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ORIGINAL ARTICLE



The role of human rhinovirus (HRV) species on asthma exacerbation severity in children and adolescents

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ABSTRACT

Objective: It is recognized that human rhinovirus (HRV) infection is an important factor in asthma exacerbations requiring hospitalization in children. However, previous studies have disagreed on the differential impact of various HRV species. We sought to assess the impact of HRV species on the severity of asthma exacerbations in children and adolescents. We also examined whether the effect of HRV species on severity was modified by age and gender. **Methods:** Virus strain was determined for 113 children with HRV detectable at the time of admission for asthma exacerbation. Patient characteristics were collected on admission and exacerbation severity was scored using several validated scales. **Results:** HRV species by itself was not associated with moderate/severe vs. mild exacerbations. Boys with HRV-C infections were more likely (OR: 3.7, 95% CI: 1.2–13.4) to have a moderate/severe exacerbation than girls with HRV-C ($p = 0.04$ for interaction term). Higher odds were observed in younger boys (3 years old: OR: 9.1, 95% CI: 1.8–47.1 vs 5 years old: OR: 3.3, 95% CI: 0.9–11.8 vs 7 years old: OR: 1.2, 95% CI: 0.2–6.6). In contrast, children with HRV-C infection and sensitized to pollen during the pollen season were less likely to have moderate/severe exacerbations ($p = 0.01$ for the interaction term). **Conclusion:** Acute asthma exacerbations are more likely to be moderate/severe in boys under 5 years of age who had HRV-C infection on admission. The opposite was found in children with sensitization to pollen during pollen season.

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Introduction

Asthma is a multifactorial disease of which the aetiology is not fully understood. It is a highly heterogeneous syndrome, rather than a single disease, and is characterized by airway hyper-responsiveness, airway inflammation and variable airflow obstruction [1]. There is no consensus on the definition of asthma phenotypes – which can be based on symptom pattern (e.g. persistent/intermittent, late-onset); trigger factors (e.g. viral, exercise induced, Aspirin sensitivity); sensitization (e.g. atopic/non-atopic); inflammation (e.g. Eosinophilic/Neutrophilic/Mixed/Pauci-granulocytic) or treatment response (e.g. steroid-sensitive/resistant) [2]. The diversity of asthma definitions is caused by the multifactorial pathogenesis of asthma, varying symptoms, dissimilar individual responses to treatment and symptom overlap with other respiratory diseases [2,3].

Globally asthma is one of the most frequent reasons for hospital admissions in children. The economic cost of childhood asthma admissions is substantial [3] and seasonal increases in admissions place a considerable extra burden on hospital services. Asthmatics are at an increased risk of anaphylaxis due to food or drug allergies [4,5] and severe uncontrolled asthma has been found to be a risk factor of fatal or near-fatal anaphylaxis [6]. Furthermore, uncontrolled asthma in childhood is a risk factor for Chronic Obstructive Pulmonary Disease [7].

Acute asthma exacerbations that require hospitalization are triggered by a number of factors. The majority of childhood asthma admissions are triggered by human rhinovirus (HRV) infection [8] with HRV-C being strongly associated with acute asthma exacerbations [9,10]. HRV-C has also been associated with increased risk of re-admission [11]. However, few studies have examined

whether the specific HRV species influences the severity of an asthma exacerbation in children [12,13].

At presentation, it is clinically important to distinguish mild asthma attacks from those at a moderate or severe level [14,15]. Moderate and severe cases may require additional intervention, such as oxygen-driven nebulization or increased dosage of systematic steroids [14]. Better understanding of severity of exacerbations at admission may allow early initiation of appropriate treatment.

In this study we sought to assess the impact of HRV-C on severity of acute asthma exacerbations in children and adolescent asthmatics. We also evaluated whether the effect of HRV species on severity was modified by age, gender or sensitization.

Methods

Study design and population

This is a sub-study of the Melbourne Air Pollen Children and Adolescent Health (MAPCAH) study, which was a hospital-based case-crossover study of hospital admissions for asthma in children and adolescents [16]. The parent study comprised 644 children and adolescents who were admitted to a large tertiary hospital in Melbourne, Australia, between September 2009 and December 2011 aged between 2 and 17 years with a principal diagnosis code of asthma (ICD10 J45) at admission. A small random sample of participants with HRV at admission were selected for inclusion into this study. The study was approved by the Royal Children's Hospital Ethics Committee and La Trobe University Human Ethics committee and all parents/guardians provided written informed consent.

