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Duration, course and caregiver burden of croup in children: two observational cohorts

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ABSTRACT

Objectives Although croup is a common respiratory illness, there is little published regarding symptom course. We aimed to assess symptom progression and caregiver burden, and whether age, sex or season and initial severity of disease are associated with symptom duration.

Design, setting and participants We conducted a secondary analysis of two Canadian prospective cohorts of children 0–16 years old diagnosed with croup; one recruited from a paediatric emergency department (ED) (307 children) between November 1999 and March 2000, and the other from 26 general EDs (1214 children) between September 2002 and April 2006. Baseline data included age, sex, season, corticosteroid treatment and clinical severity score based on the presence or absence of a barky cough, stridor at rest or with agitation and chest wall indrawing (mild, moderate or severe). For both cohorts, the child's primary caregiver was telephoned daily to collect symptom progression and psychosocial data (caregiver stress, lost sleep and work) until the child was symptom-free for over 24 hours.

Results The paediatric and general ED cohorts are reported separately; croup symptoms peaked at initial ED presentation for 96% and 77%, respectively. The longest-lived symptom was a barky cough, resolving by 34 and 47 hours for 50%, and 78 and 119 hours for 90% of children, respectively. Neither sex nor severity at presentation were significantly associated with symptom duration in either cohort. Season of illness was associated in both; age was associated in the general but not the paediatric ED cohort. The primary caregiver lost a mean (SD) of 4.1 (4.9) and 2.8 (4.7) hours of sleep during the illness.

Conclusions Most children with croup presented for care at the peak of symptom severity. Symptoms resolved for half of the children in 1.5–2 days and for 90% in 3–5 days after presentation. Caregivers experienced a significant loss of sleep.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study uses data that are approximately 20 years old.
⇒ Children with croup were enrolled at presentation for care to a paediatric emergency department (ED) and 26 general EDs.
⇒ Assessment of croup symptoms following discharge from emergency care was done by daily follow-up telephone calls by trained research assistants using standardised questions and a validated clinical score especially designed for this purpose until all symptoms had fully resolved. Research assistants also assessed caregiver stress, loss of sleep and time from work during the child's croup illness.
⇒ For the general ED cohort, the determination of disease severity at presentation for care was systematically documented by nurses; specifically, nurses documented the presence or absence of a barky cough, stridor at rest or with agitation and chest wall indrawing (mild, moderate or severe).
⇒ For the paediatric ED cohort, disease severity at presentation for care was determined by audit of physician, nurse and respiratory therapist written records for the presence or absence of a barky cough, stridor at rest or with agitation and severity of chest wall indrawing.

INTRODUCTION

Croup is a common respiratory illness of childhood, characterised by sudden onset of a barky cough, hoarse voice, and in moderate and severe cases, stridor and respiratory distress. Croup affects up to 3% of young children annually, occurring commonly between 6 months and 6 years of age, but occasionally even in adolescents.[1] Croup affects 1.4 times more boys than girls.[1 2]

Although croup is common, there are limited published data describing symptom duration, and no data published addressing when symptoms peak, which symptoms persist longer nor whether duration differs with patient age or sex, season and initial severity of disease. The only publication addressing symptom duration for croup is a systematic review that reported the duration of symptoms for several common respiratory tract infections in children drawing data from observational studies and the placebo arms of randomised controlled clinical trials.[3] This study, using pooled data from placebo arms of three croup trials (n=415),[4–6] estimated that croup symptoms resolved for 90% of

children by 2 days.[3] Because the specifics of how the three trials reported disease duration differed widely and were available only in the aggregate, there is uncertainty as to the validity of the combined results. Besides more precise and valid information on disease duration, also knowing the impact of croup on caregivers, when croup symptoms peak, which symptoms last longer and whether they vary with age, sex, season and severity of disease at initial presentation for care would be valuable for educating clinicians-in-training and families of children with croup.

