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Determinants of Cough and Caregivers' Quality of Life in Paediatric Asthma Exacerbations

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ABSTRACT

Objectives: In hospitalized and non-hospitalized children with asthma exacerbations, we evaluated the determinants of: (a) prolonged cough on day-14; and (b) asthma quality of life (QoL) questionnaires for parents (PACQLQ) on day-21. We hypothesized that children with more severe acute asthma are more likely to have prolonged cough and/or poorer PACQLQ during the recovery phase.

Design: Prospective cohort study performed during 2009-2011.

Methodology: 244 children aged 2-16 years presenting with acute asthma to the Emergency Departments of 2 hospitals were recruited. Clinical history, examination, baseline asthma severity and acute asthma severity on presentation were documented. Validated daily cough diaries and weekly PACQLQ were recorded for 14 and 21-days respectively.

Results: 34.4% and 32.2% of children who returned the day- and night-time cough diaries respectively had prolonged cough. Those on regular inhaled corticosteroids (ICS) were significantly more likely to have a daytime or night-time cough score of ≥1 on day-14 [Odds Ratio ($OR_{adjusted}$)=4.70, 95%CI 1.65, 13.35, p=0.004 and

$OR_{adjusted}$=2.65, 95%CI 1.05, 6.69, p=0.040 respectively]. PACQLQ on day-21 was significantly poorer in younger children [mean difference (MD)=-0.04 per year, 95%CI -0.08, -0.01, p=0.016], those on ICS (MD=-0.31, 95%CI -0.52, -0.09, p=0.005), leukotriene antagonists (MD=-0.42, 95%CI -0.83, -0.02, p=0.040) and in those who had an unplanned visit for asthma on day-21 (MD=-1.20, 95%CI -1.61, -0.78, p=0.0001).

Conclusions: Post an acute asthma exacerbation, children on regular ICS were more likely to have prolonged cough and poorer QoL. While this may be reflective of asthma severity or control, its association deserves further evaluation.

INTRODUCTION

Patient-reported outcomes (PROs) are increasingly appreciated as key in the evaluation of health interventions[1]. Quality of life (QoL) is one such PRO, now commonly used in clinical studies and trials[2]. Acute asthma and cough are common childhood conditions that impact on the QoL on children[3] and their parents[4]. In those with asthma, cough is particularly problematic from a patient's/parent's perspective[5], as reflected in the items selected for developing asthma-specific QoL tools, whereby cough is among the highest rated factor impacting QoL[6].

Acute asthma, a common presentation to Emergency Departments (EDs), is the subject of many publications[7,8]. However, there is paucity of data on the influence of asthma severity on the duration of cough and asthma QoL questionnaires for parents (PACQLQ)[4] following acute exacerbations. Most children with asthma exacerbations are not hospitalized but many have morbidity lasting >2 weeks[9,10].

It is likely that many factors influence the severity of acute asthma on presentation, the duration of cough and asthma QoL. These factors reflect on-going morbidity in children and include extrinsic determinants (e.g. access to service and socioeconomic influences[11]), environmental and biological factors. Data on the latter are scarce in children; possible factors include the presence of, and host response to, viral infections[8,12] and atopy[13,14]. Assessing the QoL of children and adolescents with asthma is fundamentally important as severe or uncontrolled asthma impairs the quality of sleep[15], school performance[16] and involvement in physical activities, all of which contribute to reducing QoL[17].

There are few paediatric studies that have examined the influence of asthma severity on the duration of cough and PACQLQ following acute exacerbations. One study[18] reported that lower asthma severity (intermittent/mild) predicts better QoL in children with asthma. Others have shown that the QoL of children with asthma is reduced in association with increasing asthma severity and poor symptom control[19,20]. The same group also suggested that the QoL of the family depends not only on factors related to asthma, but also on non-asthma related factors such as poverty which play an even more important role[21]. Lower socioeconomic status of the family and exposure to household moulds contributed to lower QoL[21]. Another study[22] reported better asthma control was associated with better Paediatric Allergic Disease QoL Questionnaire (PADQLQ).

