Respiratory Exacerbations in Indigenous Children From Two Countries With Non-Cystic Fibrosis Chronic Suppurative Lung Disease/Bronchiectasis

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BACKGROUND: Acute respiratory exacerbations (AREs) cause morbidity and lung function decline in children with chronic suppurative lung disease (CSLD) and bronchiectasis. In a prospective longitudinal cohort study, we determined the patterns of AREs and factors related to increased risks for AREs in children with CSLD/bronchiectasis.

METHODS: Ninety-three indigenous children aged 0.5 to 8 years with CSLD/bronchiectasis in Australia (n = 57) and Alaska (n = 36) during 2004 to 2009 were followed for > 3 years. Standardized parent interviews, physical examinations, and medical record reviews were undertaken at enrollment and every 3 to 6 months thereafter.

RESULTS: Ninety-three children experienced 280 AREs (median = 2, range = 0–11 per child) during the 3-year period; 91 (32%) were associated with pneumonia, and 43 (15%) resulted in hospitalization. Of the 93 children, 69 (74%) experienced more than two AREs over the 3-year period, and 28 (30%) had more than one ARE in each study year. The frequency of AREs declined significantly over each year of follow-up. Factors associated with recurrent (two or more) AREs included age < 3 years, ARE-related hospitalization in the first year of life, and pneumonia or hospitalization for ARE in the year preceding enrollment. Factors associated with hospitalizations for AREs in the first year of study included age < 3 years, female caregiver education, and regular use of bronchodilators.

CONCLUSIONS: AREs are common in children with CSLD/bronchiectasis, but with clinical care and time AREs occur less frequently. All children with CSLD/bronchiectasis require comprehensive care; however, treatment strategies may differ for these patients based on their changing risks for AREs during each year of care. CHEST 2014; 146(3):762–774

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ABBREVIATIONS: ARE = acute respiratory exacerbation; CF = cystic fibrosis; CSLD = chronic suppurative lung disease; HRCT = high resolution CT

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Chronic suppurative lung disease (CSLD) and bronchiectasis unrelated to cystic fibrosis (CF)¹ are relatively common among indigenous children in both high- and low-income countries.²⁻⁵ One in 68 indigenous children in central Australia⁶ and one in 63 indigenous children in Alaska's Yukon Kuskokwim Delta⁴ have bronchiectasis. In contrast, the prevalence in European children is one in 7,440 among those < 15 years of age.⁷ CSLD and bronchiectasis are both characterized by chronic or recurrent "wet" cough, obstructive lung disease, and recurrent acute respiratory exacerbations (AREs).^{8,9} AREs in people with bronchiectasis are associated with hospitalizations, declining lung function, and reduced quality of life.¹⁰ They have also been used as outcome measures in therapeutic trials in adults¹¹ and children¹² with bronchiectasis. Thus,

understanding factors associated with recurrent and severe AREs is important.

We conducted a longitudinal observational study from 2004 to 2009 of a cohort of indigenous children residing in Australia and Alaska with chronic wet cough who were diagnosed with CSLD or bronchiectasis. As part of that study, we compiled data about AREs on children before and after enrollment. The baseline clinical and socioeconomic features and upper airway microbiology of this group have been published previously.^{13,14} The purpose of this report is to (1) characterize the pattern of AREs in this cohort of children over at least 3 years of observation and (2) identify clinical features that increased the risk of recurrent and severe AREs requiring hospitalization.

Materials and Methods

Study Participants

Australian Aboriginal and Alaska Native children, aged 0.5 to 8 years, with either bronchiectasis confirmed by high-resolution CT (HRCT)^{3,15} scan or CSLD, defined by > 3 months of daily wet cough, were enrolled in the Multicentre Bronchiectasis Study in Australia and Alaska. In the Australian cohort, only children in the placebo arm of a randomized controlled trial nested within the larger study were included in this report.¹² The Australian and Alaska groups were studied concurrently, and definitions for inclusion were chosen a priori for observation during the 5-year period. Figure 1 depicts the enrollment process for eligible children, including those who underwent HRCT scans to diagnose bronchiectasis. Eligible children were identified and recruited sequentially as they presented to their regional pediatric or pulmonary clinics. Children were excluded if they (1) had an underlying cause of bronchiectasis (CF, primary ciliary dyskinesia, or immunodeficiency), (2) received treatment of cancer or diabetes, or (3) had a CNS or neuromuscular disorder that affected respiratory function. Children with at least 3 consecutive years of observation were included to characterize longitudinal trends in AREs.

Human ethics committees and institutional review boards of all participating institutions approved the study (e-Appendix 1). Parents and/or legal caregivers provided written informed consent.

