Long-Term Neurodevelopmental and Functional Outcomes of Normally Developing Children Requiring PICU Care for Bronchiolitis

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Abstract

Bronchiolitis is a common pediatric intensive care unit (PICU) illness and often affects generally healthy children, making it a promising disease in which to study long-term neurodevelopmental outcomes. We previously found that approximately 15% of critical bronchiolitis patients have evidence of post-PICU morbidity using coarse definitions available in administrative data sets. In this study, we measured neurodevelopmental outcomes using four more precise tools. Children who had previously been admitted to our PICU with bronchiolitis were included; those with evidence of developmental delay at PICU admission were excluded. Approximately 1 to 2 years after PICU discharge, the parent of each subject completed two questionnaires (Ages and Stages Questionnaire and Pediatric Evaluation of Disability Inventory Computer Adaptive Test). Each subject also underwent two in-person assessments administered by a certified examiner (Bayley Scales of Infant and Toddler Development, 3rd edition, and the Amiel-Tison neurological assessment). For each domain of each test, a score of > 1 standard deviation below the norm for the subject's age defined "moderate" disability and a score ≥ 2 standard deviations below the norm defined "severe" disability. Eighteen subjects (median ages of 3.7 months at PICU admission and 2.3 years at testing) were enrolled, 17 of whom were supported by high-flow nasal cannula and/or mechanical ventilation. Fifteen children (83%) scored abnormally on ≥ 1 test. Eight children (44%) had disabilities in ≥ 3 domains and/or ≥ 1 severe disability identified. Our findings that motor, language, and cognitive disabilities are commonly observed months to years after critical bronchiolitis require larger studies to confirm this finding, assess causality, and identify modifiable risk factors.

Keywords

- pediatrics
- critical care
- post-intensive care syndrome

Introduction

Mortality among children admitted to a pediatric intensive care unit (PICU) has decreased over time, leading many research programs to shift focus toward understanding and

improving the long-term outcomes of PICU survivors.¹ The prevalence of post-PICU morbidity, often termed the post-intensive care syndrome (PICS), has not been precisely established in children due to variability in definitions,

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assessed time points, and patient characteristics, and published rates range from 3 to > 60%.^{2,3} The study of post-PICU outcomes can be confounded by comorbidities that existed before PICU admission that may independently cause long-term morbidities, such as cancer and congenital heart disease.^{4,5} In addition, heterogeneous PICU research cohorts may include children with an acute, primary brain injury (e.g., meningitis, traumatic brain injury) that causes morbidity independent of care provided in the PICU.^{6,7} To identify modifiable PICU care practices that impact long-term morbidity, it may be advantageous to study previously healthy children with a prevalent, nonneurologic critical illness.

Bronchiolitis is one of the most common indications for PICU admission, often affects generally healthy children, and is only infrequently associated with direct neurologic insults.^{8,9} Children with critical bronchiolitis are often exposed to many purported risk factors of PICS during PICU care, including sedative medications, mechanical ventilation, bed rest/deconditioning, inflammation, hypercarbia, and hypoxemia.^{10–12} We previously reported that approximately 15% of critical bronchiolitis patients have evidence of post-PICU morbidity using two multicenter, predominantly administrative databases.¹³ However, that estimate relied on crude measures of morbidity such as receipt of rehabilitation services and performance of neuroimaging. In this study, we used more precise tools to assess the long-term outcomes of initially normally developing children who had survived critical bronchiolitis. The overall hypothesis of our research program is that a substantial number of survivors of critical bronchiolitis have unfavorable neurodevelopmental and functional outcomes that may be modifiable, and this descriptive study intends to better characterize their long-term outcomes.

Methods

With approval from the Institutional Review Board of University Hospitals of Cleveland, the parents of eligible children who were previously admitted to our PICU between January 2015 and April 2018 were contacted via postal mail. Inclusion criteria were (1) PICU admission at age < 2 years with a diagnosis of bronchiolitis and (2) age 18 to 36 months at the time of invitation to this study. Children who were already > 36 months at the onset of this study were excluded given the preferred ages to perform some of the tests used in this study. Additional exclusion criteria were (1) abnormal developmental status at the time of PICU admission and (2) any subsequent PICU admission after the index bronchiolitis admission. Both exclusion criteria were evaluated via review of the child's electronic medical record by the primary author (e.g., any mention of "developmental delay" or similar terms in the PICU "history and physical" physician note) and confirmed by questioning the parents before scheduling testing for this study.