We evaluated the determinants of prolonged cough (day- and night-time cough diaries[23]) on day-14 and PACQLQ[4] on day-21 in 244 children (hospitalized and non-hospitalized) presenting to EDs with acute asthma. We hypothesized that post an

acute exacerbation, children with more severe acute asthma are more likely to have prolonged cough (on day-14) and/or lower (i.e. poorer) PACQLQ (on day-21).

METHODS

Subjects

Children aged 2-16 years who presented with an acute asthma exacerbation to the ED at 2 hospitals [Royal Children's Hospital (RCH, Brisbane), July 2009-December 2010 and Canberra Hospital (TCH), January 2010-June 2011] were recruited. Written informed consent was obtained from a parent/carer.

Asthma was defined as recurrent (>2) episodes of wheeze and/or dyspnoea with a clinical response (decreased respiratory rate and work of breathing) to β_2-agonist[24], as diagnosed by a doctor unrelated to this study. Asthma exacerbation was defined as an acute deterioration of asthma control requiring treatment with >1 dose (>600μg via metered dose inhaler and spacer/>2.5mg nebulised) of salbutamol in an hour. Exclusion criteria for the study were presence of: an underlying respiratory disease (e.g. bronchiectasis), cerebral palsy/severe neurodevelopmental abnormality, immuno-compromised state, severe asthma (requiring continuous nebulised/intravenous salbutamol) or previously enrolled in the study. Preschool children with wheezy episodes or exacerbations with no clinical response to β_2-agonist were not included in the study. Children were medically managed by staff who were uninvolved in the study. The study was approved by the ethics committees of both hospitals (Royal Children's Hospital and Health Services District and Australian Capital Territory Health Human Research Ethics Committees).

Study Protocol

Children enrolled in this study were a subset of a previous cohort[25] where our major interests were on recovery outcomes post-exacerbation. In this study, we specifically examined the determinants of prolonged cough on day-14 and PACQLQ on day-21.

Baseline and follow-up

In the original cohort study[25], clinical history and examination were documented on a standardized data collection sheet at baseline (in ED). This included questions specific for asthma (e.g. exacerbation frequency, medications) and for acute respiratory infection symptoms (ARI: runny nose, fever, sore throat, cough, irritability, tiredness). An ARI was considered present if ≥2 symptoms were present at enrolment[26]. An Australian Functional Severity Scale for paediatric asthma[27] was used to determine baseline asthma severity. Severity of acute asthma on presentation was categorized according to Acute Asthma Score[28] and the then current Australian National Asthma Guidelines[29]. Children were treated by doctors using a standardized protocol. A nasopharyngeal aspirate (NPA) was undertaken for PCR detection of respiratory viruses, *Chlamydophila* and *Mycoplasma*. Skin prick tests (SPT) to 6 environmental allergens (dust mite, cockroach mix, cat hair, Alternaria mould, grass pollen mix and couch grass) were also performed. A wheal ≥3mm in diameter to any allergen (above negative control) was considered positive for atopy. As the SPT was done in the acute phase, we did not exclude those who had taken steroids or antihistamines. Eczema (in the last 12-months) was self-reported using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.

Validated daily cough (day- and night-time)[23] and asthma diary scales (ADS)[30] were recorded for 14-days and baseline and weekly PACQLQ[4] were recorded for 21-days. We defined prolonged cough as a cough score of ≥1 on day-14 on the prospectively

collected diary card[23]. The validated cough scale[23] utilized a verbal descriptive score of day- and night-time cough. The daytime cough scale ranged from 0 (no cough) to 5 (cannot perform most usual activity because of severe coughing) and the night-time cough scale ranged from 0 (no night cough) to 5 (distressing cough). A daytime cough score of 1 indicated cough for one or two short periods only. A night-time cough score of 1.1 indicated cough when awake overnight only; a night-time cough score of 1.2 indicated cough on going to sleep only (see supporting information). The asthma score was the average of four questions[30]. The PACQLQ[4] included 13 items with responses for each item given on a seven-point scale, ranging from 1 to 7, with 1 indicating severe impairment and 7 indicating no impairment (see supporting information). The overall score was the mean of all items, with a higher score indicating a better QoL.

