence of Medicaid insurance did not increase risk of asthma hospitalization (subset analysis data not shown).

Multivariable Analysis

Table 3 displays the multivariate analysis of the risk factors for hospitalization. Characteristics correlating with admission were similar in the multivariable analysis to those in the univariate analysis. O2 saturation <94% (OR 3.4, 95% CI 2.8, 4.1) and RR>31 (OR 3, 95% CI 2.5, 3.6) significantly increased risk. Past history of pneumonia (OR 2.8, 95% CI 2.3-3.3) or food allergy (OR 1.8, 95% CI 1.3-2.6) also strongly increased hospitalization risk. An asthma ED visit in the prior 12 months significantly increased risk of hospitalization (OR 1.8, 95% CI 1.5, 2.2), but prior oral steroid dispensing did not. Dispensing of < 6 IAI canisters (OR 1.3, 95% CI 1, 1.6) and ≥ 6 SABA canisters in the prior year (OR 2, 95% CI 1.3, 3.1) were both associated with increased risk of admission.

Asthma prediction model

We created a full asthma prediction model using the highest risk factors obtained through the multivariable analysis. Our initial clinical prediction rule (CPR) consisted of 12 predictor variables shown in Table 4. C indices were 0.78 with the trial dataset and 0.79 with the validation dataset. The top 7 risk factors most strongly associated with asthma admission are O2 saturation < 94% (OR 3.5, 95% CI 2.8, 4.4), RR > 31 bpm (OR 2.8, 95% CI 2.3, 3.5), history of pneumonia (OR 2.8, 95% CI 2.2, 3.4) or food allergy (OR 1.7, 95% CI 1.2, 2.5), prior ED visit

(OR 1.6, 95% CI 1.3, 2), IAI canisters < 6 in 12 months (OR 1.5, 95% CI 1.2, 1.8), and SABA canisters ≥ 6 in the prior 12 months (OR 1.5, 95% CI 0.9, 2.6). Using these 7 predictor variables, we developed a reduced form of the prediction model with backward logistic regression with c-indices of 0.78 in the trial cohort and 0.79 in the validation cohort.

We further simplified the prediction index to the strongest 4 risk factors to facilitate usability and maximize efficiency in Tables 4 and 5. The 4 predictor variables used are O2 saturation <94% (OR 3.3, 95% CI 2.8, 4), RR > 31 bpm (OR 3.1, 95% CI 2.6, 3.7), history of pneumonia (OR 2.7, 95% CI 2.2, 3.2), and past ED visit for asthma in the prior 12 months (OR 1.6, 95% CI 1.4, 1.94). Although history of food allergies had a higher odds ratio than prior ED asthma visit, we prioritized past ED exacerbation given that food allergy history with concomitant workup may not be available in all health care systems. This reduced prediction model yielded discrimination c-indices of 0.77 in the trial dataset and 0.78 in the validation dataset, which is comparable to the discrimination of the full prediction model and the reduced model with 7 predictor variables. Table 5 applies the reduced prediction index to 100% of the cohort. The odds ratio of admission with all 4 predictors present is 44.9 (95% CI 32.8, 61.4) which is highly significant. Our c-indices for estimating future performance of the asthma prediction model confirm a solid prediction index.

Discussion

Our study determined risk factors for asthma hospitalization and developed and internally validated an asthma predictive index for hospitalization (APIH). The predictive model is designed for children between 5-18 years of age using risk factors at presentation to the

emergency department. The APIH was created with the goal of improving outcomes, optimizing resource utilization, and supporting clinical decision. The prediction model may improve resource utilization by bypassing the need to observe for several hours after treatments are given. Also, the APIH would be useful in assisting physician decision in difficult or borderline cases. There is substantial variation in the care of asthma exacerbations in the ED, which leads to excessive costs and overutilization of resources.^{4,14} By minimizing differences in management, the APIH could improve overall outcomes.

