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Community-Acquired Pneumonia Hospitalization among Children with Neurologic Disorders

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Objective To describe and compare the clinical characteristics, outcomes, and etiology of pneumonia among children hospitalized with community-acquired pneumonia (CAP) with neurologic disorders, non-neurologic underlying conditions, and no underlying conditions.

Study design Children <18 years old hospitalized with clinical and radiographic CAP were enrolled at 3 US children's hospitals. Neurologic disorders included cerebral palsy, developmental delay, Down syndrome, epilepsy, non-Down syndrome chromosomal abnormalities, and spinal cord abnormalities. We compared the epidemiology, etiology, and clinical outcomes of CAP in children with neurologic disorders with those with non-neurologic underlying conditions, and those with no underlying conditions using bivariate, age-stratified, and multivariate logistic regression analyses.

Results From January 2010-June 2012, 2358 children with radiographically confirmed CAP were enrolled; 280 (11.9%) had a neurologic disorder (52.1% of these individuals also had non-neurologic underlying conditions), 934 (39.6%) had non-neurologic underlying conditions only, and 1144 (48.5%) had no underlying conditions. Children with neurologic disorders were older and more likely to require intensive care unit (ICU) admission than children with non-neurologic underlying conditions and children with no underlying conditions; similar proportions were mechanically ventilated. In age-stratified analysis, children with neurologic disorders were less likely to have a pathogen detected than children with non-neurologic underlying conditions. In multivariate analysis, having a neurologic disorder was associated with ICU admission for children ≥2 years of age.

Conclusions Children with neurologic disorders hospitalized with CAP were less likely to have a pathogen detected and more likely to be admitted to the ICU than children without neurologic disorders. *(J Pediatr 2016;173:188-95)*.

Pneumonia is a leading cause of pediatric hospitalization in the US.[1-3] Although children with neurologic disorders—a diverse spectrum of conditions including epilepsy, neurodevelopmental disorders, and neuromuscular disorders—comprise a small proportion of the US pediatric population,[4-6] this group is particularly vulnerable to severe complications and death from respiratory failure.[7-13] Causes of respiratory failure in these children are multifactorial and include pulmonary scarring from recurrent aspiration, ineffective cough, and chest wall or spinal abnormalities prohibiting maximal chest expansion.[9,11,14,15] Specifically, children with neurologic disorders also are at increased risk of complications and death from influenza virus and respiratory syncytial virus (RSV) infection.[16-21] However, data from prospective clinical studies describing community-acquired pneumonia (CAP) in children with neurologic disorders are limited.

We used data from the Centers for Disease Control and Prevention Etiology of Pneumonia in the Community (EPIC) study,[3] a prospective, multicenter, population-based, active surveillance study, to describe and compare the clinical characteristics, outcomes, and pneumonia etiology among children hospitalized with CAP with neurologic disorders, non-neurologic underlying conditions, and no underlying conditions.

CAP	Community-acquired pneumonia
EPIC	Etiology of Pneumonia in the Community
ICU	Intensive care unit
LOS	Length of stay
RAD	Reactive airway disease
RSV	Respiratory syncytial virus

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Methods

From January 1, 2010 to June 30, 2012, children <18 years old were enrolled in the EPIC study at Le Bonheur Children's Hospital (Memphis, Tennessee), Monroe Carell Jr Children's Hospital at Vanderbilt (Nashville, Tennessee), and Primary Children's Hospital (Salt Lake City, Utah).[3] Informed consent was obtained before enrollment. The study protocol was approved by the institutional review boards at each institution and the Centers for Disease Control and Prevention.

Children admitted to the study hospitals with signs of acute infection, respiratory symptoms, and chest radiography consistent with pneumonia within 72 hours of admission were eligible for enrollment.[3] A dedicated study radiologist at each study hospital independently reviewed chest radiography for final determination of radiographic pneumonia.[3] Children were excluded if they were recently hospitalized (<7 days for immunocompetent children, <90 days for immunosuppressed children), enrolled in the EPIC study <28 days earlier, resided in an extended care facility, had a clear alternative respiratory diagnosis, were newborns who never left the hospital, or had any of the following conditions: tracheostomy, cystic fibrosis, cancer with neutropenia, solid organ or hematopoietic stem cell transplant ≤90 days earlier, active graft vs host disease or bronchiolitis obliterans, or HIV with CD4 cell count <200 cells/mm^3 (or CD4% <14%).