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Measurements

At enrollment, study staff interviewed the parent/guardian to obtain a sociodemographic and medical history. At each study encounter, a pediatric pulmonologist or pediatrician reviewed medical records, performed an interval history and physical examination, and updated a respiratory diagnosis. Participants were seen by research staff every 3 to 6 months. Information from birth to enrollment was obtained retrospectively and from enrollment to end of the study prospectively from medical records. Both study sites provided standard clinical care for participants and nonparticipants, which included antibiotics, chest clearance techniques, asthma therapy when indicated, parental smoking cessation advice, childhood immunizations, nutritional support, and management of exacerbating factors, such as gastroesophageal reflux disease and dysphagia.

As described previously,¹² AREs were defined as acute respiratory-related episodes requiring new antibiotic treatment for any of the following reasons: increased cough, dyspnea, increased sputum volume or color intensity, new chest examination or radiographic findings, deterioration in predicted FEV₁ by > 10%, or hemoptysis. We counted all clinical encounters within 2 weeks as a single ARE. If a second presentation occurred > 14 days after the first, two episodes were counted. All medically attended AREs were captured at community-based clinics and hospitals where participants received all of their medical care. Severe AREs were defined as those needing hospitalization for treatment.

Data Management and Statistical Analysis

Data were entered at each site into a password-protected study database on a secure website. A data manager conducted regular data checks and queries to ensure data completeness and accuracy. Study definitions and procedures were identical for both sites of the study. In addition, investigators and research nurses met regularly via teleconference to discuss study progress.

Data were analyzed using the Statistical Package for Social Science v.20 (IBM) and Stata Statistical Software v13.0 (StataCorp LP). We presented means with SDs for normally distributed data, medians with ranges for nonnormally distributed data, and proportions for categorical data. All statistical tests were two-tailed, with 95% CIs calculated where appropriate. Statistical significance was defined as $P < .05$. Outcomes with ARE count data were modeled using negative binomial regression with robust SEs. Main effects included in the model were as follows: (1) age at enrollment (< 3 and ≥ 3 years), (2) country of enrollment, and (3) wheeze present at first examination. Incidence rate ratios were reported.

Figure 1 – Flowchart of patient enrollment among indigenous children aged 0.5 to 8 y with CSLD/BE. *28 children had < 3 y of follow-up in BOS because they were included in an alternative study, the Bronchiectasis Interventional Study. BE = bronchiectasis; BOS = Bronchiectasis Observational Study; CSLD = chronic suppurative lung disease; HRCT = high-resolution CT.

Binary outcomes were modeled using logistic regression and ORs described. Generalized linear models were used to examine the difference in the number of episodes (any, pneumonia episodes, or hospitalizations) (1) between Australia and Alaska Native children, (2) between children diagnosed with either CSLD or bronchiectasis, and (3) within subjects

(pairwise comparisons) over sequential 1-year time periods. Analyses were adjusted for age at enrollment, country of enrollment, and wheeze during the first physical examination. Epi Info, version 3.5.3 (Centers for Disease Control and Prevention) was used to calculate weight-for-age z-scores.

Results

Patient Enrollment and Clinical Characteristics

One hundred twenty-three Australian Aboriginal and Alaska Native children were recruited; 93 were observed for at least 3 years. Characteristics of the 93 children are listed in Table 1. The age (median = 36 months, range = 9-107 months) and sex distribution (54% boys) at recruitment were similar between sites. The diagnosis at enrollment was chronic wet cough $\pm$ radiographic pulmonary infiltrate in 47 children (51%) and bronchiectasis identified by HRCT scan in 46 children (49%). Eleven of 36 Alaskan Native children (31%) and 35 of 57 indigenous Australian children (61%) had an HRCT scan-confirmed diagnosis of bronchiectasis. Seven of 36 children (20%) in Alaska did not undergo HRCT scans because of limited air travel options.

Children in Australia and Alaska differed in several ways on enrollment (Table 1). Alaskan children were more likely to have prolonged and productive cough and to wheeze than their Australian counterparts. Children in Australia more often had lower weight-for-age z-scores and had undergone HRCT scans that demonstrated bronchiectasis. Children in Alaska were more

likely to receive bronchodilators and inhaled corticosteroids; Australian children were more likely to receive regular antibiotic treatment.

Children with bronchiectasis were younger (median age = 39 months, range = 11-103 months) than children with CSLD (median age = 49 months, range = 22-94 months). However, sex distribution (59% boys of those with bronchiectasis and 49% boys of those without bronchiectasis, $P = .35$) and age of first hospitalization (median = 36 months, range = 19-108 months for bronchiectasis and median = 27.5 months, range = 8-74 months for CSLD; $P = .19$) did not differ between the groups.

AREs Before and After Enrollment

More than 95% of children experienced an ARE in the first year of life. In the 12 months prior to enrollment, 80 of 93 children (86%) had experienced one or more AREs. At enrollment, 48 children (52%) had been hospitalized for an ARE, and 60 children (65%) had been diagnosed with pneumonia. In one-third of children, the first year of life was also part of the year prior to enrollment. Similar proportions of children in Australia and Alaska (30 of 57 [53%] and 18 of 36 [50%], respectively) had been hospitalized for an ARE before enrollment.