Eligible subjects whose parents consented to participation returned to the hospital and underwent a battery consisting of four previously established tests: 1) the Bayley Scales of Infant and Toddler Development, 3rd edition (Bay-

ley-III), (2) the Ages and Stages Questionnaire, 3rd edition (ASQ), (3) the Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CT), and (4) the Amiel-Tison neurological assessment (Amiel-Tison).

Characteristics of Tests Used

The Bayley-III is the recognized standard for measuring infant development between early infancy and 42 months of age.¹⁴ Subjects participate in a series of developmental play tasks that are administered in-person and scored by a trained examiner. The Bayley-III was used in this study to assesses three domains (cognitive, language, motor), each yielding an overall score with a mean of 100 and standard deviation of 15. The scores are used to determine the child's developmental functioning compared with a normative sample of same-aged children. All Bayley-III examinations were performed by a certified examiner (E.R.) who is required to complete annual competency recertification.

The ASQ is a validated questionnaire that consists of 30 questions answered by parents and divided into five domains (communication, fine motor, gross motor, problem solving, personal-social).¹⁵ Parents may select responses of yes, sometimes, or not yet for each question (e.g., does your child jump with both feet leaving the floor at the same time?). The ASQ is specific for the child's age, so that all 24-month-old children are evaluated with the same 30 questions but a different set of questions is used for a 27-month-old child.

The PEDI-CT is a validated electronic questionnaire that consists of a series of questions answered by the parent on a tablet device that provides scores in three domains (daily activities, mobility, and social-cognitive).¹⁶ Parents may choose one of four responses (unable, hard, a little hard, easy) about how difficult it is for their child to perform a specific task (e.g., put on socks). The PEDI-CT is an adaptive test, so that the content and number of questions is based on the parent's previous responses. The PEDI-CT questionnaire ends once the software determines that a stable score has been achieved in all three domains.

Trained clinicians can use the Amiel-Tison scale of the pediatric neurologic examination to measure the progressive increase in active tone (head control, back support, sitting, standing, and walking) and concomitant decrease in passive muscle tone during the first 2 years of life.¹⁷ The method gives a qualitative assessment of neurologic integrity, which is scored as normal, suspect, or abnormal. All Amiel-Tison examinations in this study were performed by a certified examiner (D.W.-C.) who is required to complete annual competency recertification.

Definitions of Disability

For the Bayley-III, a score of 70 to 84 (> 1 standard deviation below the age-appropriate norm) in any domain defines moderate disability and a score < 70 (≥ 2 standard deviations below the norm) in any domain defines severe disability.^{18,19} Similarly, for the ASQ and PEDI-CT, we used any score > 1 or ≥ 2 standard deviations below the norm for the subject's age to define moderate and severe disability, respectively. For the Amiel-Tison, suspect is defined as

abnormal passive muscle tone or reflexes without functional impairment and abnormal is defined as abnormal passive muscle tone or reflexes with functional impairment.

Demographics, comorbidities, use of respiratory support modalities, and length of stay (LOS) were collected from the electronic records of the child's PICU stay. Laboratory results and vital signs from early in the PICU course that were collected to calculate PRISM-3 scores were extracted. Descriptive statistics were used with results reported as *n* (%) and median (interquartile range). A sample size was not formally calculated as this is a descriptive study.

Results

We mailed study materials to the families of 232 potentially eligible subjects and 18 (8%) children completed the study. All enrolled children had the absence of developmental delay at the time of PICU admission confirmed both by chart review and parental interview. At PICU admission, median age was 3.7 (1.0–8.5) months (►Table 1). Four children had

Table 1 Characteristics of the cohort at PICU admission and long-term outcome testing