The primary objective of this study was to describe the peak and duration of croup's common symptoms in children presenting to an emergency department (ED). Secondary objectives were to determine whether age, sex, season of presentation or severity of croup at presentation were associated with duration of symptoms and describe associated caregiver stress, loss of sleep and time from work during the child's croup illness.

METHODS

We conducted a secondary analysis of two prospective cohorts of children with croup enrolled from EDs in Alberta, Canada, as part of other studies.[7 8] The first prospective cohort enrolled between 1 November 1999 and 31 March 2000 from one university-affiliated paediatric ED (Alberta Children's Hospital, in Calgary, Alberta, Canada).[7] The second prospective cohort enrolled between 1 September 2002 and 30 April 2006 from 26 general EDs across the province of Alberta, Canada.[8] Both original studies received approvals from the appropriate institutional review boards. Because enrolment in both prospective cohorts captured a minority of all children evaluated in EDs during eligible time periods, these cohorts were at risk of not being representative. To assess potential bias, we compared demographic and clinical characteristics extracted retrospectively from health records of children with croup evaluated in paediatric and general EDs for those enrolled and not enrolled in the prospective cohorts during the same study periods (figure 1).

The Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines for reporting observational studies were followed.[9]

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Prospective cohort participants

Children were eligible for the prospective cohorts if they met inclusion criteria: age 0–16 years, diagnosis of croup confirmed by the attending ED physician and their primary caregiver spoke English and had telephone access. Exclusion criteria were symptoms or signs of another potential cause of stridor other than croup; history of congenital or acquired stridor; and/or chronic pulmonary disease, asthma or severe systemic disease.

Caregivers of potential subjects were asked for consent to be contacted by a research assistant about the study following discharge. For the general ED cohort, ED staff documented at presentation the presence or absence of a barky cough, stridor at rest or with agitation and chest wall indrawing (mild, moderate or severe). For the paediatric ED cohort, an audit of physician, nurse and respiratory therapist-documented assessments of a barky cough, stridor and chest wall indrawing was extracted. The severity of croup as mild, moderate or severe was categorised using a modified Westley croup score using assessment of stridor (0–2 points) and chest wall indrawing (0–3 points) (online supplemental appendix table 1).[10] Demographics, clinical severity, date/time of visit, disposition at discharge and parental consent to be contacted were forwarded to the research assistant. For the paediatric ED cohort, the research assistant was an experienced paediatric emergency research nurse. For

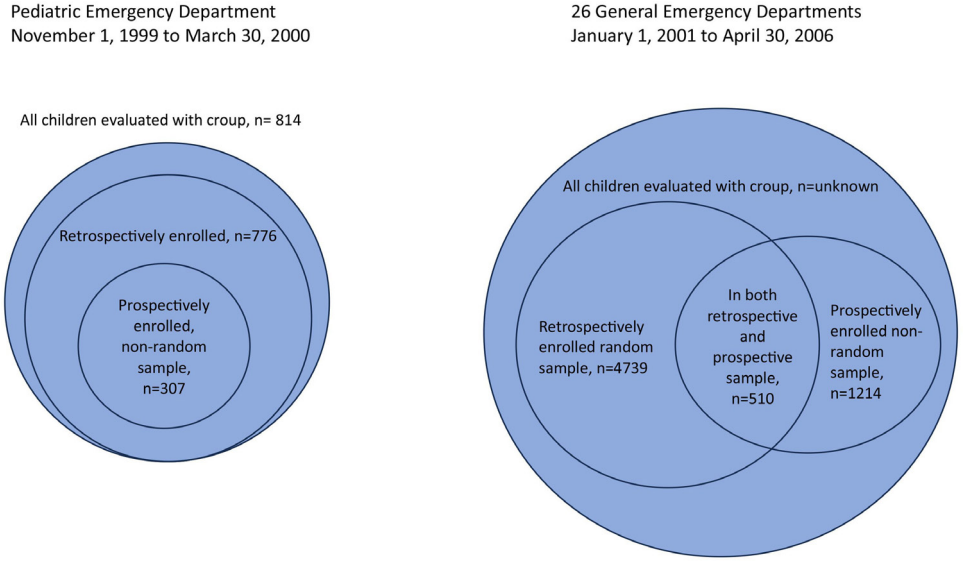

Figure 1 Study populations and enrolment.