TABLE 1 Clinical Features at Enrollment Among 93 Indigenous Children 0.5-8 Years of Age With CSLD/Bronchiectasis by Study Site

Clinical Feature	Australia (n = 57)	Alaska (n = 36)	P Value
Age at enrollment (≤ 3 vs > 3 y)	27 (47)	18 (50)	.805
Male	31 (54)	19 (53)	.880
Female caregiver completed high school ^a	5 (10)	28 (78)	.001
Having smokers in the household ^b	34 (74)	10 (39)	.003
Mother used tobacco in pregnancy ^c	33 (61)	31 (89)	.005
Current cough (past 2 wk)	38 (67)	33 (92)	.006
Productive cough, past 12 mo ^c	24 (45)	26 (72)	.012
Wheeze present at examination ^c	5 (9)	15 (44)	.001
Normal respiratory examination (ticked normal in the baseline visit) ^c	29 (53)	5 (15)	.001
Wheeze in past 12 mo ^d	17 (32)	33 (92)	.001
Regular use of antibiotics ^e	23 (40)	3 (10)	.006
Regular use of bronchodilators ^e	3 (5)	17 (59)	.001
Regular use of corticosteroids ^e	5 (9)	19 (66)	.001
Sputum ^f	17 (31)	24 (75)	.001
Weight-for-age z-scores grouped ^g			
Lowest to 0	44 (82)	9 (27)	.001
0 to highest	10 (19)	25 (74)	...
Needed mechanical ventilation ^c	11 (20)	2 (6)	.120 ^h
Bronchiectasis confirmed by HRCT scan	35 (61)	11 (31)	.004

Data are presented as No. (%). CSLD = chronic suppurative lung disease; HRCT = high-resolution CT.

^aMissing 8.

^bMissing 21.

^cMissing 4.

^dMissing 3.

^eMissing 7.

^fMissing 6.

^gMissing 5.

^hFisher exact test (two-sided) used.

During the 3 years of observation, the 93 children experienced 280 AREs (median = 2, range = 0-11 per child). Ninety-one (32%) AREs were due to pneumonia, and 43 AREs (15%) resulted in hospitalization. Sixty-nine of 93 children (74%) had more than two AREs over the 3-year period of observation. Twenty-eight children (30%) had at least one ARE in each year of observation.

The number of AREs, hospitalizations for AREs, and pneumonia episodes for children at both sites declined progressively over the 3 years of observation. The incident rate ratios of AREs between year 1 and preenrollment and for each year compared with the preceding year were all significantly lower for total AREs, hospitalizations, and AREs presenting as pneumonia (Fig 2). In addition, the overall difference in the number of AREs and episodes of pneumonia between Australia and Alaska were both significantly different ($P < .001$). However, the difference in number of AREs requiring hospi-

talization between Australia and Alaska did not reach significance ($P = .052$). In addition, the decline in frequency of AREs over 3 years occurred similarly among children with HRCT scan-proven bronchiectasis and those with CSLD (Fig 3). The pairwise (within-subject) comparisons between a year of observation and its preceding year were all significantly different (P values $< .001$ to $.029$) except for the difference in pneumonia episodes between year 2 and 3 ($P = .14$). The overall number of AREs was greater among the children with CSLD than those with bronchiectasis ($P = .015$) but not for ARE-related hospitalizations and AREs producing pneumonia ($P = .513$ and $P = .17$, respectively).

Predisposing Factors for Recurrent and Severe AREs

Table 2 lists the factors predisposing to recurrent (two or more) AREs for each year of observation.

Figure 2 – Number of AREs, pneumonia episodes, and hospitalizations per y of study for 93 Australian Aboriginal and Alaska Native children with CSLD/BE. A, $P < .001$ for the overall difference between Australia and Alaska; $P < .001$ for all pairwise comparisons (within subjects) over the different time periods. B, $P = .052$ for the overall difference between Australia and Alaska; $P = .024$ to < 0.001 for all pairwise comparisons over the different time periods. C, $P < .001$ for the overall difference between Australia and Alaska; pairwise comparisons over the different time periods were all $P < .001$ except for differences between years 2 and 3 ($P = .163$). ARE = acute respiratory exacerbation. See Figure 1 legend for expansion of other abbreviation.

Children ≤ 3 years old at enrollment were at significantly greater risk for recurrent AREs. Children with ARE-related hospitalizations in the first year of life and children with a pneumonia or a hospitalization for ARE in the 12 months before enrollment were also at greater risk for recurrent AREs (Table 2). Factors that were not associated with recurrent AREs included household tobacco smoke exposure, regular antibiotic use, and recurrent wheezing. The number of AREs in the 12 months preceding enrollment were also significantly associated with recurrent AREs in the second 12-month observation interval. The only factor associated with recurrent AREs in the third year of observation was young age at enrollment.