The methods for data collection, specimen collection, laboratory testing, and definitions for pathogen detection have been previously described.[3] Data on underlying medical conditions, including neurologic disorders, were collected through a patient/caregiver interview and medical chart review. Blood and respiratory samples were collected from patients and tested for bacterial and viral pathogens by multiple modalities including bacterial culture, real-time polymerase chain reaction, and serology with methods as previously described.[3]

We identified 3 distinct groups for analysis: children with neurologic disorders, children with non-neurologic underlying conditions, and children with no underlying conditions. We categorized disorders as neurologic disorders based on literature review.[16,22] In addition, we consulted with a behavior-development pediatrician (G.P.) to assist with categorizing neurologic disorders. Only those with possible neurologic sequelae attributable to the neurologic disorder as indicated from the literature were categorized as neurologic disorders. We defined neurologic disorders as a diagnosis of cerebral palsy, developmental delay, Down syndrome and non-Down syndrome chromosomal abnormalities, epilepsy, spinal cord abnormalities, and other neurologic disorders; if a child had a neurologic disorder and another non-neurologic underlying condition, he or she was categorized as having a neurologic disorder. Non-neurologic underlying conditions included asthma/reactive airway disease (RAD), other chronic lung disease, chronic kidney disease, chronic liver disease, congenital heart disease, diabetes mellitus, immunosuppressive conditions (either because of chronic conditions, medication use, HIV-infection with CD4 cell count >200 cells/mm^3, and nondermatologic malignancies), and pre-term birth (in those aged <2 years old, defined as born at <37 weeks gestation). Those with no underlying conditions were defined as not having a neurologic disorder or a non-neurologic underlying condition.

Statistical Analyses

We describe the type and frequency of neurologic disorders occurring among children hospitalized with CAP and enrolled in the EPIC study. We compared epidemiologic and clinical characteristics, outcomes, and pathogens detected among children with neurologic disorders, non-neurologic underlying conditions, and no underlying conditions. Our primary outcome of clinical severity was intensive care unit (ICU) admission. We also examined other clinical outcomes including hospital length of stay (LOS), ICU LOS, invasive mechanical ventilation requirement and duration, receipt of vasopressors within 72 hours of ICU admission, and death. We performed bivariate and separate age-stratified analyses comparing the characteristics between children with neurologic disorders vs non-neurologic underlying conditions, and neurologic disorders vs no underlying conditions. In addition, we conducted subgroup analyses comparing the clinical outcomes of the subset of children with neurologic disorders and no other non-neurologic underlying conditions to the outcomes of children with non-neurologic underlying conditions and no underlying conditions; however, for our primary analysis, the neurologic disorders group includes children with a neurologic disorder who may also have non-neurologic disorders because there were few differences in the outcomes between these groups and because of sample size. We performed multivariable logistic regression using stepwise elimination to further investigate clinical outcomes found to be more common among children with neurologic disorders; covariates for the regression models were based on significance on bivariate analysis and epidemiologic or biological plausibility.

Data were analyzed using SAS version 9.3 (SAS Institute, Cary, North Carolina). The χ^2 or Fisher exact tests were used to compare proportions and the Wilcoxon rank sum test was used to evaluate distribution differences between continuous variables. All comparisons were 2-sided, and P values of <.05 was considered significant.

Results

Over the 2.5-year study period, 2638 (69.4%) of 3803 eligible children were enrolled; among which, 2358 (89.4%) children had radiographic CAP. Two hundred eighty (11.9%) of 2358 children had a neurologic disorder, 934 (39.6%) had non-neurologic underlying conditions only, and 1144 (48.5%) had no underlying conditions. Among the 280 children with neurologic disorders, 146

(52.1%) had another non-neurologic underlying condition. **Table I** (available at www.jpeds.com) shows the types and frequencies of neurologic disorders among children hospitalized with CAP. Epilepsy was the most commonly reported neurologic disorder, occurring in 121 (43.2%) children; 82 (67.8%) of whom had another neurologic disorder in addition to epilepsy, the most common of which was cerebral palsy. Down syndrome was reported in 75 (26.8%) children with neurologic disorders.