the general ED cohort, the same paediatric emergency research nurse trained and supervised three research assistants. A standardised script, consent form and questionnaire were used for informed consent and to ask about croup symptoms occurring since discharge or the last telephone contact. Once enrolled, the primary caregiver (usually, the mother) was telephoned to complete the symptom questionnaire every 24 hours until all symptoms had resolved for at least 24 hours. The severity of symptoms was assessed using the Telephone Out Patient (TOP) score[7] using two elements (barky cough and stridor) (online supplemental appendix table 2).[7] Data were entered into an electronic database (customised in Access, Microsoft Office). Based on our experience from conducting extended follow-up for croup randomised trials that recrudescence of symptoms is rare,[4–6] we ended follow-up after symptoms had resolved for 24 hours or more.

Retrospective cohort participants

Alberta ED administrative data sets were interrogated for the paediatric and general EDs during the specified enrolment periods for children aged 0–16 years with a discharge diagnosis of croup (ICD9-CM 4640–4644, 4660, 47875). All children with these ICD9 codes evaluated in paediatric and general EDs that evaluated fewer than 30 children per year with these codes had their health records audited. For general EDs that evaluated more than 30 children with these ICD9 codes per year, a random selection of 30 records per year was audited.

Demographics, clinical assessments, treatments and disposition data were entered into the electronic database. Croup diagnosis and severity were determined by reviewing written health records. Children not documented to have a barky cough in the ED were classified as not having croup and excluded from the retrospective cohort. Children who had a barky cough documented were considered to have croup, and the severity of their symptoms was classified using a modified Westley croup score using two elements (stridor and chest wall indrawing) (online supplemental appendix table 1).[10] The observations resulting in the greatest severity from among physicians, nurses and respiratory therapists were used. We calculated the modified Westley croup score in two ways and reported both. First, if a symptom was not documented as either present or absent, we assumed the child was asymptomatic and assigned a score of zero for that symptom. Second, if either symptom was not documented, we categorised this child as having missing data and did not calculate a total score.

Study outcomes

Because the two prospective cohorts were drawn from different clinical settings with differing levels of clinical expertise in managing this childhood disease recruitment sites, we thought it important not to pool the results and report study outcomes separately for each prospective cohort.

Primary outcome was the duration of symptoms in days from the date of enrolment at assessment until the date of the resolution of all croup symptoms, including a barky cough, stridor and chest wall indrawing. Secondary outcomes were the timing of peak croup symptoms measured by TOP score[7] (online supplemental appendix table 2) relative to enrolment at initial ED assessment; time from reported start of croup symptoms until time of enrolment at initial ED assessment; determination of which symptom was most long-lived; demographic or clinical variables associated with symptom duration; number of hours of sleep and days of work for wages lost by primary caregiver (usually, the mother); and perceived stress expressed by the caregiver. Stress was measured by 7-point Likert scale (extremely calm, very calm, somewhat calm, coping, somewhat stressed, very stressed, extremely stressed), which were collapsed for analysis into three categories: ‘calm’, ‘stressed’ and ‘coping’. For hours of sleep lost, the caregiver was asked to estimate the number of hours of sleep they had lost the prior night. To determine days of work for wages lost, the caregiver was asked if in the prior 24 hours they had missed work due to their child’s illness.

Sample size and statistical considerations

The power of the prospective cohorts was not assessed a priori as they were created for other purposes and hence fixed in size. No hypotheses on effect sizes were assumed. Proportions were used to describe categorical variables. Means and SD, or medians and IQRs were used, as appropriate, to describe continuous or discrete variables. Cox regression for time to symptom resolution was used to estimate the relationship of the following variables with it: age, sex, severity of croup at presentation and season of presentation (defined as 1 January to 31 May, 1 June to 31 August and 1 September to 31 December).