Follow-up phone calls occurred 24-48 hours after enrolment and on days-7, 14 and 21 where PACQLQ and adverse events including unscheduled representations to a health facility were recorded. End points were exacerbation of asthma requiring corticosteroids, admission into hospital and/or at day-21 (whichever occurred first).

Statistical analyses

Data for the association between measures of prolonged cough (day- and night-time cough score of ≥1 on day-14) and PACQLQ on day-21 with possible determinants including measures of recovery outcomes were first examined using univariable analyses (Chi-squared or Fisher's exact test). This was then followed by multivariable logistic regression (factors with $p \leq 0.20$) to examine the association between possible determinants and measures of prolonged cough, and linear regression for the possible

determinants of PACQLQ on day-21, while considering potential contributors. Two-tailed p-value of <0.05 was considered significant. SPSS v.26.0 was used.

RESULTS

One hundred and twenty-five children returned the daytime cough diaries and 121 returned the night-time cough diaries. Of these, 43 (34.4%) had prolonged daytime cough and 39 (32.2%) had prolonged night-time cough (see flowchart in supporting information). Two hundred and seventeen children returned the PACQLQ. The characteristics of the 125, 121 and 217 children respectively included in this study were similar to those from the original 244 children[25] (Table 1). Univariable analyses showed that prolonged daytime (p=0.002) and night-time (p=0.018) cough scores on day-14 were significantly higher in those on inhaled corticosteroids (ICS) compared to those without a history of ICS usage (Table 2). Those with prolonged daytime cough scores on day-14 were also significantly higher in those with a history of current eczema in the last 12 months (p=0.023). Other factors, notably age, sex, being on leukotriene receptor antagonists (LTRA), having a diagnosed allergy, pet exposure, tobacco smoke exposure, ARI presence, hospitalization, atopy, presence of virus and bacteria or having an unplanned visit for asthma by day-14 or 21 were not significantly associated with either prolonged day- or night-time cough (Table 2). In the multivariable regression, those on ICS were significantly more likely to have a daytime cough score of ≥1 on day-14 [Odds Ratio $(OR)_{adjusted}$=4.70, 95%CI 1.65, 13.35, p=0.004] and a night-time cough score of ≥1 on day-14 ($OR_{adjusted}$=2.65, 95%CI 1.05, 6.69, p=0.040). That for current eczema in the last 12 months was no longer significant (p=0.124).

For PACQLQ on day-21, univariable analysis (Table 3) revealed that factors associated with lower (i.e. poorer) QoL were: younger age, those on regular ICS and those who had an unplanned visit for asthma on day-21. Factors that were not statistically significant include being on LTRA, tobacco smoke exposure and being hospitalized. On multivariable analyses, PACQLQ on day-21 was significantly lower in those of younger age [mean difference (MD)=-0.04 per year, 95%CI -0.08, -0.01, p=0.016], on ICS (MD=-0.31, 95%CI -0.52, -0.09, p=0.005), LTRA (MD=-0.42, 95%CI -0.83, -0.02, p=0.040) and in those who had an unplanned visit for asthma on day-21 (MD=-1.20, 95%CI -1.61, -0.78, p=0.0001).

DISCUSSION

We examined the factors associated with prolonged cough (day- and night-time cough diaries) and PACQLQ in 244 children with hospitalized and non-hospitalized acute asthma exacerbations. Children on ICS were significantly more likely to have prolonged (both day- and night-time) cough by day-14. In addition, children of a younger age, on ICS, LRTA and in those who had an unplanned visit for asthma on day-21 had significantly poorer PACQLQ on day-21.

Like our previous paper[25], one of our study's important aspects includes the focus on asthma recovery outcomes. There is little research in this area despite the importance of asthma exacerbations and its burden on children and their families[17,31]. We focused on patient-oriented and validated outcomes (PACQLQ and cough scales) as PROs are increasingly being used in the evaluation of health interventions but are limited in routine clinical care compared to objective measures, particularly in young children. As such, our study's data is important in identifying the children who are more likely to have a longer duration of symptoms beyond the immediate exacerbation phase.