Data collection methods

Methods of the MAPCAH study have been described in detail earlier [16]. Briefly, during their hospital stay all participants underwent a skin prick test (SPT), and nasal and throat swabs (NTSs) were also obtained to test for respiratory viral infections. A detailed questionnaire was administered to obtain data on lifestyle factors, management of asthma and family history. Out of the 644 MAPCAH participants, HRV was detected in 447 (70%) and the species of HRV was subsequently successfully classified in 114 (26%) of these participants.

We were able to access clinical records of the treatment at admission for 113 of 114 participants with HRV classification, who thus comprised the participants in this sub-study. We were unable to access clinical records for one participant because the record was in use, despite multiple attempts at record retrieval, so this participant

had to be excluded from the sub-study. Presence of wheeze, temperature, pulse and respiratory rate, oxygen saturation, whether there was a repeat admission and all necessary factors to determine severity were extracted from these records.

Definition of the outcome variable: asthma severity

We used the Preschool Respiratory Assessment Measure (PRAM) [18], the Pulmonary Score (PS) [19] and the respiratory rate—accessory muscle use—decreased breath sounds severity score (RAD) [20] severity scores as both construct and criterion validity of these scores have been established [21,22].

The PRAM severity score assessed suprasternal retraction, scalene muscle contraction, air entry, wheezing and O₂ saturation to produce a score out of 12; with 0 indicating no clinically meaningful symptoms and 12 indicating severe airway obstruction [18]. It was split into categories of: <5 mild airway obstruction; 5–8 moderate airway obstruction and ≥9 severe airway obstruction [18]. The PS was a continuous scale from 0 (very mild exacerbation) to 9 (very severe exacerbation) assessed on three criteria: respiratory rate, wheezing and sternomastoid muscle use [19]. The RAD dichotomously assessed three factors: respiratory rate, accessory muscle use and decrease in breath sounds – to produce a summary score from 0 to 3, with three being a severe acute asthma attack [20].

Respiratory viral infection data

Viral respiratory illnesses at admission were assessed by detection of respiratory viruses in NTSs using a sensitive nested multiplex polymerase chain reaction (PCR), amplifying specific and conserved sequences of picornaviruses (including rhinoviruses) using primers as described by Druce and colleagues [23]. Briefly, all samples were spiked with an internal control (bovine viral diarrhoeal virus) and total viral nucleic acids extracted from nasopharyngeal aspirates using a total nucleic acid isolation kit. Reverse transcription was performed using methods previously described [23]. HRV was detected qualitatively using conventional primers targeting the 5'UTR and subsequently classified by sequencing products using primers targeting the VP4 gene [24]. HRV species were identified as either HRV-A/B or HRV-C following alignment of sequences and phylogenetic analysis using MEGA version 5.0 [25].

Other variables

Age in years, sex and allergies were obtained from the clinical records. Parental history of asthma/allergies and diagnosis of hay fever were recorded in an

interviewer-administered questionnaire completed by study participants. Parental history of asthma/allergies was dichotomously recorded according to the answers given to the questions “Has the child’s mother ever had any of the following? [Asthma | Hay fever | Eczema | Food allergy]” and “Has the child’s father ever had any of the following? [Asthma | Hay fever | Eczema | Food allergy].” Hay fever was identified dichotomously according to the question “Has your child ever been diagnosed with hayfever by a doctor?”

Sensitization was determined by SPTs to a panel of pollens (rye grass, seven grass mix, birch pollen, English plantain and 10 tree mix), fungal allergens (*Alternaria* and *Cladosporium*), common food allergens (egg white and peanut), house dust mite and cat allergen together with positive histamine and negative saline controls (Hollister-Stier, Spokane, WA, USA; Alyostal, Antony, France). Sensitization was defined as a SPT wheal size of 3 mm or greater to one or more allergens in the presence of a positive histamine and negative saline skin test wheal.

Statistical methods

Mann-Whitney U tests and Welch t-tests were used to test the difference in central measures between those with HRV-C and those with HRV-A/B for the different severity scores. The effect of HRV species on the severity of asthma attacks was then modelled in several ways. The severity indices were ordered categorical variables: 0–12 for the PRAM index, 0–9 for the PS index and 0–3 for the RAD index. Given the clinically important split between mild asthma exacerbations and those of a moderate or severe level [14], we dichotomized the severity indices resulting in an outcome of either mild or moderate/severe exacerbation [18–20] which was then modelled using logistic regression with a logit transformation. We also considered ordinal regression models without categorizing the severity scales. However, the ordinal models offered no additional insight into the findings from the logistic regression analyses and were therefore omitted for brevity. Models were adjusted for age, sex, hay fever, parental history of asthma and sensitization to any (at least one) of the tested allergens if they changed the estimated effect sizes for the HRV species and outcome by 10% and/or were significant at the 5% level. Interaction terms were considered for sex, age and sensitization at admission with a p value of 0.1 level of significance.