RESULTS

Study populations

Prospective cohorts of children with croup included 307 from the paediatric ED and 1214 from the 26 general EDs. None of the children were referred from other healthcare institutions, and follow-up was complete for all children in both prospective cohorts. Retrospective cohorts of children identified using ICD coding from health administrative data sets included 776 from the paediatric ED and 4739 from 26 general EDs. Figure 1 illustrates the interrelationships between cohorts. Table 1 shows demographics, clinical severity at ED presentation, corticosteroid treatment and disposition of children for all cohorts and their subsets. These subset descriptions allow comparison of those enrolled and not enrolled into prospective cohorts to assess for potential participation bias (ie, for the paediatric ED, ‘all prospective’ vs ‘only retrospective’, and for the general ED, ‘both retrospective and prospective’ vs ‘only retrospective’).

Table 1 Baseline demographics and clinical characteristics of children with croup evaluated in paediatric and general emergency departments (EDs)

	Paediatric ED All children evaluated with croup n=814			26 general EDs All children evaluated with croup (n=unknown)				
	All retrospective n=776 (%)	Only retrospective n=469 (%)	All prospective n=307 (%)	All retrospective n=4739 (%)	Only retrospective n=4229 (%)	Both retrospective and prospective n=510 (%)	Only prospective n=704 (%)	All prospective n=1214 (%)
Age								
0–12 months	141 (18.2)	92 (19.6)	49 (16.0)	877 (18.5)	787 (18.6)	90 (17.7)	115 (16.7)	205 (17.1)
>1–3 years	375 (48.3)	221 (47.1)	154 (50.2)	2019 (42.6)	1794 (42.4)	225 (44.1)	288 (41.7)	513 (42.8)
>3–6 years	184 (23.7)	113 (24.1)	71 (23.1)	1222 (25.8)	1076 (25.4)	146 (28.6)	186 (27.0)	332 (27.7)
>6–9 years	54 (7.0)	27 (5.8)	27 (8.8)	404 (8.5)	369 (8.7)	35 (6.9)	79 (11.5)	114 (9.5)
>9–12 years	19 (2.5)	13 (2.8)	6 (2.0)	155 (3.3)	144 (3.4)	11 (2.2)	12 (1.7)	23 (1.9)
>12 years	3 (0.4)	3 (0.6)	0 (0)	62 (1.3)	59 (1.4)	3 (0.6)	10 (1.5)	13 (1.1)
Missing	0	0	0	0	0	0	14 (2.0)	14 (1.2)
Sex								
Sex (% male)	464 (60.1)	273 (58.6)	191 (62.4)	3017 (63.7)	2703 (63.9)	314 (61.6)	454 (64.7)	768 (63.4)
Missing	4	3	1	1	1	0	2	2
Seasonal period for illness presentation								
1 January to 31 May	262 (33.8)	154 (32.8)	108 (35.2)	2340 (49.4)	2121 (50.2)	219 (42.9)	375 (53.3)	594 (48.9)
1 June to 31 August	0	0	0	492 (10.4)	492 (11.6)	0	1 (0.1)	1 (0.1)
1 September to 31 December	514 (66.2)	315 (67.2)	199 (64.8)	1907 (40.2)	1616 (38.2)	291 (57.1)	328 (46.6)	619 (51.0)
Missing	0	0	0	0	0	0	0	0
Severity at ED presentation (see online supplemental appendix table 3 summarising missing severity data for general ED cohort)								
Mild	316 (40.7)	213 (45.4)	103 (33.6)	3537 (74.6)	3213 (76.0)	324 (63.5)	479 (68.0)	803 66.1)
Moderate	422 (54.4)	229 (48.8)	193 (62.9)	1174 (24.8)	995 (23.5)	179 (35.1)	215 (30.5)	394 (32.5)
Severe	38 (4.9)	27 (5.8)	11 (3.6)	28 (0.6)	21 (0.5)	7 (1.4)	10 (1.4)	17 (1.4)
Missing	0	0	0	0	0	0	0	0
Corticosteroid treatment in ED								
Corticosteroid (% treated)	541 (69.7)	292 (62.3)	249 (81.1)	3555 (75.0)	3087 (73.0)	468 (91.8)	635 (90.2)	1103 (90.9)
Missing	0	0	0	0	0	0	0	0
Disposition from ED								