Uncontrolled asthma symptoms not only affect children physically but can impair them socially, emotionally and educationally[32]. The impact of asthma in children in turn results in additional burden on their parents/carers. Work productivity impairment of caregivers have been shown to become significantly greater among parents of children with uncontrolled asthma[32,33]. Cough is particularly problematic from patients'/parents' perspective in children with asthma, impacting on QoL[5]. This information is potentially important in identifying children who are more likely to have prolonged symptoms and hence its consequences. Results could aid in counselling parents of children who have a history of more severe acute asthma with regards to the on-going morbidity and the duration of clinical recovery from the exacerbation.

There may be some possible reasons why ICS prolong recovery in asthma exacerbations but these are only speculative. The most likely reason is that children on ICS have more severe asthma pre-exacerbation, thus impacting also on post-exacerbation recovery. Another possibility is prolongation of the effect of viral infection as virus replication may be enhanced by ICS. Puhakka et al[34] studied the effects of intranasal corticosteroids and found that its treatment induced prolonged shedding of viable rhinoviruses. Thomas and colleagues[35] demonstrated that corticosteroids suppress host innate immune responses, reducing early protective mechanisms and enhancing respiratory virus infections. Also, ICS may be associated with an increased risk of pneumonia or lower respiratory infection in adults with asthma[36]. Nevertheless, it is important to be cognizant that the benefit of ICS in children with asthma is well documented and the question whether the ICS use may be a reason for prolonged cough cannot be answered by the design of our study.

In addition to the effect of ICS on cough and PACQLQ, we also found that the PACQLQ score was lower in carers of children of younger age compared to that of older children. It is speculative but this may be related to the uncertainty or concern felt amongst parents of younger children more often than those of older children[37].

Although we have described new clinical data relating to recovery, our study has several limitations. Firstly, we did not examine lower airway bacterial infection. Children with bacterial infections may have a more prolonged recovery period from an asthma exacerbation[38]. Secondly, prolonged cough may represent uncontrolled asthma, but there are many other causes of prolonged cough[39-41] that we could not evaluate. Also, for cough scores, we used patient subjective scores (although validated) and a relevant outcome (QoL) rather than objective measures e.g. cough counts. While the severity of cough defined on diary cards may not be representative of cough frequency measured objectively, there is a strong relationship[23]. Nevertheless, to fully assess cough outcomes, a combination of both subjective and objective scores would be beneficial. Also, a confident diagnosis of asthma may be challenging in preschool children aged ≤5 years, as recurrent wheezing in children in this age group may not be asthma[42]. Finally, we did not collect data on somatometrics, antihistamine use prior to SPT or adherence to medications that may influence the recovery period.

In conclusion, in children on ICS, their recovery from an acute asthma exacerbation is slower with regard to the outcomes of day- and night-time cough and QoL. While this may be reflective of asthma severity or control, its association deserves further evaluation as severe acute asthma has a significant impact on the QoL and productivity of children and their caregivers and families.

Contributors

LT contributed to the conception and design, acquisition of data, analysis and interpretation of data, and writing of the manuscript. MDC contributed to the interpretation of data and revision of the manuscript. JPA and GBM contributed to supervision and revision of the manuscript. ABC contributed to the conception and design, supervision, interpretation of data and revision of the manuscript. All authors approved the final manuscript.

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TABLE 1 - Characteristics of Children Included in Analyses

	Daytime cough diaries	**Night-time cough diaries**	**PACQ LQ**
Children, n (% of total)	125 (51.2)	121 (49.6)	217 (88.9)
Age (years), median (IQR)	4.5 (3.5)	4.5 (3.4)	4.5 (3.5)
Sex, n (Female:Male)	43:82	40:81	74:143
Environmental tobacco smoke exposure n (%)	27 (21.6)	24 (19.8)	60 (27.6)
On inhaled corticosteroids n (%)	51 (40.8)	49 (40.5)	81 (37.3)
On leukotriene receptor antagonist n (%)	8 (6.4)	7 (5.8)	15 (6.9)