All results in tables are presented as odds ratios and 95% confidence intervals (CIs). All statistical tests were two sided with a p value of 0.05 considered statistically significant. All of the statistical analyses were performed using R software version 3.2.5 [26].

Results

Of 113 children in this study 80 (71%) were male, with mean age 5.08 years (SD 3.18). More than half of the children were infected with HRV-C on admission (Table 1). SPTs found that most children were sensitized to house dust mites (HDMs) or pollen and 29 (26%) were sensitized to a food allergen (egg or peanut). The majority of children ($n = 57$) had one or more parents with a history of asthma. There were no significant differences in age or sex between children with HRV-C and those with HRV-A/B. The characteristics of the participants included in this study were similar to participants with HRV who were not included in this study. (Table E1 in supplementary documents).

The estimated effect of the HRV species and its association with the PRAM, PS and RAD scores are shown in Table 2. The regression analyses for all scores showed no statistically significant findings when comparing children with HRV-C to those with HRV-A/B.

Interaction analysis

We conducted an interaction analysis of age and sex and HRV species, as well as an interaction analysis of sensitization to the tested allergens and HRV species. A boy with HRV-C was significantly more likely (OR: 3.73 95% CI: 1.18–13.43) to have a moderate/severe asthma attack than a girl with HRV-C in a stratified analysis ($p = 0.04$ for the interaction term) (Table 3). This difference can be seen to greatest effect in the younger age groups but not in the HRV-A/B group. There was no evidence of an interactive effect with sensitization to HDM, food or cat allergens. However, when restricted to patients admitted during the pollen season in Melbourne (September to February, $n = 77$) in those who were sensitized to pollen, HRV-C was no longer the dominant species associated with asthma severity ($p = 0.01$ for the interaction term).

Discussion

HRV-C has been reported to be associated with more severe asthma, but to date there is limited data. Our study suggests that HRV-C may not be an independent risk factor for severe exacerbations among asthmatics. However there was an interaction observed between age and gender on asthma severity if HRV-C infection was detected. The odds of having a moderate/severe asthma exacerbation were significantly higher in boys under 5 years of age with HRV-C infection. These findings are of interest, providing important insights into gender and age differences among children with HRV-C and occurrence of moderate/severe at admission. However, the findings should be

Table 1. Characteristics of 113 patients with asthma exacerbation included in studies.

Variable	N = 113 n (%)	HRV-C n (%)	HRV-A/B n (%)	p-value
HRV		63 (53%)	50 (47%)	
Sex				0.71
Male	80 (71%)	46 (73%)	34 (68%)	
Female	33 (29%)	17 (27%)	16 (32%)	
Age (years) mean SD	5.1 ± 3.2	4.6 ± 2.8	5.6 ± 3.6	0.11
Age (years—categories)				0.21
2–5	75 (66%)	45 (71%)	30 (60%)	
6–12	33 (29%)	17 (27%)	16 (32%)	
13–17	5 (4%)	1 (2%)	4 (8%)	
Sensitisation at recruitment				
HDM ^a	66 (58%)	37 (59%)	29 (58%)	0.99
Pollens	56 (50%)	32 (51%)	24 (48%)	0.85
Food	29 (26%)	18 (29%)	11 (22%)	0.53
Fungi ^b	23 (23%)	14 (25%)	9 (20%)	0.75
Hay fever	58 (51%)	31 (49%)	27 (54%)	0.75
Family history of asthma and allergies ^c				
Asthma	58 (53%)	33 (53%)	25 (52%)	0.99
Hay fever	72 (65%)	36 (58%)	36 (75%)	0.10
Eczema	44 (40%)	25 (40%)	19 (40%)	0.99
Food allergy	16 (15%)	7 (11%)	9 (19%)	0.41
Clinical characteristics at presentation				
Respiratory Rate (per minute) mean SD	40 ± 11	42 ± 12	37 ± 10	0.02
Heart Rate (per minute) mean SD	138 ± 21	140 ± 22	135 ± 20	0.26
O ₂ Saturation ^d (%) mean SD	93 ± 3.9	93 ± 3.5	93 ± 4.4	0.25
Biphasic Wheeze	64 (56%)	41 (68%)	23 (43%)	0.06
Length of stay (days) mean SD	1.3 ± 0.8	1.3 ± 0.8	1.3 ± 0.8	0.86
Moderate/severe asthma exacerbation				
PRAM ^a	68 (60%)	36 (57%)	32 (64%)	0.59
PS ^a	54 (48%)	33 (52%)	21 (42%)	0.36
RAD ^a	75 (66%)	43 (68%)	32 (64%)	0.78

Note.