Continued

Table 1 Continued

	Paediatric ED All children evaluated with croup n=814			26 general EDs All children evaluated with croup (n=unknown)			
	All retrospective n=776 (%)	Only retrospective n=469 (%)	All prospective n=307 (%)	All retrospective n=4739 (%)	Only retrospective n=4229 (%)	Both retrospective and prospective n=510 (%)	Only prospective n=704 (%)	All prospective n=1214 (%)
Discharge home	721 (92.9)	423 (90.2)	298 (97.1)	3773 (79.6)	3329 (78.7)	436 (85.5)	642 (92.4)	1078 (89.5)
Admit to the general ward	47 (6.1)	38 (8.1)	9 (2.9)	947 (20.0)	882 (20.9)	73 (14.3)	53 (7.6)	126 (10.5)
Admit PICU/ transfer	8 (1.0)	8 (1.7)	0	19 (0.4)	18 (0.4)	1 (0.2)	0	1 (0.1)
Missing	0	0	0	0	0	0	9 (1.3)	9 (0.7)

PICU, Paediatric Intensive Care Unit.

Age

In retrospective cohorts, children aged 1–3 years comprised the largest group of children with croup (between 40% and 50%), with few older than 9 years (<5%). Ages were similar between those children prospectively enrolled versus not enrolled for both paediatric and general EDs.

Sex

As expected, a larger proportion of boys were diagnosed with croup than girls (in paediatric and general ED retrospective cohorts, 60% and 64%, respectively). Breakdowns were similar between those prospectively enrolled and those not enrolled for both paediatric and general EDs.

Season of illness

The general EDs retrospective cohort, the only one designed to accurately represent the seasonal distribution of croup presentations across a full calendar year, showed 49.4% of children presented in January/May, 40.2% in September/December and 10.4% in June/August. Neither prospective cohort enrolled children during the summer months. The paediatric and general ED prospective cohorts had 33.8% and 48.9% of children presented in January/May and 64.8% and 51.0% presented in September/December, respectively.

Croup severity

Of 776 children retrospectively evaluated in the paediatric ED, the majority (54.4%) presented with moderate croup. Of 4739 in the general ED, the majority (74.6%) presented with mild croup. Children evaluated in the paediatric ED were more likely to have severe respiratory distress than those in the general ED (4.9% vs 0.6%), respectively. In paediatric and general ED prospective cohorts, relatively more children with moderate and severe croup were enrolled than not enrolled (66.4% vs 54.6%) and (33.9% vs 24.0%), respectively. However, none of the seven children (0.9%) admitted to the intensive care unit from the paediatric ED retrospective cohort were enrolled in the prospective cohort, and, for both cohorts, smaller proportions of children enrolled were hospitalised than those not enrolled.

Corticosteroid treatment

Of children managed in the paediatric (n=776) and general EDs (n=4739), similar percentages (69.7% vs 75.0%, respectively) received corticosteroid. Comparing enrolled and not enrolled into prospective cohorts, those enrolled were more likely to receive corticosteroids (paediatric ED, 81.1% vs 62.3%; general ED, 90.2 vs 73.0%).

Disposition

In retrospective cohorts, children in the paediatric ED were more likely to be discharged than those in general EDs (92.9% vs 79.6%). In the prospective cohorts, those enrolled were more likely to have been discharged home

than those not enrolled (paediatric ED, 97.1% vs 90.2%; general ED, 89.5% and 78.7%).