Table 3 lists the adjusted ORs for these same clinical factors and the risk of severe ARE resulting in hospitalization for the first 2 years of observation. By the third year of study, only three children were hospitalized, rendering comparisons between hospitalized and nonhospitalized patients meaningless. Age at enrollment, female caregiver education, and regular use of bronchodilators were significantly associated with severe AREs in the first year of follow-up. Children who had a normal respiratory examination at enrollment were significantly less likely to have a severe ARE in the first year of follow-up. The only feature associated with severe AREs in the second year of observations was young age at enrollment.

Figure 3 – Number of AREs, pneumonia episodes, and hospitalizations per y of study for 93 children by diagnosis of CSLD and BE. A, $P = .015$ for the overall difference between children with CSLD and confirmed BE; $P < .001$ for all pairwise comparisons (within subjects) over the different time periods. B, $P = .513$ for the overall differences between children with CSLD and confirmed BE; $P < .001$ for all pairwise comparisons over the different time periods. C, $P = .170$ for the overall difference between children with CSLD and BE; pairwise comparisons over the different time periods ranged from $P = .029$ to $P < .001$, except for the difference between years 2 and 3 ($P = .14$). See Figure 1 and 2 legends for expansion of abbreviations.

TABLE 2] Characteristics Associated With ≥ 2 ARES in the First 12, 12 to 24, and 24 to 36 Mo After Enrollment Among Indigenous Children With CSLD/Bronchiectasis

Characteristic	First 12 Mo After Enrollment			> 12-24 Mo			> 24-36 Mo		
	<2 Episodes (n = 46), No. (%) or Median (Range)	2+ Episodes (n = 47), No. (%) or Median (Range)	Adjusted OR ^a or IRR ^b (95% CI)	<2 Episodes (n = 59), No. (%) or Median (Range)	2+ Episodes (n = 34), No. (%) or Median (Range)	Adjusted OR ^a or IRR ^b (95% CI)	<2 Episodes (n = 71), No. (%) or Median (Range)	2+ Episodes (n = 22), No. (%) or Median (Range)	Adjusted OR ^a or IRR ^b (95% CI)
Baseline visit									
Age at enrollment, ≤ 3 vs > 3 y	15 (33)	30 (64)	4.34 (1.77-10.62)	25 (42)	20 (59)	1.90 (0.77-4.69)	29 (41)	16 (73)	3.90 (1.30-11.69)
Male	25 (54)	25 (53)	0.98 (0.40-2.42)	33 (56)	17 (50)	0.84 (0.34-2.08)	40 (56)	10 (46)	0.74 (0.26-2.10)
Female caregiver completed high school ^c	16 (38)	17 (40)	1.47 (0.36-6.01)	15 (28)	18 (56)	3.68 (0.90-15.10)	21 (31)	12 (67)	3.98 (0.81-19.68)
Having smokers in the household ^d	17 (50)	27 (71)	1.78 (0.55-5.79)	26 (55)	18 (72)	2.07 (0.59-7.24)	34 (60)	10 (67)	1.78 (0.35-9.02)
Mother used tobacco in pregnancy ^e	31 (71)	33 (73)	1.12 (0.39-3.22)	43 (75)	21 (66)	0.36 (0.12-1.09)	47 (68)	17 (85)	2.13 (0.51-9.03)
Premature at birth ^f	9 (23)	15 (34)	2.80 (0.90-8.68)	12 (23)	12 (39)	3.63 (1.16-11.40)	19 (30)	5 (25)	1.36 (0.37-4.95)
< 2,500 g at birth ^g	8 (20)	12 (27)	1.84 (0.59-5.75)	10 (19)	10 (31)	3.23 (1.03-10.08)	15 (23)	5 (23)	1.40 (0.38-5.16)
Mechanical ventilation as a neonate ^e	5 (12)	8 (17)	2.47 (0.66-9.24)	7 (11)	6 (15)	2.27 (0.62-8.23)	9 (13)	4 (18)	2.86 (0.65-12.62)
Breastfed as an infant ^h	37 (82)	32 (71)	0.52 (0.17-1.63)	47 (83)	22 (67)	0.46 (0.15-1.42)	54 (78)	15 (71)	0.78 (0.22-2.81)
First year of life ⁱ									
Had ≥ 1 ARE, all	45 (98)	46 (98)	0.46 (0.03-8.12)	58 (98)	33 (97)	0.29 (0.16-5.17)	69 (97)	22 (100)	...
Median number of AREs, all	4 (0-10) 203 episodes	5 (0-12) 263 episodes	1.21 (0.95-1.54) ^b	4 (0-10) 254 episodes	6 (0-12) 212 episodes	1.35 (1.07-1.71) ^b	4 (0-12) 333 episodes	6 (1-11) 133 episodes	1.17 (0.92-1.48) ^b

(Continued)

TABLE 2] (continued)