^aHDM: house dust mites; PRAM: preschool respiratory assessment measure; PS: pulmonary score; RAD: respiratory rate—accessory muscle use—decreased breath sounds severity score.

^bIncomplete data; n = 101.

^cFamily history was not available for all study participants due to issues such as adoption and uncertainty of childhood diagnosis; n = 110 complete records were obtained.

^dPulse oximeter reading in room air.

interpreted with caution since low patient numbers and lack of power may have precluded detection of differences in girls with HRV-C. Finally, our data suggest that children admitted during the pollen season and sensitized to pollen and who had HRV-C infection were less likely to have moderate/severe asthma exacerbations.

Few studies have examined the role of HRV species and assessment of asthma within a hospital setting. Our findings are broadly consistent with a study by Iwane and colleagues [13] who reported no significant difference in clinical characteristics (including indicators of severity) between hospitalized children with HRV-C and those with HRV-A. However, our study has extended their findings as they did not utilize an asthma severity score, but simply reported on a number of clinical indicators of severity – intensive care unit (ICU) admission, mechanical ventilation and length of hospital stay. Additionally, they did not report adjustments by age or gender, precluding further comparisons.

In contrast, a study by Bizzintino et al [12] reported stronger associations between HRV-C and high asthma severity scores as compared to HRV-A/B in age and

gender-adjusted regression models. The differences in our findings could be due to a number of factors. There were differences in scoring methods since they used a modification of the 1991 US National Institute of Health asthma guidelines, whilst we utilized several severity scores that have been validated [16–20]. It is also possible that the participants enrolled in the current study were, on average less severe, and age and gender-specific strata effects of HRV-C and asthma severity were not examined.

Our investigation is the first to look at the potential interaction between the species of HRV and sensitization as a risk factor of severity of acute asthma exacerbations. Although we found no interaction between HDM, food or cat allergens and asthma severity we did find that sensitization to pollen during the pollen season interacted with HRV genotypes to become a significant risk factor of moderate/severe asthma exacerbations. As noted this finding should be interpreted with caution given the reduction in sample size and increase in HRV-C proportion (60% HRV-C positive) during the pollen season.

An interaction between viral respiratory infections and allergic sensitization has been demonstrated to increase

Table 2. Logistic regression models for asthma severity scores.

	PRAM OR (95% CI)	PS OR (95% CI)	RAD OR (95% CI)
HRV – C	0.75 (0.35, 1.60)	1.52 (0.72, 3.24)	1.21 (0.55, 2.66)
HRV – C Age (years)	0.60 (0.26, 1.35) 0.83 (0.72, 0.94)**	1.36 (0.63, 2.95) 0.88 (0.76, 0.99)*	1.07 (0.47, 2.39) 0.88 (0.78, 0.99)*
HRV – C Sex (M)	0.75 (0.35, 1.61) 0.99 (0.43, 2.27)	1.49 (0.70, 3.19) 1.59 (0.70, 3.70)	1.22 (0.56, 2.69) 0.79 (0.32, 1.88)
HRV – C Age (years) Sex (M)	0.61 (0.26, 1.35) 0.83 (0.72, 0.94)** 0.92 (0.38, 2.18)	1.35 (0.62, 2.93) 0.88 (0.76, 0.99)* 1.55 (0.67, 3.66)	1.08 (0.47, 2.46) 0.88 (0.77, 0.99)* 0.76 (0.30, 1.81)
HRV – C Hay fever	0.75 (0.35, 1.60) 1.00 (0.47, 2.14)	1.49 (0.70, 3.19) 0.60 (0.28, 1.26)	1.19 (0.54, 2.62) 0.68 (0.30, 1.48)
HRV – C Family history of asthma	0.80 (0.35, 1.77) 0.65 (0.29, 1.42)	1.69 (0.77, 3.77) 0.54 (0.24, 1.17)	1.47 (0.64, 3.36) 0.61 (0.26, 1.38)
HRV – C Sensitisation (any)	0.73 (0.34, 1.56) 0.82 (0.30, 2.12)	1.57 (0.75, 3.36) 0.91 (0.35, 2.35)	1.19 (0.54, 2.61) 0.68 (0.22, 1.83)
HRV – C Age (years) Sex (M) Hay fever Family history of asthma Sensitisation (any)	0.61 (0.26, 1.40) 0.80 (0.68, 0.92)** 0.82 (0.32, 2.04) 1.11 (0.47, 2.65) 0.64 (0.27, 1.50) 1.09 (0.34, 3.34)	1.49 (0.67, 3.33) 0.87 (0.75, 1.00) 1.64 (0.68, 4.05) 0.66 (0.29, 1.53) 0.74 (0.33, 1.65) 1.121 (0.38, 3.29)	1.30 (0.55, 3.03) 0.88 (0.76, 1.01) 0.69 (0.26, 1.76) 0.85 (0.35, 2.05) 0.57 (0.23, 1.34) 0.73 (0.20, 2.38)

