Children with high risk to develop asthma by the Pediatric Asthma Risk Score have more acute symptoms at presentation for wheezing than those who are low risk.

Kelsi Pomeroy, MS[1]; Ashley N Stoner, MD[2]; John C Kincaid, MD[2]; Claire Putt, BA[1,2]; Kurt C Schwalm, BS[3]; Darrell Dinwiddie, PhD[3]; Joshua L Kennedy, MD[1,2]

[1]Arkansas Children's Research Institute, [2]University of Arkansas for Medical Sciences, Little Rock, AR;
[3]University of New Mexico Heath Science Center, Albuquerque, NM

Arkansas Children's HOSPITALS • RESEARCH • FOUNDATION archildrens.org

UAMS UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES uams.edu

Abstract

Rationale: The Pediatric Asthma Risk Score was recently validated to provide physicians with information regarding their patients' future risk of developing asthma. We wanted to know if infants and toddlers with high risk (HR) for future asthma would present with more acute symptoms during wheezing events than those with low risk (LR). We were also interested in biomarkers that would predict similarly.

Methods: We recruited 210 subjects ages 0-4 years from the Emergency Department. Baseline Pediatric Respiratory Symptoms (PRS) Scores were recorded. Pediatric Asthma Risk Score was obtained for each subject. Nasopharyngeal swabs were used to detect the presence of multiple viruses by viral genome sequencing. Nasal filter paper was used to collect nasal mucosal lining fluid, and after elution, inflammatory mediators were analyzed using bead-array immunoassay.

Results: Those subjects with HR for asthma had higher symptom scores by PRS than those with LR (HR, mean [SD], 7.11 [3.96]; LR, 3.83 [3.17]; p<0.0001). High risk patients with any viral infection at the time of presentation trended towards more symptoms than HR patients without viral infection (HR +virus, 9.182 [3.710]; HR -virus, 5 [1.826]; p=0.06).

Conclusions: Acute symptom scores at the time of wheezing illnesses are worse in those at HR for future asthma. More work is required to determine if symptom scores actually predict future asthma in these subjects.

Introduction

It is estimated that out of the approximately 6.1 million children with asthma, 53.7% have experienced at least one asthma exacerbation.[1] In 2015, there were approximately 1.5 million emergency department visits with asthma as the primary diagnosis.[2] Sixty to eighty percent of children with asthma exacerbations will have an associated viral infection.[3,4,5] Defining future risk for asthma and exacerbations of asthma has been an evolving field over the years, especially as it relates to viral infection.

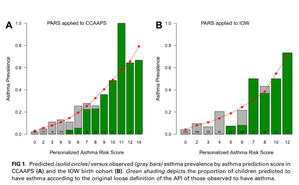


FIG 1. *Predicted (solid circles) versus observed (gray bars)* asthma prevalence by asthma prediction score in CCAAPS **(A)** and the IOW birth cohort **(B)**. *Green shading* depicts the proportion of children predicted to have asthma according to the original loose definition of the API of those observed to have asthma.

Recently, a group designed and validated the Pediatric Asthma Risk Score. The authors evaluated 762 children from a birth cohort, of which 589 developed asthma at the age of 7. They found that there were 6 predictors of development of future asthma:

1) Parental Asthma (2 points)
2) Eczema before age 3 years (2 points)
3) Wheezing apart from colds (3 points)
4) Wheezing before age 3 years (3 points)
5) African-American Race (2 points)
6) Skin prick test positive to >1 aero and/or food allergens (2 points)

These markers accurately predicted asthma at age 7, and the findings were repeated in a different cohort. PARS increased sensitivity of API by 11%.[6]

We wanted to know if infants and toddlers with high risk (HR) for future asthma would present with more acute symptoms during wheezing events than those with low risk (LR). We were also interested in biomarkers that would predict similarly.

Methods

- Children (7 days - 4years) seen in ED with:
  - Wheezing: (n=101) and Not wheezing (n=109)
  - Active respiratory symptoms
  - Samples: Nasopharyngeal swab (Viral determinations) and Filter Paper (inflammatory mediators by Luminex)
- Standardized tool to assess acute symptoms
  - **Pediatric Respiratory Symptoms (PRS) Score[7]**