Children with neurologic disorders were significantly older (median: 4.2 years, IQR: 1.7-9.8 years) than those with non-neurologic underlying conditions (median: 2.7 years, IQR: 1.3-6.2 years) and those with no underlying conditions (median: 1.8 years, IQR: 0.8-4.8 years). Children with neurologic disorders were significantly more likely than children with non-neurologic underlying conditions to have congenital heart disease (30.4% vs 9.3%) and chronic lung disease (12.5% vs 6.3%) but were less likely to have asthma/RAD (29.6% vs 74.5%) (**Table II**).

The presence of respiratory symptoms and fever on presentation was similar among all children, however, compared with children with non-neurologic underlying conditions and no underlying conditions, children with neurologic disorders were significantly more likely to have reported symptoms of seizures, as well as hypoxia and altered mental status documented on clinical examination (**Table II**). Of those with verified vaccination status, the proportion of children who received pneumococcal and *Haemophilus influenzae* type b vaccination was high in all 3 groups, ranging from 80.1%-86% (**Table II**); the proportion of children who received influenza vaccination was low in all 3 groups but significantly higher among children with neurologic disorders (41.7%) than those with non-neurologic underlying conditions (27.3%) or no underlying conditions (28.7%).

Children with neurologic disorders were significantly less likely to have a respiratory pathogen detected (69.4%) compared with children with non-neurologic underlying conditions (84.4%) and those with no underlying conditions (81.4%) (**Table III**). RSV was identified significantly less frequently in children with neurologic disorders (17.6%) compared with both children with non-neurologic underlying conditions (27.8%) and no underlying conditions (30.7%). Adenovirus also was significantly less commonly detected among children with neurologic disorders (5.4%) vs those with non-neurologic underlying conditions (12.9%) and no underlying conditions (11.2%). In addition, rhinovirus was significantly less commonly detected among children with neurologic disorders (24.8%) compared with children with non-neurologic underlying conditions (35.5%) but was similarly detected among children with no underlying conditions (22.2%). The proportions of bacterial detections were similar among all 3 groups except for *Streptococcus pneumoniae*, which was similar among children with neurologic disorders (1.9%) and non-neurologic underlying conditions (2.1%) but significantly more commonly detected in children with no underlying conditions (5.1%). In age-stratified analysis, the frequency of any pathogen detection decreased with increasing age in all comparison groups (**Table IV**; available at www.jpeds.com).

Children with neurologic disorders were significantly more likely to have longer hospital LOS compared with children with non-neurologic underlying conditions and no underlying conditions. Children with neurologic disorders were significantly more likely to be admitted to the ICU (36.4%) than those with non-neurologic underlying conditions (19.8%) and no underlying conditions (18.4%) (**Table V**). **Table VI** (available at www.jpeds.com) shows the characteristics of children hospitalized with CAP admitted to the ICU. The proportion of children requiring invasive mechanical ventilation was similar in all 3 groups (28.1%-38.1%) as was the proportion of children with documented receipt of vasopressors within 72 hours of ICU admissions (5.4%-9.5%). In age-stratified analysis, children with neurologic disorders still were significantly more likely to have hospital LOS >3 days and be admitted to the ICU compared with children with non-neurologic underlying conditions or no underlying conditions but the odds of those outcomes increased with older age (data not shown). Of the 3 deaths among children hospitalized with CAP; 1 was a child with a neurologic disorder and 2 were children with no underlying conditions. In a subgroup analysis of the clinical outcomes comparing a subset of children with neurologic disorders without other non-neurologic underlying conditions with children with non-neurologic underlying conditions and no underlying conditions, children with only neurologic disorders and no other underlying conditions still had longer hospital LOS and were more likely to require ICU admission, but there were no significant differences found in ICU LOS or requirements for or duration of invasive mechanical ventilation (**Table VII**; available at www.jpeds.com), similar to findings in the main analysis.