History of eczema ever present n (%)	74 (59.2)	71 (58.7)	130 (59.9)
Current eczema in the last 12 months n (%)[a]	57 (46.0)	54 (45.0)	94 (43.9)
Diagnosed allergy n (%)	40 (32.0)	38 (31.4)	66 (30.4)
Pet exposure n (%)	85 (68.0)	83 (68.6)	139 (64.1)
Acute respiratory infection present n (%)[a,b]	65 (53.7)	62 (53.0)	116 (55.0)
Positive skin prick test n (%)[a]	85 (81.7)	81 (81.0)	140 (75.3)
NPA virus and bacteria detected n (%)[a]	91 (82.7)	89 (84.0)	164 (82.0)
Hospitalized n (%)	92 (73.6)	89 (73.6)	165 (76.0)
Representation for asthma within 7 d	14 (11.3)	13 (10.7)	23

n (%)[a]			(10.6)
Representation for asthma within 14 (%)[a]	15 (12.1)	15 (12.4)	21 (9.7)
Representation for asthma within 21 days; n (%)[a]	7 (5.7)	6 (5.0)	14 (6.5)

Environmental tobacco smoke exposure indicates presence of any smoker in the household; [a]Denominator different as data was missing; [b]Acute respiratory infection considered present if ≥2 symptoms (runny nose, fever, sore throat, cough, irritability, tiredness) present at enrolment. NPA: nasopharyngeal aspirate;

PACQLQ: asthma quality of life questionnaires for parents.

TABLE 2 - Determinants of Prolonged Cough on Day 14 (Univariable Analysis)

	Daytime Score ≥1 n (%)	Odds ratio (95% CI)	p	Night-time Score ≥1 n (%)	Odds ratio (95% CI)	p

Age (years)			0.95 (0.83, 1.08)	0.40	0.91 (0.79, 1.05)	0.18
Sex	Female (ref)	15 (34.9)			11 (27.5)	
	Male	28 (34.1)	0.97 (0.45, 2.10)	1.00	28 (34.6)	1.39 (0.61, 3.20) 0.53
Inhaled corticosteroids	No (ref)	17 (23.0)			17 (23.6)	
	Yes	26 (51.0)	3.49 (1.61, 7.54)	0.00	22 (44.9)	2.64 (1.21, 5.77) 0.01
Leukotriene	No (ref)	41 (35.0)			37 (32.5)	

receptor antagonist	Yes	2 (25.0)	0.62 (0.12, 3.20)	0.71	2 (28.6)	0.83 (0.15, 4.49)	1.00
Current eczema	No (ref)	17 (25.4)			17 (25.8)		
	Yes	26 (45.6)	2.47 (1.16, 5.26)	0.02	22 (40.7)	1.98 (0.91, 4.30)	0.11
Allergy	No (ref)	26 (30.6)			25 (30.1)		
	Yes	17 (42.5)	1.68 (0.77, 3.65)	0.22	14 (36.8)	1.35 (0.60, 3.04)	0.53
Pet exposure	No (ref)	11 (27.5)			10 (26.3)		

	Yes	32 (37.6)	1.59 (0.70, 3.62)	0.316	29 (34.9)	1.50 (0.64, 3.52)	0.406
Environmental tobacco smoke exposure	No (ref)	32 (32.7)			30 (30.9)		
	Yes	11 (40.7)	1.42 (0.59, 3.41)	0.495	9 (37.5)	1.34 (0.53, 3.40)	0.627

		Daytime Score ≥1 n (%)	**Odds ratio (95% CI)**	**p**	**Night-time Score ≥1 n (%)**	**Odds ratio (95% CI)**	**p**
Acute respiratory infection	No (ref)	19 (33.9)			16 (29.1)		
	Yes	23 (35.4)	1.07 (0.50,	1.000	22 (35.1)	1.34 (0.61,	0.554