Variable	<i>n</i> (%) or median (IQR)
Age at admission, mo	3.7 (1.0–8.5)
Female	4 (22%)
Race	
African-American	10 (56%)
Caucasian	8 (44%)
Past medical history at PICU admission	
Premature birth	4 (22%)
Congenital heart disease	1 (6%) ^a
Other congenital malformation	0 (0%)
Cancer	0 (0%)
Genetic disorder	0 (0%)
Metabolic disorder	0 (0%)
Fever ($\geq 38.5^{\circ}\text{C}$) ^b	3 (17%)
Leukocytosis ($> 15,000$ WBC per mm^3) ^b	2 (11%)
Thrombocytosis ($> 500,000/\mu\text{L}$) ^b	1 (6%)
Hyperglycemia (> 200 mg/dL) ^b	1 (6%)
Systolic hypotension (< 70 mm Hg) ^b	0 (0%)
PICU length of stay, d	2.6 (1.8–3.7)
Hospital length of stay, d	4.4 (3.3–6.3)
Interval between PICU admission and testing, y	1.8 (1.7–2.2)
Age at testing, y	2.3 (1.9–2.8)

Abbreviations: IQR, interquartile range; PICU, pediatric intensive care unit; WBC, white blood cell.

^aPatent ductus arteriosus.

^bCollected as part of PRISM-3 score.

comorbid conditions identified, all of whom were born prematurely. Two additional children had previously required hospitalization to the general ward for bronchiolitis. Three children were febrile early in their PICU course and three others had laboratory evidence of inflammation (leukocytosis, thrombocytosis, or hyperglycemia). During PICU admission, 17 children received high-flow nasal cannula (HFNC) support for a median duration of 48 (20–56) hours, two of whom also received invasive mechanical ventilation (IMV) (►Table 2). Of the 15 children who received HFNC but not IMV, median peak flow was 8 (8–10) liters per minute with concurrent maximum oxygen fractions of 0.40 (0.33–42.5). Duration of IMV was 4.5 and 5.8 days in the two subjects who received it, both of whom were born prematurely. Venous blood gases showed respiratory acidosis ($\text{pH} < 7.20$ and $\text{PCO}_2 \geq 80$) in both subjects. The worst ratios of oxygen saturation to inspired oxygen fraction (S:F ratio) for these two children were 108 and 142. Both IMV patients received narcotics and benzodiazepines; one also received chloral hydrate and the other also received dexmedetomidine.

The median interval between PICU admission and testing was 1.8 (1.7–2.2) years and median age at testing was 2.3 (1.9–2.8) years. In each of the three multidomain tests (►Fig. 1), disabilities were most commonly seen in the language-related domain (ASQ: communication, PEDI-CT: social-cognitive, Bayley-III: language). Overall, 15 children (83%) scored abnormally on at least one test (►Tables 3–5). Seven of these children (39%) had only 1 or 2 abnormal scores that were all at the moderate/suspect level. Eight children (44%) had disabilities in ≥ 3 domains and/or ≥ 1 severe disability identified. All 8 of those children had disability in both a purely motor domain (ASQ: fine/gross motor, PEDI-CT: mobility, Bayley-III: motor, Amiel-Tison) and at least one additional domain (e.g., cognitive, language). Seven of these 8 children had disabilities identified using 2 or more of the tests.

All 4 children born prematurely had disabilities identified in more than 1 domain. Of the 14 children born at term, 5 (36%) had disabilities in ≥ 3 domains and/or ≥ 1 severe disability identified. For both the 3 subjects with no disabilities and the 8 subjects with severe/numerous disabilities, the median age at PICU admission was 5.0 months. For the children with 1 or 2 moderate/suspect disabilities, the median age at PICU admission was 2.5 months.

Discussion

In this small cohort of children with grossly normal development at the time of PICU admission for bronchiolitis, we commonly identified motor, language, and cognitive disabilities months to years after critical illness. Nearly half of the subjects had disabilities noted in multiple domains and by using multiple testing techniques. Though our methods preclude any establishment of causality, our findings nonetheless show that some PICU patients with bronchiolitis have long-term unfavorable outcomes, even when development appears grossly normal at PICU admission. Larger studies are