Characteristic	First 12 Mo After Enrollment				> 12-24 Mo			> 24-36 Mo	
	<2 Episodes (n = 46), No. (%) or Median (Range)	2+ Episodes (n = 47), No. (%) or Median (Range)	Adjusted OR ^a or IRR ^b (95% CI)	<2 Episodes (n = 59), No. (%) or Median (Range)	2+ Episodes (n = 34), No. (%) or Median (Range)	Adjusted OR ^a or IRR ^b (95% CI)	<2 Episodes (n = 71), No. (%) or Median (Range)	2+ Episodes (n = 22), No. (%) or Median (Range)	Adjusted OR ^a or IRR ^b (95% CI)
Had ≥ 1 ARE, hospitalized	33 (72)	43 (92)	3.86 (1.05-14.17)	44 (75)	32 (94)	4.19 (0.86-20.43)	56 (79)	20 (91)	1.80 (0.34-9.50)
Median number of AREs, hospitalized	2 (0-5) 75 episodes	2 (0-9) 108 episodes	1.34 (0.96-1.86) ^b	2 (0-5) 95 episodes	2 (0-9) 88 episodes	1.51 (1.11-2.06) ^b	2 (0-6) 128 episodes	2 (0-9) 55 episodes	1.25 (0.92-1.71) ^b
Had ≥ 1 pneumonia	34 (74)	38 (81)	1.46 (0.50-4.24)	44 (75)	28 (82)	1.38 (0.46-4.15)	54 (76)	18 (82)	1.10 (0.30-4.04)
Median number of pneumonias	2 (0-6) 90 episodes	2 (0-10) 123 episodes	1.21 (0.84-1.75) ^b	2 (0-6) 123 episodes	2 (0-10) 90 episodes	1.10 (0.79-1.55) ^b	2 (0-8) 149 episodes	2 (0-10) 64 episodes	1.16 (0.78-1.72) ^b
12 mo prior to enrollment ⁱ									
Had ≥ 1 ARE, all	35 (76)	45 (96)	3.96 (0.73-21.50)	48 (81)	32 (94)	2.20 (0.40-12.24)	59 (83)	21 (96)	1.39 (0.14-14.19)
Median number of AREs, all	2 (0-7) 100 episodes	5 (0-13) 246 episodes	1.92 (1.45-2.53) ^b	3 (0-10) 174 episodes	4.5 (0-13) 172 episodes	1.38 (1.08-1.76) ^b	3 (0-10) 240 Episodes	4 (0-13) 106 episodes	1.00 (0.76-1.30) ^b
Had ≥ 1 hospitalized ARE	15 (33)	33 (70)	4.39 (1.56-12.34)	25 (42)	23 (68)	3.17 (1.07-9.93)	33 (47)	15 (68)	1.68 (0.50-5.66)
Median number of AREs, hospitalized	0 (0-3) 20 episodes	1 (0-11) 78 episodes	2.56 (1.43-4.61) ^b	0 (0-4) 41 episodes	1 (0-11) 57 episodes	1.86 (1.10-3.15) ^b	0 (0-6) 61 Episodes	1 (0-11) 37 episodes	1.38 (0.73-2.59) ^b
Child had ≥ 1 pneumonia	22 (48)	38 (81)	3.82 (1.22-11.92)	34 (56)	26 (77)	1.61 (0.51-5.13)	41 (58)	19 (86)	2.52 (0.56-11.37)
Median number of pneumonias	0 (0-4) 40 episodes	2 (0-7) 115 episodes	2.15 (1.43-3.23) ^b	1 (0-6) 80 episodes	2 (0-7) 75 episodes	1.17 (0.82-1.68) ^b	1 (0-6) 99 episodes	2 (0-7) 56 episodes	1.25 (0.84-1.86) ^b
At enrollment									
Current cough, past 2 wk	36 (78)	35 (75)	0.59 (0.18-1.87)	45 (76)	26 (77)	0.59 (0.18-1.9)	52 (73)	19 (86)	1.59 (0.36-6.90)
Wet/productive cough past 12 mo ^e	27 (60)	23 (52)	0.57 (0.21-1.54)	31 (54)	19 (59)	0.78 (0.29-2.11)	37 (54)	13 (65)	0.94 (0.29-3.05)

(Continued)

TABLE 2] (continued)

