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ASTHMA AND PROTRACTED BRONCHITIS: WHO FARES BETTER  
DURING AN ACUTE RESPIRATORY INFECTION?

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Original Article

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## *Abstract*

Acute respiratory illnesses (ARI) are common in children and symptoms range from days to weeks.

*Aim:* The aim of the study was to determine if children with asthma have more severe ARI episodes compared to children with protracted bronchitis and controls.

*Methods:* Parents prospectively scored their child's next acute respiratory illness using the CARIFS and validated cough diary (on days 1 to 7, 10 & 14 of illness). Children were age and season matched.

*Results:* On day 10 and 14 of illness children with protracted bronchitis had significantly higher median CARIFS when compared with children with asthma and healthy controls. On day-14, the median CARIFS were: asthma = 4.1 (IQR 4.0), protracted bronchitis = 19.6 (IQR 25.8) and controls = 4.1 (IQR 5.25). The median cough score was significantly different between groups on day 1, 7, 10 and 14 ( $p < 0.001$ ). A significantly higher proportion of children with protracted bronchitis (63%) were still coughing at day 14 in comparison to children with asthma (24%) and healthy controls (26%).

*Conclusion:* Children with protracted bronchitis had the most severe ARI symptoms and higher percentage of respiratory morbidity at day 14 in comparison to children with asthma and healthy controls.

## ***Introduction***

Acute respiratory infections (ARI) are common in children, varying from 4 episodes per year in the first 2 years of life to 2-3 episodes per year when aged 2 to 5 years.(1) The morbidity of acute respiratory infections (ARI) in children include cough and non-specific symptoms such as irritability.(2) Among individuals, these symptoms vary in severity and length of illness.(1) Cough related to ARI generally resolves between 1 to 3 weeks in most children.(3, 4) Although health practitioners often view ARIs as a benign self-limiting illness, parental concerns regarding the length and severity of their children's symptoms and illness often lead to presentation to their family doctor.(1, 5) Furthermore to ameliorate the symptoms of ARIs, "over-the-counter" cold and cough medications are often used.(6) Indeed "over-the-counter" cough and cold medications costs the community billions of dollars each year despite the lack of evidence on their efficacy.(7)

In children with asthma, ARIs often lead to acute exacerbations of asthma.(8) Acute asthma exacerbations in children are a common presentation to emergency departments and are a substantial economic burden on healthcare system.(9) Additionally, it places a burden on the children, their parents and families and is associated with a decrease in their quality of life.(10, 11) Yet, there are no studies (PubMed search - May 2007) that have examined the severity or length of ARI symptoms in children with acute asthma.

Children with some conditions such as tracheomalacia and protracted bronchitis have prolonged coughing(12) illnesses. Cough is the most common symptom presenting to

doctors in USA(13) and Australia, and one of the most common symptom of an acute respiratory infection. Protracted bronchitis is a recently described entity(14) that has probably been recognized but not well described until recently.(15) It is clinically defined as (a) the presence of isolated chronic moist cough, (b) resolution of cough with appropriate antibiotics, (c) absence of pointers suggestive of alternative specific cough (12) and (d) positive bronchoalveolar lavage culture (growth of  $>10^4$  colony forming units/ml). (14) One likely contributing factor to PB is innate immunity dysfunction.(16) Whether children with PB have more severe ARI symptoms are however unknown.

Measurement of the severity of ARI symptoms are however limited as there are few validated instruments. One validated instrument is the Canadian Acute Respiratory Illness Scale (CARIFS)(17) which has been utilized in several settings.(18) Another validated instrument is that for the symptom of cough (19), a common symptom of ARIs.

The aim of our study was to determine if children with asthma or protracted bronchitis have more severe ARI symptoms at presentation and at days 7, 10 and 14 using validated scales (CARIFS and cough score)(17, 19) compared to controls. We also examined (using a validated cough score(19)) if children with asthma or protracted bronchitis were more likely to have a persistent cough on day 14 than controls. We hypothesised that children with asthma have more severe and/or prolonged ARI symptoms than the other two groups.