			2.26)			2.93)
Hospitalized	No (ref)	13 (39.4)			12 (37.5)	
	Yes	30 (32.6)	0.74	0.525	27 (30.3)	0.73 0.511
			(0.33,			(0.31,
			1.70)			1.69)
Skin prick test positive	No (ref)	10 (52.6)			9 (47.4)	
	Yes	24 (28.2)	0.35	0.058	22 (27.2)	0.41 0.103
			(0.13,			(0.15,
			0.98)			1.16)
NPA virus and bacteria detected	No (ref)	9 (47.4)			6 (35.3)	
	Yes	27 (29.7)	0.47	0.179	27 (30.3)	0.80 0.776
			(0.17,			(0.27,
			1.28)			2.38)
Unplanned visit by day 14	No (ref)	35 (32.1)			31 (29.2)	
	Yes	7 (46.7)	1.85	0.383	8 (53.3)	2.77 0.079
			(0.62,			(0.92,

			5.51)			8.28)
Unplanned visit by day 21	No (ref)	37 (31.9)			37 (32.5)	
	Yes	4 (57.1)	2.85 (0.61, 13.37)	0.220	1 (16.7)	0.42 (0.05, 3.69) 0.663

On univariable analysis, inhaled corticosteroids was associated with prolonged daytime and night-time cough. Current eczema was also associated with

prolonged daytime cough on univariable analysis. On multivariable analysis, the only factor that remained significant was *inhaled corticosteroids.*

Ref: reference; NPA: nasopharyngeal aspirate.

(%) = % of determinant who returned the daytime or night-time cough diaries on day 14 i.e. n/total number of determinant x 100.

TABLE 3 - Determinants of PACQLQ on Day 21 (Univariable Analysis)

	Mean (SD)	**Difference (95% CI)**	**p**
Age (years)	0.17 (Spearman correlation)		0.010

Sex	Female (ref)	6.38 (0.81)		
	Male	6.44 (0.84)	0.05 (-0.18, 0.29)	0.658
Inhaled corticosteroids	No (ref)	6.52 (0.76)		
	Yes	6.25 (0.91)	-0.27 (-0.51, -0.03)	0.025
Leukotriene receptor antagonist	No (ref)	6.44 (0.79)		
	Yes	6.08 (1.26)	-0.36 (-0.80, 0.07)	0.102
Current eczema[a]	No (ref)	6.40 (0.89)		
	Yes	6.45 (0.75)	0.05 (-0.18, 0.27)	0.679
Allergy	No (ref)	6.44		0.496

		(0.82)		
	Yes	6.36 (0.84)	-0.08 (-0.32, 0.16)	
Pet exposure	No (ref)	6.44 (0.76)		
	Yes	6.41 (0.87)	-0.04 (-0.27, 0.20)	0.756
Environmental tobacco smoke exposure	No (ref)	6.38 (0.80)		
	Yes	6.51 (0.90)	0.13 (-0.12, 0.38)	0.312
Acute respiratory infection[a]	No (ref)	6.46 (0.78)		
	Yes	6.37 (0.88)	-0.10 (-0.32, 0.13)	0.413
Hospitalized	No (ref)	6.50 (0.69)		0.440

	Yes	6.39 (0.87)	-0.10 (-0.36, 0.16)	
Skin prick test positive[a]	No (ref)	6.24 (1.01)		
	Yes	6.51 (0.72)	0.27 (-0.05, 0.60)	0.094
NPA virus and bacteria[a] detected	No (ref)	6.25 (1.13)		
	Yes	6.45 (0.77)	0.20 (-0.19, 0.60)	0.309
Unplanned visit by day 14[a]	No (ref)	6.44 (0.82)		
	Yes	6.25 (0.93)	-0.19 (-0.57, 0.19)	0.318
Unplanned visit by day 21[a]	No (ref)	6.51 (0.76)		
	Yes	5.25 (0.80)	-1.25 (-1.67, -0.84)	0.0001

On univariable analysis, factors associated with lower (i.e. poorer) QoL were age, inhaled corticosteroids and unplanned visit for asthma on day 21. On multivariable analysis, these factors remained significant. PACQLQ: asthma quality of life questionnaires for parents; ref: reference; NPA: nasopharyngeal aspirate.

[a]*Denominator different as data was missing.*