Characteristic	First 12 Mo After Enrollment			> 12-24 Mo			> 24-36 Mo		
	<2 Episodes (n = 46), No. (%) or Median (Range)	2+ Episodes (n = 47), No. (%) or Median (Range)	Adjusted OR ^a or IRR ^b (95% CI)	<2 Episodes (n = 59), No. (%) or Median (Range)	2+ Episodes (n = 34), No. (%) or Median (Range)	Adjusted OR ^a or IRR ^b (95% CI)	<2 Episodes (n = 71), No. (%) or Median (Range)	2+ Episodes (n = 22), No. (%) or Median (Range)	Adjusted OR ^a or IRR ^b (95% CI)
Wheeze present at examination ^e	9 (21)	11 (24)	0.92 (0.29-2.97)	13 (23)	7 (21)	0.48 (0.14-1.59)	16 (24)	4 (19)	0.40 (0.10-1.62)
Normal respiratory examination (ticked normal in the baseline visit) ^e	18 (42)	16 (35)	1.00 (0.35-2.89)	23 (41)	11 (33)	0.93 (0.32-2.68)	24 (35)	10 (48)	3.37 (0.90-12.55)
Wheeze in past 12 mo ^h	24 (53)	26 (58)	0.81 (0.25-2.63)	27 (47)	23 (70)	1.58 (0.48-5.17)	37 (54)	13 (62)	0.50 (0.11-2.26)
Regular use of antibiotics ^g	15 (36)	11 (25)	0.68 (0.24-1.94)	18 (33)	8 (25)	1.00 (0.34-2.95)	22 (34)	4 (19)	0.72 (0.19-2.70)
Regular use of bronchodilators ^g	5 (12)	15 (34)	4.12 (0.84-20.16)	9 (17)	11 (34)	2.90 (0.60-14.14)	15 (23)	5 (24)	0.37 (0.07-2.16)
Regular use of corticosteroids ^g	6 (14)	18 (41)	4.58 (0.99-21.30)	10 (19)	14 (43)	4.87 (1.05-22.51)	15 (23)	9 (43)	2.39 (0.48-11.84)
Sputum ^{i,k}	21 (48)	20 (47)	0.87 (0.32-2.39)	29 (51)	12 (40)	0.41 (0.14-1.23)	34 (50)	7 (37)	0.36 (0.10-1.34)
Weight for age z-scores grouped ^l									
Lowest to 0	26 (61)	27 (60)	1.36 (0.42-4.40)	37 (67)	16 (49)	0.51 (0.16-1.65)	43 (62)	10 (53)	0.93 (0.22-3.85)
0 to Highest	17 (40)	18 (40)	1.00	18 (33)	17 (52)	1.00	26 (38)	9 (47)	1.00

The time period studied included 0-11 mo and 30 d, 12 mo to 23 mo and 30 d, and 24 mo to 35 mo and 31 d. ARE = acute respiratory exacerbation; IRR = incidence rate ratio. See Table 1 legend for expansion of other abbreviation.

^aMultivariable logistic regression model adjusting for age at enrollment (<3 or ≥3 y), country of enrollment, wheeze present at first examination; ORs were reported.

^bNegative binomial regression model including age at enrollment (<3 or ≥3 y), country of enrollment, and wheeze present at first examination; IRRs were reported.

^cMissing 8.

^dMissing 21.

^eMissing 4.

^fMissing 10.

^gMissing 7.

^hMissing 3.

ⁱFor 41 children (33%) who were <2 y at baseline, the periods of 12 mo prior to enrollment and first year of life may overlap.

^jChildren either coughed up sputum at the last clinic or parents reported presence of sputum.

^kMissing 6.

^lMissing 5.

TABLE 3 Characteristics Associated With ≥ 1 ARE Requiring Hospitalization in the First 12 and ≥ 12 -24 Mo After Enrollment Among Indigenous Children With CSLD/Bronchiectasis

Characteristic	First 12 Mo After Enrollment			> 12 -24 Mo		
	1+ Hosp Episode (n = 28), No. (%) or Median (Range)	No Hosp Episode (n = 65), No. (%) or Median (Range)	Adjusted OR ^a or IRR ^a (95% CI)	1+ Hosp Episode (n = 13), No. (%) or Median (Range)	No Hosp Episode (n = 80), No. (%) or Median (Range)	Adjusted OR ^a or IRR ^a (95% CI)
Baseline visit						
Age at enrollment, ≤ 3 vs > 3 y	20 (71)	25 (39)	4.06 (1.44-11.43)	10 (77)	35 (44)	4.34 (1.09-17.24)
Male	15 (54)	35 (54)	0.76 (0.28-2.10)	6 (46)	44 (55)	0.65 (0.19-2.25)
Female caregiver completed high school ^c	16 (62)	17 (29)	6.70 (1.40-32.14)	6 (46)	27 (38)	1.41 (0.26-7.56)
Having smokers in the household ^d	11 (58)	33 (62)	0.79 (0.22-2.91)	7 (70)	37 (60)	1.48 (0.27-7.99)
Mother used tobacco in pregnancy ^e	21 (78)	43 (69)	1.09 (0.32-3.80)	8 (62)	56 (74)	0.41 (0.10-1.71)
Premature at birth ^f	8 (33)	16 (27)	2.77 (0.79-9.69)	2 (18)	22 (31)	0.69 (0.13-3.76)
Mean full term birth weight $< 2,500$ g ^g	6 (25)	14 (23)	1.16 (0.32-4.21)	2 (18)	18 (24)	0.77 (0.14-4.23)
Mechanical ventilation required as a neonate ^e	4 (16)	9 (14)	2.71 (0.62-11.89)	0 (0)	13 (17)	...
Child was breastfed ^h	18 (67)	51 (81)	0.75 (0.22-2.51)	9 (69)	60 (78)	0.86 (0.20-3.81)
Weight-for-age grouped ⁱ						
Lowest to 0	14 (54)	39 (63)	1.36 (0.35-5.25)	7 (54)	46 (61)	0.98 (0.20-4.91)
0 to Highest	12 (46)	23 (37)	1.00	6 (46)	29 (39)	1.00
First year of life						
Child had ≥ 1 ARE, all	27 (96)	64 (99)	0.08 (0.01-1.61)	13 (100)	78 (98)	...
Median number of AREs (range), all	4.5 (0-11) 154 episodes	5 (0-12) 312 episodes	0.95 (0.76-1.18)	6 (2-10)	4 (0-12)	1.13 (0.90-1.42)
Child had ≥ 1 ARE, hospitalized	25 (89)	51 (79)	1.66 (0.39-7.05)	12 (92)	64 (80)	2.24 (0.26-19.72)
Median number of AREs (range), hospitalized	2 (0-9) 63 episodes	2 (0-6) 120 episodes	1.05 (0.76-1.46)	2 (0-4)	2 (0-9)	1.13 (0.76-1.69)
Child had ≥ 1 pneumonia	24 (86)	48 (74)	1.57 (0.43-5.71)	11 (85)	61 (76)	1.41 (0.26-7.49)
Median number of pneumonia episodes (range)	2 (0-10) 81 episodes	2 (0-8) 132 episodes	1.16 (0.81-1.67)	3 (0-6)	2 (0-10)	1.22 (0.77-1.91)