Note.

**p*-value < 0.05.

***p*-value < 0.01.

Table 3. Estimates for the odds ratios (and 95% confidence intervals) for the difference between boys and girls from the logistic regression of the PS score at different age cut points.

	HRV – C ^a		HRV – A/B ^b		<i>p</i> -value of interaction term
	Estimate	95% CI	Estimate	95% CI	
All age groups and boys	3.73	(1.18, 13.43)*	0.62	(0.183, 2.067)	0.04
Age (years) and being boy					0.02
2	15.19	(1.98, 116.27)**	0.15	(0.02, 1.31)	0.04
3	9.09	(1.76, 47.06)**	0.20	(0.03, 1.31)	0.04
4	5.44	(1.39, 21.38)*	0.28	(0.06, 1.41)	0.04
5	3.26	(0.90, 11.76)	0.39	(0.09, 1.69)	0.07
6	1.95	(0.47, 8.11)	0.55	(0.13, 2.32)	0.52
7	1.16	(0.21, 6.64)	0.76	(0.16, 3.68)	0.53
8	0.70	(0.08, 5.99)	1.06	(0.17, 6.52)	0.25
9	0.42	(0.03, 5.71)	1.47	(0.17, 12.44)	0.16
10	0.25	(0.01, 5.59)	2.05	(0.17, 24.88)	0.13
11	0.15	(0.01, 5.56)	2.86	(0.16, 51.22)	0.11
12	0.09	(0.00, 5.60)	3.98	(0.15, 107.40)	0.10

Note.

^aThe interactive effect of age and sex on children with HRV C; *n* = 60.

^bThe interactive effect of age and sex on children with HRV A/B; *n* = 53.

**p*-value < 0.05 for the stratified analysis.

***p*-value < 0.01 for the stratified analysis.

both the likelihood of asthma exacerbations and the severity of the symptoms [27,28]. A case-control investigation [27] of 287 children aged 7–12 years found the presence of both a HRV viral infection and sensitization (particularly children with high titers of IgE antibodies to dust mite allergen) to be a significant risk factor for acute asthma exacerbations but pollen sensitization was not reported. While HRV strains were classified, the researchers did not factor this into their analysis. To date

comparable studies in the context of pollen sensitization and identification of HRV species have not been conducted.

Strengths and limitations

A major strength of this study is the use of multiple validated scoring systems to determine severity of exacerbation from clinical data since this strategy may reduce

potential bias in the definition of severity. Sensitization data on each participant were also available, allowing a comprehensive investigation of factors that may be associated with HRV species and asthma severity. A potential limitation is the small sample size used to construct estimates and this is reflected in the width of the confidence intervals. A larger sample would clearly be needed to determine more precise overall estimates of the increase in odds of having a moderate/severe asthma exacerbation associated with particular HRV species. Although this potential limitation should be considered when interpreting the results, the number of factors identified as relevant to include in the modelling was low thereby reducing the likelihood of spurious associations.

Conclusion

In summary, we have found that boys under 5 years of age with acute asthma linked to HRV-C infection have significantly increased odds of having a moderate/severe exacerbation. Moreover, children with HVR-C infection who exacerbate during the pollen season appear to have milder exacerbations. This research contributes to the growing body of evidence that HRV-C maybe associated with more severe asthma admissions, that age and gender may be important and that pollen sensitization may modulate asthmatic responses. Larger studies examining the role of HRV species are necessary to confirm these findings. Overall, a better understanding of the virological and clinical variables that impact asthmatics at time of exacerbation will help to improve management of this important condition.

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