Table 2 Patient-specific variables: demographics and clinical information

Patient	Admission age (mo)	Age at testing (y)	Gender	Race	Comorbidity	Peak respiratory support
1	< 1	1.8	Male	Caucasian	None reported	HFNC
2	< 1	1.8	Male	Caucasian	None reported	None
3	1	3.2	Female	African American	None reported	HFNC
4	1	1.9	Male	Caucasian	None reported	HFNC
5	1	2.5	Male	Caucasian	None reported	HFNC
6	1	1.9	Male	Caucasian	Prematurity (36 wk)	HFNC
7	2	2.5	Male	African American	Prematurity (32 wk)	HFNC
8	2	1.8	Male	Caucasian	None reported	HFNC
9	3	2.1	Male	African American	None reported	HFNC
10	3	2.1	Male	Caucasian	None reported	HFNC
11	5	3.7	Male	African American	None reported	HFNC
12	7	3.3	Male	African American	None reported	HFNC
13	7	1.8	Male	African American	None reported	HFNC
14	9	2.8	Female	African American	Prematurity (24 wk)	IMV
15	10	2.8	Female	African American	Prematurity (26 wk), PDA	IMV
16	11	2.1	Male	African American	None reported	HFNC
17	14	3.4	Male	Caucasian	None reported	HFNC
18	18	2.4	Female	African American	None reported	HFNC

Abbreviations: HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation; PDA, patent ductus arteriosus.

warranted to confirm this finding, assess causality, and identify modifiable risk factors.

This is not the first study to report unfavorable long-term outcomes after critical bronchiolitis. Among 35 children requiring PICU care for bronchiolitis between 1992 and

1994, > 25% had a “fair” or worse quality of life as measured using the Royal Alexandra Hospital for Children Measure of Function between 3 and 24 months after PICU discharge, though changes in practice over the interceding two decades may limit comparison.²⁰ Our group previously used the

Fig. 1 Distribution of scores among test-domains. For each domain of each test, the number of children with scores in the normal range (black), moderate disability range (dark gray), and severe disability range (light gray) is shown. One child was unable to complete the Bayley-Language and Bayley-Motor tests.

Table 3 Patient-specific outcomes: scores on ASQ

Patient	Ages and Stages Questionnaire				
	Communication	Gross motor	Fine motor	Problem solving	Personal-social
1	20 ^a	10 ^b	45	40	50
2	60	40	40	45	40
3	60	55	45	60	60
4	30	50	40	50	55
5	55	55	30 ^a	30 ^a	50
6	20 ^a	35 ^a	50	50	55
7	55	45 ^a	20 ^a	55	40 ^a
8	30	55	50	55	60
9	30 ^a	50	40 ^a	30 ^a	35 ^a
10	60	60	60	40	60
11	60	60	50	50	60
12	30 ^a	60	50	40	55
13	55	55	45	40	50
14	30 ^b	30 ^b	40	25 ^b	45
15	20 ^b	30 ^b	30 ^a	20 ^b	60
16	45	40	45	55	35 ^a
17	45	55	15 ^b	55	45
18	60	50	50	55	50

Abbreviation: ASQ, Ages and Stages Questionnaire.

^aModerate disability.

^bSevere disability.

Pediatric Health Information Systems database to evaluate for evidence of neurofunctional morbidity after hospital discharge among PICU patients with bronchiolitis.¹³ We identified evidence of morbidity in 12% of subjects that included use of rehabilitation services and feeding tubes after hospital discharge from their PICU admission. Given the high prevalence of critical bronchiolitis, there is urgent need to prospectively evaluate the long-term outcomes of these children using granular testing.

There are multiple reasons why a child with critical bronchiolitis may have unfavorable developmental outcomes. First, children with critical bronchiolitis may have preexisting developmental delay. In a recent study, 5% of young children with acute respiratory infections had neurological disorders.⁸ However, our study was designed to exclude children with developmental delay at the time of PICU admission. Second, the viruses that cause bronchiolitis may directly harm the central neurologic system. Respiratory syncytial virus, the most common cause of bronchiolitis, impairs learning in mice and has been detected in cerebrospinal fluid during human bronchiolitis.^{21,22} Third, children with critical bronchiolitis may be exposed to a litany of factors related to illness severity and/or critical care that may cause neurofunctional morbidity, including hypoxia, hypercarbia, sedative medications, hypotension, inflammation, mechanical ventilation, and others.^{9,11,23} These factors are more modifiable, and therefore may be more appropriate

targets of studies aiming to improve long-term outcomes. Several of the subjects in our study had one or more of these conditions documented, and others may have had exposures that were not captured in our retrospective study. It is possible that the deleterious effects of these exposures begin before PICU admission and may continue after it, which may in part explain how children with a median PICU LOS of 2.6 days commonly had abnormal outcomes. Future work should consider the effects of pre- and post-PICU factors as well.