Variable	0 points	1 points	2 points	3 points
RR				
<2 mo		≤60	61-69	≥70
2-12 mo		≤50	51-59	≥60
1-2 yr		≤40	41-44	≥45
2-3 yr		≤34	35-39	≥40
4-5 yr		≤30	31-35	≥36
6-12 yr		≤26	27-30	≥31
>12 yr		≤23	24-27	≥28
Retractions	None	Subcostal or intercostal	2 of the following: subcostal, intercostal, substernal, OR nasal flaring (infant)	3 of the following: subcostal, intercostal, substernal, suprasternal, supraclavicular OR nasal flaring / head bobbing (infant)
Dyspnea				
0-2 years	Normal feeding, vocalizations and activity	1 of the following: difficulty feeding, decreased vocalization or agitated	2 of the following: difficulty feeding, decreased vocalization or agitated	Stops feeding, no vocalization, drowsy or confused
2-4 years	Normal feeding, vocalizations and play	1 of the following: decreased appetite, increased coughing after play, hyperactivity	2 of the following: decreased appetite, increased coughing after play, hyperactivity	Stops eating or drinking, stops playing, OR drowsy and confused
>4 years	Counts to ≥10 in one breath	Counts to 7-9 in one breath	Counts to 4-6 in one breath	Counts to ≤3 in one breath
Auscultation	Normal breathing, no wheezing present	End-expiratory wheeze only	Expiratory wheeze only (greater than end-expiratory wheeze)	Inspiratory and expiratory wheeze OR diminished breath sounds OR both

- **Pediatric Asthma Risk Score Assessment (PARS)[6]**

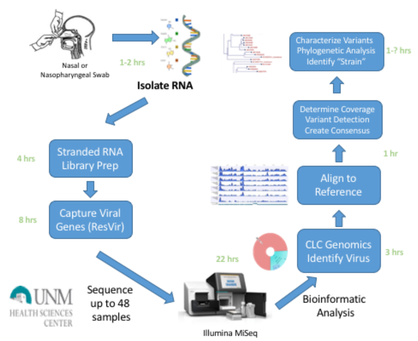
Pediatric Asthma Risk Score (PARS) Scoring Sheet

	Possible Scores		
	No	Yes	Child's Score
1. Parental Asthma	0	2	
2. Eczema before age 3 years	0	2	
3. Wheezing apart from colds	0	3	
4. Wheezing before age 3 years	0	3	
5. African-American Race	0	2	
6. SPT positive to ≥ 2 aero and/or food allergens	0	2	
Child's PARS (add lines 1-6 above):			

Patient Score Interpretation

Score	Risk of Asthma by age 7 years		Interpretation
0	3%	LOW RISK	Children with these scores have a 1 in 33 [score of 0] to a 1 in 9 [score of 4] risk of developing asthma by age 7 years
1	6%		
2	8%		
3	11%		
4	15%	MODERATE RISK	Children with these scores have a 1 in 7 risk [Score of 5] to a 1 in 3 [Score of 8] risk of developing asthma by age 7 years
5	19%		
6	25%		
7	32%		
8	40%	HIGH RISK	Children with these scores have a 2 in 3 [Score of 9] to a 4 in 5 [Score of 14] risk of developing asthma by age 7 years
9	49%		
10	58%		
11	66%		
12	79%		

- Viral Genome Sequencing
  - **34 Respiratory Viruses**



- Luminex of Nasal Filter Papers
  - **42 cytokines**

Results

Table I. Demographics

	Cohort (n=210)	Wheezing (n=101)	Not Wheezing (n=109)	Low Risk (n=134)	Moderate Risk (n=47)	High Risk (n=29)
Sex, % Male	58.1	61.1	54.3	52.9	65.2	71.4
Age, (years, [SD])	1.395 [1.187]	1.413 [1.312]	1.412 [1.008]	1.194 [1.168]	1.700 [1.360]	1.408 [1.125]
Race						
Caucasian (%)	41.9	41.1	41.5	48.5	33.3	25.0
African American (%)	59.5	63.3	55.7	50.0	68.9	89.3
Asian (%)	1.0	1.1	0	0	2.2	0
Ethnicity						
Hispanic (%)	4.8	4.4	4.7	3.676	11.1	0

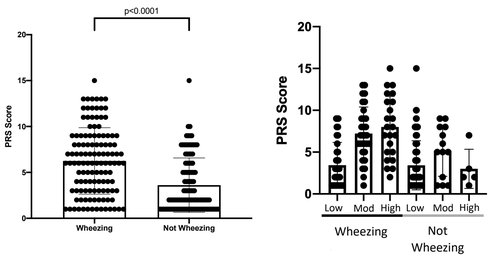


Figure 2: Acute Symptoms at Presentation. A) Acute symptoms were highest in subjects who were wheezing compared to those who were not at presentation (p<0.0001). B) Acute symptoms were highest in those with high risk by PARS and wheeze compared to subjects with low risk of asthma and wheezing at presentation (p<0.05).