Duration of symptoms (overall and by subpopulations)

Barky cough was the longest-lived symptom in both prospective cohorts. Stridor or indrawing was reported to occur on the same last day as and after the last day of a barky cough in 20 (6.5%) and 1 (0.3%), respectively, of 307 children in the paediatric ED cohort, and 194 (17.8%) and 43 (4.0%), respectively, of 1088 with complete data in the general ED cohort. The presence or absence of a barky cough and stridor, and severity of indrawing using TOP score by day of follow-up are presented in online supplemental appendix table 4.

Croup symptoms resolved in 50% of all children by 34 and 47 hours, and in 90% by 78 and 119 hours, in the paediatric and general ED cohorts, respectively. With adjustment for covariates, there was no difference in time to symptom resolution by sex, corticosteroid treatment or croup severity at presentation. The time to resolution of croup symptoms, however, varied with season; medians comparing children presenting in January/May versus September/December for the paediatric and general ED cohorts, adjusted for covariates, were 26.0 vs 35.5 and 43.0 vs 53.0 hours, respectively. Time to resolution of croup symptoms in children less than 1 year of age was significantly longer for one cohort but not for the other. Median duration for the paediatric and general ED cohorts comparing children less than 12 months versus 1–3 years of age were 33.0 versus 39.0 and 61.5 versus 48.2 hours, respectively. Figure 2 shows predicted survival curves for the two prospective cohorts for both season and age.