We evaluated long-term developmental outcomes using four different tests, each with different properties. Both ASQ and PEDI-CT rely on parental responses, while the Bayley-III and Amiel-Tison are direct assessments of the child's skills by a trained professional. We identified disabilities with both approaches. Seven of the eight children with disabilities in ≥ 3 domains and/or ≥ 1 severe disability had abnormal scores obtained by both parental response and direct evaluation. Interestingly, only two children had disabilities identified by PEDI-CT, and the relative inability of this parental questionnaire to identify pediatric disability increases the importance of direct measures of long-term outcomes after PICU care. Future studies should aim to better understand how the performance of different tools compares in children recovering from critical illness.

This is the first detailed assessment of long-term developmental outcomes of previously normally developing children with critical bronchiolitis. However, our study has

Table 4 Patient-specific outcomes: scores on PEDI-CT and Bayley-III

Patient	Pediatric Evaluation of Disability Inventory			Bayley Scales of Infant Development-III		
	Daily activities	Mobility	Social-cognitive	Cognitive	Language	Motor
1	52	49	53	95	77 ^a	73 ^a
2	58	59	57	85	100	94
3	51	49	34 ^a	90	103	94
4	58	54	52	110	103	97
5	49	56	47	90	89	82 ^a
6	55	55	53	105	106	91
7	54	56	50	95	97	88
8	59	58	54	85	74 ^a	82 ^a
9	53	59	50	70 ^a	59 ^b	85
10	60	63	56	105	83 ^a	91
11	63	58	54	95	97	110
12	50	63	45	80 ^a	83 ^a	88
13	51	57	54	85	94	85
14	50	49	49	75 ^a	71 ^a	76 ^a
15	52	48	44	65 ^b	74 ^a	70 ^a
16	82	57	45	85	91	91
17	40	60	36 ^a	95	Noncooperative	Noncooperative
18	56	57	54	90	100	82 ^a

Abbreviations: Bayley-III, Bayley scales of infant and toddler development, 3rd edition; PEDI-CT, pediatric evaluation of disability inventory computer adaptive test.

^aModerate disability.

^bSevere disability.

Table 5 Patient-specific outcomes: scores on Amiel-Tison and overall

Patient	Amiel-Tison	Number of abnormal test domains	
		Moderate/suspect	Severe/abnormal
1	Abnormal	3	2
2	Suspect	1	0
3	Normal	1	0
4	Normal	0	0
5	Normal	3	0
6	Normal	2	0
7	Normal	3	0
8	Normal	2	0
9	Normal	5	1
10	Suspect	2	0
11	Normal	0	0
12	Normal	3	0
13	Normal	0	0
14	Normal	3	3
15	Normal	3	4

(Continued)

Table 5 (Continued)

Patient	Amiel-Tison	Number of abnormal test domains	
		Moderate/suspect	Severe/abnormal
16	Normal	1	0
17	Normal	1	1
18	Normal	1	0

several limitations. First, our sample size is modest, precluding analyses to identify factors associated with unfavorable outcomes. However, it is still the largest cohort of critical bronchiolitis survivors undergoing detailed testing of long-term developmental outcomes. Second, it may be a biased sample, as parents with concerns about their child's development may have been more likely to respond to the study invitation. For these reasons, we only reported descriptive statistics and did not formally test the hypothesis that subjects' scores are worse than normal using statistical methods. Both of these limitations may be addressed in future larger studies that prospectively enroll subjects at PICU admission. Third, it is not possible to evaluate causality, and it is possible that the disabilities identified were

unrelated to the child's critical illness. This includes the possibility that some subjects had developmental delay prior to PICU admission that was not identified using either the chart review or parental interview. Significant delay is a risk factor for severe bronchiolitis and would warrant documentation in a PICU admission note, but the absence of documentation does not confirm the absence of delay. Thus, our findings are best interpreted as hypothesis-generating and best used in the design of future studies.

In conclusion, among 18 children who were developing normally at the time of PICU admission for critical bronchiolitis, only three had completely normal scores on developmental tests performed approximately 1 to 2 years later. Eight children had multiple and/or severe disabilities identified. Larger, prospective studies are needed to better establish the incidence and causality of unfavorable developmental outcomes after critical bronchiolitis, compare parent-reported outcomes to objective direct measures, and to identify modifiable risk factors that may eventually lead to improved long-term outcomes.

Conflict of Interest
None declared.

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