To our knowledge, this is the first study to comprehensively investigate risk factors in the pediatric population to create an APIH for acute asthma exacerbation. While most asthma severity scores focus solely on clinical findings, we also examined important aspects such as history of pneumonia or atopy, family history of atopy, medication compliance, and socioeconomic status to personalize the predictive model.^{5-10,15} Importantly, the reduced predictive index had a similar predictive accuracy as the full model. The full model requires knowledge of past IAI and SABA dispenses which may be difficult to obtain in all emergency departments while the 4-risk-factor model does not require those elements. Utilization of 4 risk factors creates a more practical model which leads to efficiency without compromising precision.

Another strength of this study is the large patient sample as it includes all pediatric members in Kaiser Permanente Southern California. The patient sample is comparable to the general regional Southern California population, with similar distribution of gender, age, ethnicity, and socioeconomic status. This suggests that our APIH could be generalizable to that of the Southern California population.¹⁶ The diagnosis of asthma was based on ICD9 codes or two dispensing

records for ICS or SABA to capture a wide range of patients including those with intermittent asthma. When we calculated the total number of pediatric patients with asthma according to this criteria, it reached approximately 7% of the total Kaiser pediatric cohort, which is close to the California pediatric asthma prevalence of 9.1-11.5% in 2014.^{17,18} In order to increase specificity for the diagnosis of asthma, we checked the number of patients who met both criteria: ICD 9 codes and ≥ 2 dispensing records of ICS or SABA, but the prevalence was 3.2% which is lower than the prevalence for asthma previously reported. In addition, only 15.7% of pediatric patients who had ≥ 2 dispensing records of ICS or SABA did not have an asthma diagnosis in our total cohort. Therefore, our study used a broader inclusion criteria to encompass pediatric patients with asthma.

Combining clinical findings at ED presentation with key elements of past medical history yields high odds ratio for hospital admission (44.9) in our model. Most studies using asthma severity tools based on clinical findings or vitals report lower odds ratios for admission. In Paniagua's analysis of asthma severity predictors, the highest odds ratio using pulmonary score (respiratory rate, retractions, wheezing) was 6.2.¹⁹ Horeczko's study utilized diastolic hypotension at triage which was a unique predictor but was significantly more pronounced in children 1-6 years old compared to those 6-18 years old.²⁰ A prospective study found that maternal smoking was the only independent predictor (IRR 3.2) for hospitalization but did not include clinical findings.²¹ Another study using PRAM score as a predictor for asthma hospitalization found that 3 hour PRAM scores showed higher odds ratio (2.05) compared to triage PRAM scores (1.82).²² Our study utilizes initial factors at presentation to the ED and there is no minimum observation time.

The strongest predictors in our APIH were O2 desaturation and tachypnea. Hypoxemia is due to bronchospasm causing ventilation perfusion mismatch in severe asthma exacerbation.²³⁻²⁵ Tachypnea occurs to compensate for pulmonary obstruction.²⁶ This emphasizes that vital signs are the most crucial components in assessment of severity. The other 2 risk factors highly associated with admission were history of pneumonia and any ED asthma visits in the prior year. Asthma is a risk factor for pneumonia, but our study also suggests that patients with prior pneumonias tend to have more severe asthma exacerbations requiring hospitalization.^{27, 28} Repeated emergency department visits have been known to be associated with a higher risk of asthma hospitalization.²⁹⁻³¹

Our study demonstrates additional predictor variables significant for asthma admission which include IAI non-adherence, SABA overuse, history of food allergies, and family history of asthma. Multiple studies have shown that adherence to inhaled corticosteroids reduces the rate of hospitalization.³²⁻³⁵ Frequent users of short acting beta agonists are more likely to be admitted to the hospital for asthma exacerbations.^{36,37} Asthmatics who have food allergies are at risk for frequent hospitalizations for asthma and life- threatening asthma.^{38,39} We found family history of asthma to be an independent risk factor for asthma admission, which confirms the results of a prior study.⁴⁰

Variables that did not significantly increase hospitalization risk included prior hospitalization, oral steroid use in the past year, and Medicaid insurance. These were unexpected findings given that past literature has documented previous admissions and systemic steroid use associated with higher hospitalization rates.^{41,42} We had excluded hospitalizations outside of Kaiser Southern