## ***Methods & Materials***

### *Subjects*

Three groups of children were recruited: children with asthma (n=72), children with protracted bronchitis (n=19) and healthy controls (n=23). The two first groups were primarily from other studies. Children with asthma were recruited from an emergency department during an acute exacerbation of the child's asthma. Asthma was defined as recurrent (>2) episodes of wheeze and/or dyspnoea with a clinical response (decreased respiratory rate and work of breathing) to beta<sub>2</sub> agonist. An asthma exacerbation was defined as acute deterioration of asthma control requiring treatment with more than a single dose (>600ug via metered dose inhaler and spacer or >2.5mg nebulised) of salbutamol in an hour. The children with asthma were prescribed either 3 or 5 days of oral prednisone and no difference was found between the groups, as also described by others.(20) Parents of children with protracted bronchitis (as defined above) were from another study.(14) The children from this study underwent sweat tests and other pathological investigations to exclude presence of other respiratory illnesses such as cystic fibrosis.(14) The parents were approached during an outpatients visit. The parents were asked to document their next ARI episode. Each child with protracted bronchitis had undergone a bronchoscopy to determine if any airway lesion was present. Children were excluded if tracheomalacia or bronchomalacia was present.(21) Controls were recruited from a convenient sample of family and friends; they had no history of smoking, or presence of asthma. The parents were asked to document the next ARI episode once the child had 24 hours of runny nose, cough, sore throat and/or fever. Exclusion criteria were children with neuro-developmental dysfunction, cardiorespiratory illnesses (eg cystic fibrosis or tracheomalacia) or children with any

type of immunodeficiency. Written informed consent was obtained and the studies were approved by our institution's ethics committee.

### *Protocol*

All parents completed two types of daily diary cards (CARIFS(17) and cough(19)) for the first 7 days and on days 10 and 14 of illness at enrolment (for asthma group) or during the next episode when their child was unwell with an ARI (for the protracted bronchitis group and controls). The parents of children with protracted bronchitis and controls were asked to start filling out the diary cards after their child had been sick for at least 24 hours with symptoms of cough, runny nose, sore throat and/or fever. The protracted bronchitis group and controls were age and season matched for the asthma group (Winter period = April to September; Summer period= October to March). Reminders were sent to the later two groups on a monthly basis.

### *Canadian Acute Respiratory Illness and Flu Scale (CARIFS)*

CARIFS (Table 1) was “developed as a parentally assessed disease severity measure appropriate for acute respiratory infection, including influenza, in children”.(18) The scale consists of 18 items that included measurements of symptoms (eg. cough), function (eg. play) and parental impact (eg. clinginess).(17) Each item has a 4-point ordinal score; “Major Problem”=3, “Moderate Problem”=2, “Minor Problem”=1 and “No Problem”=0. In addition, items could also be scored as “Don’t know or Not Applicable”. Each set of parents completed diary cards for the morning (AM) and evening (PM). The final daily accumulated score is derived from addition of all the

scores, divided by the total number of questions answered multiplied by 36 (the total number of questions that could have been answered for both AM and PM).



### *Cough Diary*

The validated cough diary utilised was one that included a measure of impact.<sup>(19)</sup> The child's cough was scored as follows: 0 = no cough; 1 = cough for one or two short periods only; 2 = cough for more than two short periods; 3 = frequent coughing but does not interfere with school or other activities; 4 = frequent coughing which interferes with school or other activities; and 5 = cannot perform most usual activities due to severe coughing.

### Statistical analysis

The children were categorized into 3 groups: asthma, protracted bronchitis or healthy controls. Non-parametric analysis was used as the data were not normally distributed. Kruskal Wallis or Mann Whitney test was used for three and two group comparisons respectively. Chi square was used to compare categorical variables. Spearman correlation coefficient was used to measure the relationship between variances. SPSS version 13 was used for all statistical calculations. A 2-tailed p value of  $\leq 0.05$  was considered significant.

## Results

The demographics (age, gender, season of ARI) of the children enrolled were matched (Table-2). The median age (IQR) of the combined group was 3.8 (3.8), with 64 boys and 50 girls. The median age (IQR) of the 3 groups of children were; asthma = 3.8 years (3.8), protracted bronchitis = 3.3 (3.9) and controls = 3.9 (3.4),  $p = 0.49$ . Of the 72 children with asthma, 39 were male and 33 were female. In the group of 19 children with protracted bronchitis, 12 were male and 7 were female. The healthy control group had 14 males and 9 females. There was no significant difference in gender among the groups ( $p = 0.87$ ). There was also no significant difference between the seasons when dividing the year into 2 seasons; Winter period (April to September) and Summer period (October to March). Sixty-five of the illnesses began in the season April – September and 49 between October and March. In the winter period, 43 ARIs were from children with asthma, 11 from protracted bronchitis group and 10 from healthy controls. In the summer season, the numbers were 29, 8 and 13 ARIs respectively. There was no significant difference among the 3 groups ( $p = 0.391$ ) in relation to the seasons.

On day-1 of the ARI there was no difference between the median accumulated CARIFS score,  $p = 0.168$ . The median CARIFS score were: group with asthma = 34 (IQR 34.8), group with protracted bronchitis = 36 (IQR 36.6) and controls = 24.4 (28.0) (figure 1). However, children with protracted bronchitis had a significantly higher median CARIFS score than children with asthma and controls on days 10 and 14 of illness,  $p < 0.001$  and  $p < 0.001$  respectively. On day-14, the median CARIFS score were: asthma = 4.1 (IQR 4.0), protracted bronchitis = 19.6 (IQR 25.8) and controls = 4.1 (IQR 5.25) (figure 1).