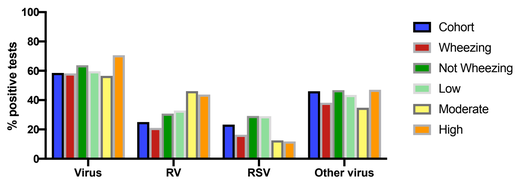


Figure 3: Frequency of Positive Viral Tests Comparing Cohorts. (Other Virus includes: Adenovirus, Human Metapneumovirus, Human Parainfluenza Virus, and Influenza.)

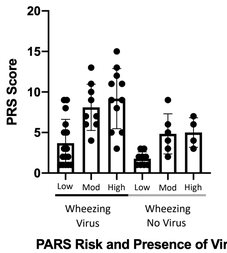


Figure 4: Acute Symptoms at Presentation. Represents acute symptoms at presentation comparing PARS risk in subjects with and without virus in only those who were wheezing at presentation. Wheezing subjects with highest risk to have asthma based on PARS AND a virus had the highest acute symptoms at the time of presentation compared to low risk wheezing with virus (p<0.05).

Results

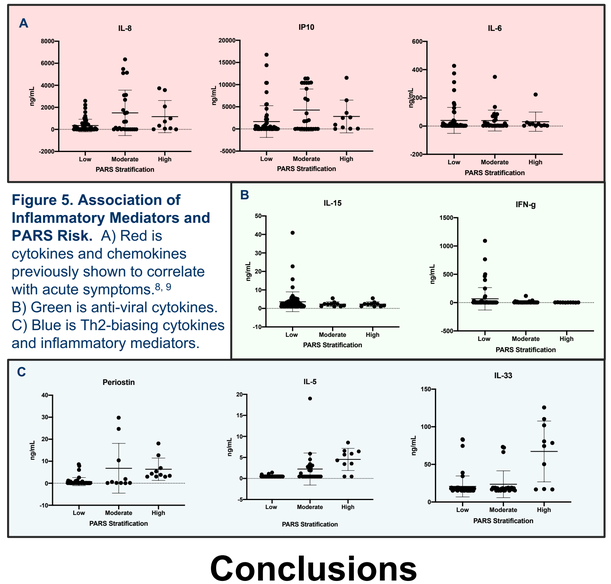


Figure 5. Association of Inflammatory Mediators and PARS Risk. A) Red is cytokines and chemokines previously shown to correlate with acute symptoms.[8, 9] B) Green is anti-viral cytokines. C) Blue is Th2-biasing cytokines and inflammatory mediators.

Conclusions

- **Acute symptoms are worse at presentation for subjects who present with wheezing and high risk for future asthma by PARS.**
- **Frequency of viruses is similar between RV and RSV in a population 0-4 years old with and without wheezing.**
  - RV trends higher in subjects with moderate or high risk for future asthma compared to RSV.
- **Viral infection causes increased acute symptoms in those with high risk for asthma and wheezing at presentation.**
- **Inflammatory mediators may be useful in determining asthma risk.**
  - Antiviral cytokines trend lower in subjects at high risk for future asthma.
  - Th2 biasing cytokines trend higher in those with high risk for future asthma.

References

1. https://www.cdc.gov/asthma/most_recent_data.htm, accessed 1/25/2020
2. National Hospital Ambulatory Medical Care Survey: 2015 Emergency Department Summary Tables. US Dept of Health and Human Services, CDC, National Center for Health Statistics. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2015_ed_web_tables.pdf
3. Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. BMJ. 1995; 310:1225–1229.
4. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. BMJ.1993; 307(6910):982–986.
5. Heymann PW, Carper HT, Murphy DD, Platts-Mills TA, Patrie J, McLaughlin AP, et al. Viral infections in relation to age, atopy, and season of admission among children hospitalized for wheezing. J Allergy Clin Immunol. 2004; 114(2):239–247.
6. Biagini Myers, et al. A Pediatric Asthma Risk Score to better predict asthma development in children. J Allergy Clin Immunol. 2018; 143 (5): 1803-10.
7. Rutman L, Migita R, Spencer S, Kaplan R, Klein EJ. Standardized Asthma Admission Criteria Reduce Length of Stay in a Pediatric Emergency Department. Acad Emerg Med 2016; 23:289-96.
8. Quint, et al. Serum IP-10 as a biomarker of human rhinovirus infection at exacerbation of COPD. Chest. 2010 Apr. 137(4): 812-822.
9. Kelsey, et al. Association of IL-8 and neutrophils with nasal symptom severity during acute respiratory infection. J Med Virol. 2015 Feb; 87 (2): 330-337

Funding: This work was funded by NIH NIAID (1K08AI121345-01A1), NIH NCATS (KL2TR000063, UL1TR000039), NIH NIGMS (P20GM121293), Arkansas Biosciences Institute, Marion B Lyon New Scienstist Development Award, and UAMS Clinician Scientist Program.