California medical centers because we could not obtain pertinent data, which may have impacted our analysis. It is possible that there is a lower threshold to give systemic steroids in primary care and urgent care clinics, which may have decreased the association of systemic steroids with admission. Oral steroids may be given in advance of need more frequently in recent years because of their inclusion into the management plan for exacerbation in 2007 NAEPP Asthma Guidelines⁴⁵. Children with Medicaid insurance were less likely to need admission compared to those who did not. Published studies show conflicting data regarding lower socioeconomic status as a risk factor for asthma hospitalization.^{26,41,43,44} In our study, pediatric patients with Medicaid insurance have higher rates of ED asthma visits but lower rates of ED hospitalization compared to the non-Medicaid population. This disparity may reflect differing point of service choices, with Medicaid patients more likely to choose ED to access care for less severe asthma exacerbations.

Limitations of this study stem primarily from the retrospective data collection and analysis. Our study excluded emergency visits or hospitalizations outside of Kaiser Permanente Southern California hospitals because of the inability to obtain in depth information on these cases. However only 1.2% (149/12,422) of Kaiser members were evaluated outside of Kaiser hospitals. (Figure 1) In addition, we did not separately evaluate the necessity of hospitalization as hospitalization and ED discharge were based on the ED clinicians' decision. With the retrospective nature of our study, we were unable to analyze exam findings in detail. Although most providers noted wheezing, there was not enough specific documentation on inspiratory or/and expiratory wheezing, prolonged expiratory phase, and retractions. This study also did not include a sub-analysis on hospital readmissions as each ED visit or hospital admission was

considered independent if more than 7 days apart. Our study used ICD 9 coding of asthma and pneumonia which is dependent on physician clinical judgement. Pneumonia may be over-diagnosed and not all children with pneumonia may have received imaging. Our study did not corroborate the patient's history of pneumonia which may incur a bias in this specific risk factor. Nonetheless, the fact that prior coding of a pneumonia diagnosis is a strong predictor of asthma hospitalization and a key component of our predictive model is a novel finding. In addition, we did not look at blood pressure as an independent risk factor. Our data on parental smoking status was sparse, so it was not incorporated into our study.

We have developed and internally validated an APIH for children with asthma exacerbation in the ED. The APIH is simple and straightforward with four variables: hypoxemia, tachypnea, history of pneumonia, and prior ED visits. With a strong predictive power, the APIH can be used as a clinical adjunct for providers in their initial evaluation. This prediction index has the capacity to expedite triage, enhance resource utilization, and improve clinical management. Prospective studies would be recommended to externally validate this hospitalization predictive model before implementation into clinical practice.

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Figure Legend

Figure 1: Diagram of patients included in the study population.

Tables

Table 1: Clinical characteristics of study population: patients discharged from the ED and patients hospitalized for asthma exacerbation

	ED Discharge (n= 11,199)	Hospitalization (n= 867)
Median Age (IQR)	10 [7, 13]	9 [7, 12]
Gender, n (%)		
Male	7191 (64%)	558 (64%)
Ethnicity, n (%)		
White	1504 (13%)	157 (18%)
African American	3031 (27%)	194 (22%)
Hispanic	5711 (51%)	372 (43%)
Asian	666 (6%)	77 (9%)
Other/Unknown	287 (3%)	67 (8%)
Medicaid	4165 (37%)	263 (30%)
Past Medical History		
Pneumonia	1894 (17%)	357 (41%)
Allergic Rhinitis	2997 (27%)	201 (23%)
Food Allergies	499 (5%)	72 (8%)
Eczema	1942 (17%)	192 (22%)
Eosinophilic Esophagitis	8 (1%)	2 (0.2%)
Urticaria	358 (3%)	29 (3%)
Family History		
Asthma	3207 (29%)	369 (43%)
Allergic Rhinitis	598 (5%)	58 (7%)
Eczema	1075 (10%)	107 (12%)
Allergies	887 (8%)	97 (11%)
IAI canisters in prior 12 mo		
< 6 canisters	7813 (70%)	611 (71%)
≥ 6 canisters	3386 (30%)	256 (30%)
SABA canisters in prior 12 mo		
< 6 canisters	10836 (97%)	827 (95%)
≥ 6 canisters	363 (3%)	40 (5%)
PO steroids in prior 12 mo	5429 (49%)	346 (40%)