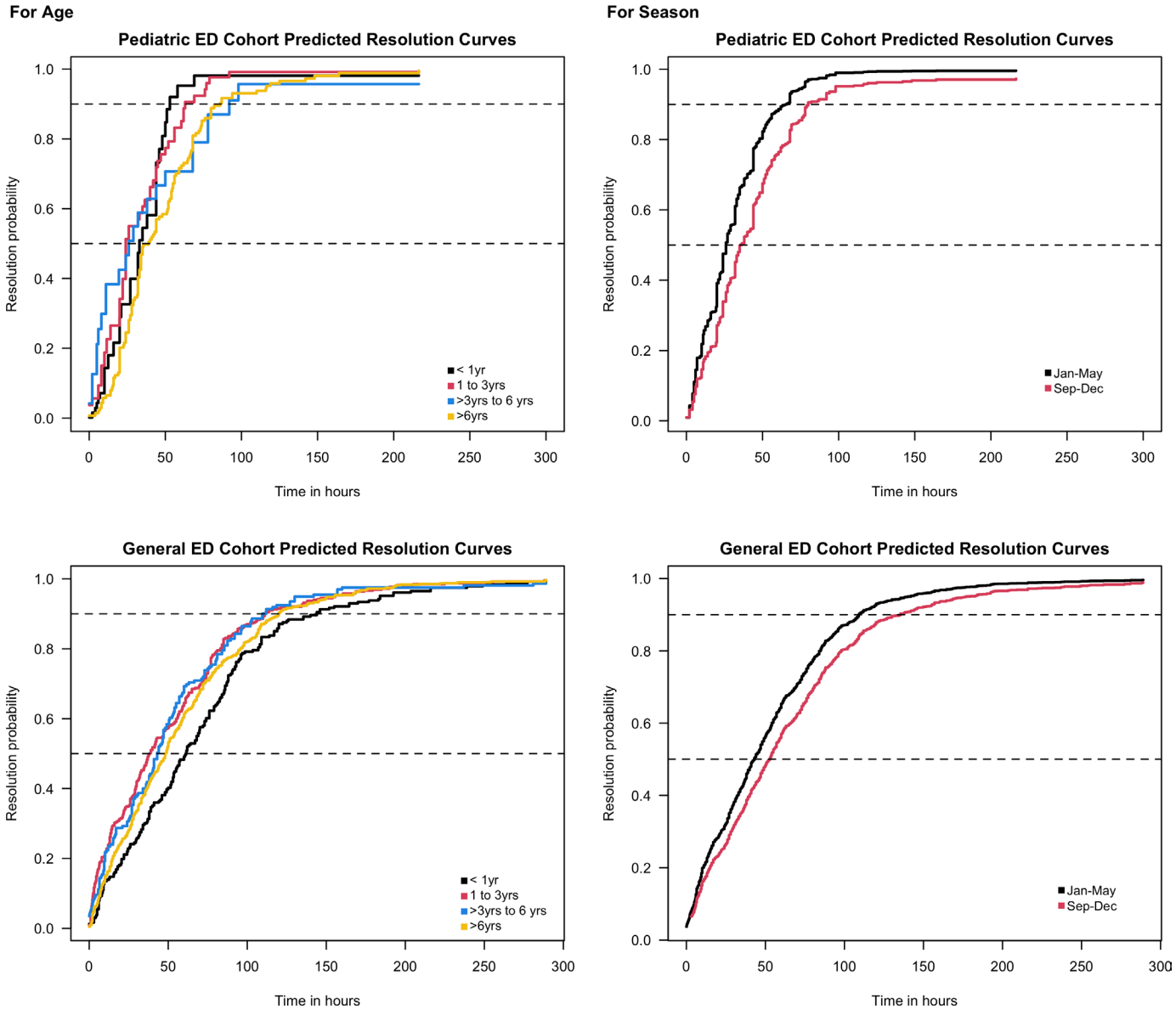

Figure 2 Predicted croup symptom resolution curves for age and season of presentation. ED, emergency department.

Onset of symptoms prior to ED presentation

Time from onset of a barky cough until ED presentation was a median of 0.6 days (IQR 0.9) and 0.4 days (IQR 1.0) for paediatric and general ED prospective cohorts, respectively.

Timing of peak symptoms (overall and by subpopulation)

Most children experienced their worst symptoms at ED presentation at the time of enrolment into prospective cohorts. Specifically, in the paediatric (n=307) and general ED (n=1084) cohorts, 95.7% and 77.3% experienced their worst symptoms in the ED, 2.3% and 20.6% on follow-up day 1, 2.0% and 1.6% on day 2 and 0% and 0.5% on day 3, respectively. Of those who experienced their worst symptoms in the ED, 16.2% of paediatric ED and 31.6% of general ED cohorts had the same severity score at least one subsequent day (online supplemental appendix table 5).

Burden of croup on caregivers

Caregivers' level of stress was recorded daily (online supplemental appendix table 6). On day 1, 48.4% from paediatric ED (n=311) and 27.0% from general EDs (n=1246) reported feeling stressed. Caregivers of children seen at general EDs reported experiencing faster resolution of stress than those evaluated at paediatric ED (14.4% vs 24.1% on day 2, 10.9% vs 9.1% on day 3 and 1.9% vs 9.5% on day 4 of follow-up). The primary caregiver of children in paediatric (n=307) and general ED (n=1214) cohorts missed a mean (SD) of 4.1 (4.9) and 2.8 (4.7) hours of sleep, and 0.6 (0.8) and 0.2 (0.5) days of work for wages, respectively, over the course of their child's illness.

DISCUSSION

We found symptoms were at peak severity at the initial ED presentation for the majority of children. Children's longest-lived symptom was a barky cough, which resolved for about half of children in 1.5–2 days, and for 90% of children in 3–5 days. Neither sex nor illness severity at presentation predicted symptom duration. However, children with croup presenting from September to December took longer on average to resolve symptoms than those presenting from January to May. Children less than 12 months of age appeared to take longer to resolve their symptoms than older children in the larger general ED cohort, but not in the smaller paediatric ED cohort. We found that croup places a significant burden on primary caregivers in stress, sleep loss and work for wages missed.

Demographics, sex and seasonal distributions of children with croup identified in our retrospective and prospective cohorts are consistent with classic epidemiology studies of croup by Denny[1] and Chapman.[2] That the children evaluated in the paediatric ED were, on average, more severe compared with general EDs is not surprising and could be explained by parents self-referring to a paediatric hospital due to their child's degree of respiratory distress.