(Continued)

TABLE 3] (continued)

Characteristic	First 12 Mo After Enrollment			> 12-24 Mo		
	1+ Hosp Episode (n = 28), No. (%) or Median (Range)	No Hosp Episode (n = 65), No. (%) or Median (Range)	Adjusted OR ^a or IRR ^b (95% CI)	1+ Hosp Episode (n = 13), No. (%) or Median (Range)	No Hosp Episode (n = 80), N (%) or Median (Range)	Adjusted OR ^a or IRR ^b (95% CI)
12 mo Prior to enrollment						
Child had ≥ 1 ARE (all)	25 (89)	55 (85)	0.37 (0.06-2.19)	13 (100)	67 (84)	...
Median number of AREs (all)	4.5 (0-13) 149 episodes	3 (0-8) 197 episodes	1.18 (0.91-1.55)	4 (1-10)	3 (0-13)	0.96 (0.69-1.32)
Child had ≥ 1 ARE, hospitalized	21 (75)	27 (42)	3.06 (0.93-10.08)	11 (85)	37 (46)	4.88 (0.87-27.24)
Median number of AREs, hospitalized	1 (0-11) 50 episodes	0 (0-5) 48 episodes	1.42 (0.84-2.39)	1 (0-6)	0 (0-11)	1.70 (0.85-3.37)
Child had ≥ 1 pneumonia	21 (75)	39 (60)	0.56 (0.15-2.08)	11 (85)	49 (61)	1.70 (0.28-10.17)
Median number of pneumonia episodes	3 (07) 74 episodes	1 (0-6) 81 episodes	1.30 (0.88-1.91)	2 (0-6)	1 (0-7)	1.31 (0.87-1.97)
Symptoms and signs at enrollment						
Current cough, past 2 wk	24 (86)	47 (72)	0.91 (0.23-3.67)	12 (92)	59 (74)	2.83 (0.31-25.81)
Productive cough past 12 mo ^e	19 (70)	31 (50)	1.47 (0.48-4.45)	10 (77)	40 (53)	2.47 (0.57-10.71)
Wheeze present at clinical examination ^e	10 (37)	10 (16)	1.85 (0.56-6.11)	4 (31)	16 (21)	1.10 (0.25-4.80)
Normal respiratory examination ^e	4 (15)	30 (48)	0.30 (0.08-0.99)	2 (15)	32 (42)	0.34 (0.07-1.80)
Wheeze in past 12 mo ^h	19 (73)	31 (48)	1.03 (0.26-4.05)	9 (69)	41 (53)	1.15 (0.22-5.98)
Regular use of antibiotics ^g	5 (22)	21 (33)	0.89 (0.25-3.18)	2 (20)	24 (32)	0.66 (0.12-3.79)
Regular use of bronchodilators ^g	11 (48)	9 (14)	8.11 (1.40-47.14)	2 (20)	18 (24)	0.36 (0.04-3.64)
Regular use of corticosteroids ^g	12 (52)	12 (19)	4.60 (0.94-22.51)	4 (40)	20 (26)	1.83 (0.22-15.19)

Hosp = hospital. See Table 1 and 2 legends for expansion of other abbreviations.