Table 2: Univariate association of risk factors for asthma admission

	OR	95% CI
Ethnicity		
African American vs. Caucasian	0.61	0.49- 0.76
Latino vs. Caucasian	0.62	0.51- 0.76
Asian vs. Caucasian	1.11	0.83- 1.48
Other/Unknown vs. Caucasian	2.24	1.64- 3.06
O2 Saturation <94 vs. ≥ 94 %	5.03	4.25- 5.96
RR >31 vs. ≤ 31	4.68	3.96- 5.53
Past Medical History		
Pneumonia	3.44	2.98- 3.97
Allergic Rhinitis	0.83	0.70- 0.97
Food Allergies	1.95	1.51- 2.52
Eczema	1.36	1.15- 1.61
Eosinophilic Esophagitis	3.81	0.87- 16.74
Urticaria	1.06	0.73- 1.56
Family History		
Asthma	1.85	1.61- 2.13
Allergic Rhinitis	1.44	1.09- 1.90
Eczema	1.47	1.18- 1.84
Allergies	1.33	1.08- 1.65
Asthma ED visit in prior 12 mo	1.81	1.57- 2.09
Asthma Hospitalization in prior 12 mo	2.70	2.20- 3.31
IAI canisters in prior 12 mo <6 vs. ≥ 6	1.03	0.89- 1.20
SABA canisters in prior 12 mo ≥ 6 vs. <6	1.46	1.05- 2.04
PO Steroids in prior 12 mo	0.71	0.61- 0.81

Table 3: Multivariate association of risk factors for asthma admission

	OR	95% CI
Ethnicity		
African American vs. Caucasian	0.58	0.43- 0.77
Latino vs. Caucasian	0.68	0.53- 0.88
Asian vs. Caucasian	1.06	0.74- 1.51
Other/Unknown vs. Caucasian	2.87	1.87- 4.39
O2 Saturation <94 vs. $\geq$ 94 %	3.36	2.78- 4.06
RR >31 vs. $\leq$ 31	2.95	2.45- 3.56
Past Medical History		
Pneumonia	2.78	2.31-3.33
Allergic Rhinitis	0.82	0.66- 1.01
Food Allergies	1.84	1.33- 2.55
Eczema	1.15	0.93- 1.43
Eosinophilic Esophagitis	0.84	0.15- 4.82
Urticaria	0.76	0.47- 1.23
Family History		
Asthma	1.68	0.92- 3.05
Allergic Rhinitis	0.96	0.64- 1.44
Eczema	0.86	0.62- 1.19
Allergies	1.12	0.83- 1.52
Asthma ED visit in prior 12 mo	1.8	1.48- 2.18
Asthma Hospitalization in prior 12 mo	1.21	0.91- 1.61
IAI canisters in prior 12 mo <6 vs. $\geq$ 6	1.26	1.03- 1.55
SABA canisters in prior 12 mo $\geq$ 6 vs. <6	1.99	1.26- 3.13
PO Steroids in prior 12 mo	0.45	0.37- 0.55

Table 4: Reduced asthma prediction model with internal validation using validation cohort

	Asthma Hospitalization with Odds Ratio (95% CI)	
	Trial Dataset	Validation Dataset
SpO2 <94%	3.6 (2.9- 4.4)	3 (2.1- 4.2)
Respiration Rate >31	2.8 (2.3- 3.6)	3.7 (2.7- 5.1)
Pneumonia History	2.8 (2.2- 3.4)	2.5 (1.8- 3.4)
Asthma ED Visit in 12 mo	1.6 (1.3- 2)	1.8 (1.3- 2.5)

Table 5: Final reduced asthma prediction model using entire cohort population

Predictors	Odds Ratio	95% CI
SpO2 <94%	3.3	2.8- 4.0
Respiration Rate >31	3.1	2.6- 3.7
Pneumonia History	2.7	2.2- 3.2
Asthma ED Visit in 12 mo	1.6	1.4- 2.0
All 4 Risk Factors vs. No Risk Factors	44.9	32.8-61.4

Figure 1