Both prospective cohorts had similar distributions to our retrospective cohorts for age, sex and season of illness, although they had slightly more severe symptoms. Both prospective cohorts were more likely to be treated with corticosteroids and discharged home than those not enrolled. The high percentage of corticosteroid treatment in our prospective cohorts is likely similar to current treatment patterns in North American EDs.[11–14] Therefore, it is unlikely that our findings regarding disease severity and duration are significantly biased, thus our findings are likely to be broadly generalisable to children with croup assessed now and into the future, as well as across a wide range of settings in global temperate zones.

Given clear evidence from randomised trials and systematic reviews,[3–6 15 16] it is surprising that corticosteroid treatment was not predictive of symptom duration. We attribute this to two reasons. First, since treatment was not randomised, children receiving corticosteroids likely were different in factors associated with symptom duration than those not treated, thus confounding the effect of corticosteroids. Second, since only a minority were untreated with corticosteroids (19% in paediatric ED and 9% in general ED cohorts), the resultant small sample size was likely underpowered to detect an effect.

Our findings provide important information for the education of parents and healthcare trainees that is either new or more precise and detailed than that previously published. First, half of children resolve their croup symptoms by 2 days and 90% by 5 days. This differs from a previous publication that 90% resolved croup symptoms in 2 days.[3] Second, most children's symptoms did not worsen following discharge with a minority experiencing worse symptoms in the days following ED discharge. This finding is novel. Third, children diagnosed from September to December take somewhat longer to resolve croup symptoms than those diagnosed from January to May. This finding is also novel, and we speculate it is most likely due to the known and persistent differences in viral aetiology over the calendar year.[17] Fourth, croup places a significant burden on primary caregivers in terms of reported stress, sleep loss and work for wages missed. This expands on a previous report.[5]

Our study has several limitations. First, our prospective cohorts were not completely representative of all children with croup evaluated in the paediatric and general EDs at the time of enrolment. While those enrolled appear to be representative demographically and by season of occurrence, they were more severe, on average, than those not enrolled. Second, dependence on medical chart audit for assessing clinical severity at presentation for the prospective paediatric ED cohort and for all children not enrolled in the prospective cohorts has recognised limitations and therefore is potentially less accurate. This is most likely to be significant for the children in the general EDs who were not enrolled in the prospective cohort as their health record documentation was substantially less complete

than that in the paediatric ED. Three, children with a diagnosis of asthma were excluded from both prospective cohorts. Since children with recurrent croup are known to have asthma,[18] this may have created a potential bias by excluding those children with recurrent croup. Lastly, both cohorts were recruited approximately two decades ago. However, the information on disease progression is likely unchanged given the continuity of croup management and epidemiological and virological patterns up until and following the COVID-19 pandemic. However, for those children whose croup symptoms are caused by SARS-CoV-2, it is possible that they may have different disease patterns.[19]

CONCLUSION

Our results provide the most comprehensive information to date on the course of croup at discharge from care. Clinicians can use our findings to confidently advise caregivers of the expected severity and duration of croup symptoms in children, and provide general guidance as to stress, loss of sleep and loss of work they may experience.

Contributors CLB made substantial contributions to the methodology, data curation and formal analysis. She wrote the first draft of the manuscript and reviewed and edited the manuscript and gave final approval of the version submitted. AN-A made substantial contributions to the methodology, data curation and formal analysis. He wrote sections of the first draft of the manuscript and reviewed and edited the manuscript and gave final approval of the version submitted. JW made substantial contributions to the conceptualisation/design, methodology, investigation, supervision, data curation and resources of the study. She reviewed and edited the manuscript and gave final approval of the version submitted. DWJ made substantial contributions to the conceptualisation/design, methodology, investigation, supervision, funding acquisition, data curation, formal analysis and resources of the study. He reviewed and edited the manuscript and gave final approval of the version submitted. DWJ is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by University of Calgary Conjoint Health Research Ethics Board. REB reference file number: E-101622; University of Calgary and University of Alberta Conjoint Health Research Ethics Board. REB reference file number: B-141001-MED. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Complete datasets for all study cohorts are available.

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