### *Cough scores*

On day 1 median cough scores were significantly different between groups ( $p < 0.001$ ); median (IQR) in the group with asthma was 3.0 (1.45), protracted bronchitis = 3.0 (2.0), and healthy control = 1.0 (1.0). The median scores were also significantly different between groups on days 7, 10 and 14. By day 14 the median cough scores (IQR) were: asthma group = 0 (1.0), protracted bronchitis group = 2.0 (2.0), and healthy control group = 1.0 (1.25). (figure 2)

When those with asthma were compared to those with PB, the groups were similar on day 1 ( $p = 0.83$ ) but the asthma group had a significantly lower score on days 7, 10 and 14 of ARI ( $p$  for all  $< 0.001$ ). Similarly, healthy controls did not significantly differ from children with PB on day 1 ( $p = 0.08$ ) but differed significantly on day 7, 10 and 14  $p = 0.03$ ,  $p = 0.02$  and  $p = 0.02$  respectively. The scores in children with asthma and the healthy controls were more similar on day-7 ( $p = 0.56$ ), day-10 ( $p = 0.21$ ) and day-14 ( $p = 0.5$ ) but significantly differed on Day-1 ( $p < 0.001$ ) (Table 3).

When evaluated by proportions, there was a significant difference between the groups with children with PB had the highest proportion still coughing on days 7, 10 and 14 (Table 4). The proportion of children with asthma who were coughing were significantly higher than controls on day 1 ( $p < 0.001$ ) but similar to controls on days 7, 10 and 14 ( $p = 0.56$ ,  $0.21$  and  $0.05$  respectively). Cough scores significantly related to CARIFS scores on all days (day-1,  $r_s = 0.574$ ,  $p < 0.001$ ; day-7,  $r_s = 0.477$ ,  $p < 0.001$ ; day-10,  $r_s = 0.639$ ,  $p < 0.001$ ; and day-14,  $r_s = 0.499$ ,  $p < 0.001$ ).

## Discussion

This is the first study to compare the severity of acute respiratory illnesses as measured by CARIFS and cough scores in children with asthma, protracted bronchitis and healthy children. We have demonstrated that children with asthma had more severe scores than controls in the early phase of the asthma exacerbation but not in the later phase (D10 onwards). In contrast, children with protracted bronchitis had the most severe scores and 63% were still coughing by day 14.

Despite the commonality of ARIs, there is relatively little data on the impact and effect of ARIs in children. In the validation phase of CARIFS, Jacob et al(17) reported that by day-14, 80% of their study subjects had a CARIFS score of less than 3. Butler et al(22) stated that <7% of their 240 subjects were still unwell at day-14 as scored using CARIFS. Both these studies were of children who were presenting to their general practitioner with ARI, ie they were children from the community and thus likely to be otherwise well children. Our data on healthy controls were similar with their data as we found that the controls had day-14 CARIFS scores of 4.1. However we could not find any study on (Pubmed search 29 May 2007) using CARIFS on children with asthma. Thus this study is unique as we examined if children with asthma have more severe ARI episodes at presentation and at days 7, 10 and 14 using validated scales (CARIFS and cough score). Authors have described that children with asthma are likely to have more ARIs(9) and thus it is biologically possible that children with asthma also have more severe ARIs. However we found that on subjective scoring using CARIFS, parents of children with asthma reported similar profiles to controls on days 10 onwards. Using the CARIFS, children with asthma had higher score only on day 7 but by day 10, had

similar score to controls. The cough diary scores of children with asthma were higher than controls on day-1 but not on other days. The differences found between the 2 scales is not surprising as the scales utilized were designed to measure different things. Furthermore it is known that the severity of cough has a poor relationship to severity of asthma.(23, 24)

In our study, children with protracted bronchitis had the highest CARIFS score on days 7, 10 and 14 and this was significantly higher than children with asthma or healthy controls. Protracted bronchitis is a condition characterized by isolated chronic (>4 weeks) wet cough that responds to antibiotics.(14) One possible reason why the severity of ARI is higher in this group is the presence of dysfunction of the innate immunity such as reduced expression of Toll-like receptors 2 and 4 in the airway cells.(16)