^aMultivariable logistic regression model adjusting for age at enrollment (< 3 or ≥ 3 y), country of enrollment, wheeze present at first examination; ORs were reported.^bNegative binomial regression model included age at enrollment (< 3 or ≥ 3 y), country of enrollment, and wheeze present at first examination; IRRs were reported.^cMissing 8.^dMissing 21.^eMissing 4.^fMissing 10.^gMissing 7.^hMissing 3.ⁱMissing 5.

Discussion

This is the first longitudinal prospective study, to our knowledge, describing patterns of AREs among young children with CSLD/bronchiectasis. It is also the first to examine the risks of recurrent and severe AREs in children with these conditions. In this bicountry cohort, we found that those most likely to experience AREs are very young children who have experienced multiple and/or severe AREs (associated with hospitalization) in the first year of life and in the year prior to enrollment. Previous studies involving indigenous and nonindigenous children have reported that bronchiectasis is often preceded by a serious respiratory infection in the first year of life.^{4,16} However, we found that most of these risk factors became less robust in years 2 and 3 of follow-up. We speculate that intervening time, growth, healing, and clinical care reduce the impact of early life events in children with CSLD/bronchiectasis. Although the clinical features and medications for these children in Australia and Alaska differed in several ways, the course of AREs was similar between the sites, with fewer AREs in each subsequent year of observation. This contrasts with preschool-aged children with CF in Australia and New Zealand identified by newborn screening who experience an increase in AREs with each year of life.¹⁷

Children in this cohort included those with bronchiectasis (confirmed by HRCT scan) and those with CSLD. The latter group, which included children who underwent HRCT scan without bronchiectasis and those who did not receive CT scans, were similar to those with confirmed bronchiectasis at baseline except that they were older.¹³ We made the assumption that both groups have impaired airway clearance, increased airway secretions, recurrent lower airway infection, and are managed similarly.^{12,18} We found that both groups had similar historical features prior to enrollment and both experienced fewer AREs in each year of observation while receiving specialty care.

There are few prospective observational cohort studies of children with non-CF bronchiectasis. Those published 40 to 50 years ago did not benefit from HRCT scans, new diagnostic methods to detect underlying conditions, newer potent antibiotics, airway clearance modalities, and improved access to health care.^{19,20} Reports document that AREs in children with bronchiectasis unrelated to CF average 1.5 AREs (range = 0-9) per year.²¹⁻²³ In most studies, the average age at diagnosis of bronchiectasis was 5 to 9 years, but all series included children diagnosed at < 1 year of age.^{4,23-25} One-half of

the children in our study were < 3 years old at enrollment, and our report represents a unique insight into the longitudinal course of children with CSLD/bronchiectasis diagnosed early in life.

There are several implications of our study. First, identifying factors associated with recurrent and severe AREs over time may help determine which children might benefit most from close monitoring and aggressive treatment strategies. Of particular importance are data related to hospitalizations, as these severe AREs have not only cost and social dislocation implications but also represent the sole factor associated with lung function decline in children with bronchiectasis.²² Our data suggest that younger children may benefit from more aggressive care to reduce AREs than older children. Children with severe pulmonary infections and those with recurrent lower respiratory tract infections early in life are more likely to have severe and recurrent AREs for at least 2 years. What constitutes aggressive treatment may be population-specific. Alaskan children had more wheezing and were treated more often with asthma-related medications. There was no association between reduced ARE risk and regular use of antibiotics or corticosteroids. Early treatment regimens for high-risk children will require further study. Second, our findings also indicate that age-matching and control groups are necessary for therapeutic trials in which AREs are an outcome measure of efficacy, given that all participants experienced fewer AREs over time. Last, our data support previous studies^{22,26,27} showing that comprehensive medical care improves outcomes. Data from several retrospective cohort studies have shown that optimized respiratory care improves initial lung function and prevents medium-term lung function decline.^{22,26,27}

This study has several limitations. Although AREs were defined a priori, the definition was intentionally broad and based on the variable features of an ARE in children with HRCT scan-confirmed bronchiectasis.²⁸ Using the decision to start new antibiotics has been used previously to evaluate long-term antibiotic use in children with bronchiectasis.¹² The second limitation is that we studied only indigenous populations in two regions. Given their high prevalence of CSLD and bronchiectasis, these results may not apply to other children in developed countries. In addition, observation bias may exist, as different research team members collected data, and interview questions were not validated in each setting. We sought to minimize this bias by using standardized data collection forms and structured interview

questions. In addition, the presence of tobacco smoke exposure was obtained by history alone and may be underreported by the families. Finally, information about medical history before enrollment was obtained retrospectively and, therefore, subject to coding and interpretive uncertainties. However, all episodes of AREs were obtained from medical chart review using the same ARE definition.

This study has identified clinical and historical features that are associated with recurrent and severe AREs among children with CSLD/bronchiectasis. Ideally, this information can be used to individualize treatments in young children with either diagnosis. In future studies, risk factors that influence other clinical outcomes, such as lung function tests and radiographic severity of disease, will help to individualize care further.

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Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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