Another possible reason is that the subjective reporting as our results have to be interpreted with the knowledge that parental reporting of childhood respiratory symptoms can be biased and parental perceptions are likely to play an important role.(25) However, as young children are unable to verbally express themselves adequately, it is standard practice for parents to be proxy assessors of their young child. Moreover the burden of illness is real and Juniper and colleagues have shown that physicians are poor assessors of the burden of illness.(26) Nevertheless biased reporting as the reason why children of different groups have significant different scores are unlikely as we have previously shown the number of coughs objectively recorded on a cough-meter per subjective score unit in diaries completed by parents of children with

chronic cough was significantly higher than that of diaries completed parents of otherwise well children.(27) This suggests that parents of children with chronic cough are unlikely to exaggerate the severity of their child's cough. Also Wyke and colleagues had shown that the higher severity of cough in socio-economically deprived children was real and not because of parental exaggeration.(28)

Our study was also limited by the small sample size in the controls. A larger sample size in the protracted bronchitis group and healthy controls would have been beneficial. In addition to the limited sample size, this study looked at one episode of illness only and limited to a 14 day period. A further limitation is that we do not have polymerase chain reaction (PCR) data for viral detection on these children. The children with asthma were recruited during an exacerbation and received oral corticosteroids which could influence the morbidity of this group. Family history or personal history of atopy was not reported in any of our groups. Children with atopy have more prolonged respiratory symptoms. Given these limitations, our study's findings should be confirmed in other cohorts and include a longer follow-up phase.

In conclusion, children with protracted bronchitis had the most severe ARI symptoms and higher percentage of respiratory morbidity at day 14. In comparison to controls, children with asthma had more severe ARI symptoms only in the early phase (at and before 7 days). As protracted bronchitis is an important and common cause of chronic cough in children (21) and possibly antecedent to chronic lung disease, further research studies to ascertain the natural history and mechanisms underlying protracted bronchitis(29, 30) are important.

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*Table One:* CARIFS(17) as completed by parents of children with asthma, protracted bronchitis and healthy controls.

	Major Problem	Moderate Problem	Minor problem	No Problem	Don't know/ Not applicable
Fever					
Cough					
Poor appetite					
Not sleeping well					
Irritable					
Feels unwell					
Low energy, tired					
Not playing well					
Crying more than usual					
Needing extra care					
Clinginess					
Nasal congestion, runny nose					
Vomiting					
Not interested in what's going on					
Unable to get out of bed					
Headache					
Sore throat					
Muscle aches and pains					

*Table Two:* Demographics of study participants divided into children with asthma, protracted bronchitis and healthy controls.

	Asthma group N=72	Protracted bronchitis N=19	Controls N=23
Median age (IQR)	3.8 (3.8)	3.3 (3.9)	3.9 (3.4)
Sex			
Male (%)	39 (54.2)	12 (63.2)	14 (60.9)
Female	33 (45.8)	7 (36.8)	9 (39.1)
Season			
Winter (%)	43 (59.7)	11 (57.9)	10 (43.5)
Summer	29 (40.3)	8 (42.1)	13 (56.5)

*Table Three:* Median cough score and interquartile range (IQR) of 3 groups on days 1, 7, 10 and 14.

<b>Children with</b>	<b>Day 1</b>		<b>Day 7</b>		<b>Day 10</b>		<b>Day 14</b>	
	<b>Median</b>	<b>IQR</b>	<b>Median</b>	<b>IQR</b>	<b>Median</b>	<b>IQR</b>	<b>Median</b>	<b>IQR</b>
<b>Asthma</b>	3.0	1.45	1.0	1.0	0	1.0	0	1.0
<b>Protacted bronchitis</b>	3.0	2.0	2.5	1.25	2.0	2.0	2.0	2.0
<b>Controls</b>	1.0	1.0	1.0	2.75	1.0	2.0	1.0	1.25

*Table Four:* Proportion of children with asthma (A), protracted bronchitis (PB) and healthy controls (C) coughing at day 1, 7, 10, 14 of acute respiratory illness as per cough diary (19)

<b>Children with</b>	<b>Day 1</b>		<b>Day 7</b>		<b>Day 10</b>		<b>Day 14</b>	
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
<b>Asthma</b>	49	68	31	43	20	28	14	24
<b>Protacted bronchitis</b>	12	63	13	68	14	74	12	63
<b>Controls</b>	8	35	7	30	6	26	6	26
<b>p value</b>	<0.001		<0.001		<0.001		<0.001	

p by Kruskal Wallis comparing the 3 different groups on a particular day of ARI

*Figure Legend*

Figure One: Daily median CARIFS as reported by the parents of children with asthma (diamonds), protracted bronchitis (squares) and healthy controls (triangles) on day-1 of acute respiratory illness (ARI), day-7 of ARI, day-10 of ARI and day-14 of ARI.

Figure Two: Median cough scores of children with asthma (diamonds), protracted bronchitis (squares) and healthy controls (triangles) against the day of acute respiratory illness (day 1, 7, 10 and 14)