Because children with neurologic disorders (with and without other non-neurologic underlying conditions) were more likely to require ICU admission, we developed multivariable logistic regression models for the outcome of ICU admission which included the presence of a neurologic disorder; asthma/RAD; congenital heart disease; chronic lung disease; age group; race/ethnicity; report symptoms of seizures; presence of hypoxia; and tachypnea. Because age group was determined to be an effect modifier with neurologic disorders (P value <.01), we also created separate regression models stratified by age group; we excluded asthma/RAD from the <2-year-old age group because of the uncertainty of accurate diagnosis at that age. Using a stepwise elimination method, race/ethnicity and reports symptoms of seizures documented in the medical record fell out of the model and were removed from all final models. In separate multivariable logistic regression models stratified by age group, which included the presence of a neurologic disorder, asthma/RAD (in the 2- to 4-year-old and 5- to 17-year-old age groups only), congenital heart disease, chronic lung disease, hypoxia, tachypnea, and the following interaction terms: neurologic disorder and congenital heart disease, congenital heart disease

Table II. Characteristics of children hospitalized with CAP with and without neurologic disorders

Characteristics	Group 1 Any neurologic disorder (n = 280) No. (%)	Group 2 Non-neurologic underlying condition (n = 934) No. (%)	Group 3 No underlying condition (n = 1144) No. (%)	*P* value Group 1 vs 2	*P* value Group 1 vs 3
Male	160 (57.1)	524 (56.1)	607 (53.1)	.76	.22
Race/ethnicity					
Non-Hispanic white	137 (48.9)	314 (33.6)	488 (42.7)	<.01	.06
Non-Hispanic black	66 (23.6)	420 (45.0)	295 (25.8)	<.01	.45
Hispanic	62 (22.1)	132 (14.1)	258 (22.6)	<.01	.88
Other	15 (5.4)	68 (7.3)	103 (9.0)	.26	.05
Age groups					
<2 y	79 (28.2)	389 (41.7)	587 (51.3)	<.01	<.01
2-4 y	72 (25.7)	246 (26.3)	277 (24.2)	.84	.60
5-17 y	129 (46.1)	299 (32.0)	280 (24.5)	<.01	<.01
Insurance status					
Public	177 (63.2)	637 (68.2)	654 (57.2)	.12	.07
Parent's education					
Some college or more	179 (63.9)	557 (59.6)	676 (59.1)	.20	.14
Non-neurologic underlying condition					
Any non-neurologic underlying condition	146 (52.1)	934 (100)	NA	<.01	NA
Congenital heart disease	85 (30.4)	87 (9.3)	NA	<.01	NA
Asthma/RAD	83 (29.6)	696 (74.5)	NA	<.01	NA
Chronic lung disease	35 (12.5)	59 (6.3)	NA	<.01	NA
Preterm birth (<37 wk)	26/79 (32.9)	192/389 (49.4)	NA	<.01	NA
Immunosuppressive condition	12 (4.3)	27 (2.9)	NA	.25	NA
Other conditions*	14 (5.0)	43 (4.6)	NA	.78	NA
Vaccination receipt status†					
H influenzae type B vaccine	183/213 (85.9)	543/631 (86.1)	534/625 (85.4)	.96	.86
Pneumococcal vaccine	142/167 (85.0)	487/577 (84.4)	462/577 (80.1)	.72	.71
Influenza vaccine	111/266 (41.7)	230/844 (27.3)	271/943 (28.7)	<.01	<.01
Social factors					
Lives in household with smoker	81/278 (29.1)	361/929 (38.9)	388/1137 (34.1)	<.01	.11
Daycare attendance	41/202 (20.3)	253/757 (33.4)	287/961 (29.9)	<.01	<.01
Reported symptoms					
Cough	255 (91.1)	898 (96.2)	1077 (94.1)	<.01	.06
Fever	251 (89.6)	851 (91.1)	1053 (92.1)	.46	.19
Shortness of breath	197 (70.4)	710 (76.0)	750 (65.6)	.06	.13
Vomiting/nausea	114 (40.7)	518 (55.5)	651 (56.9)	<.01	<.01
Diarrhea	64 (22.9)	253 (27.1)	401 (35.1)	.16	<.01
Seizures	47 (16.8)	10 (1.1)	19 (1.7)	<.01	<.01
Clinical findings					
Chest indrawing	149/276 (54.0)	542/925 (58.6)	587/1135 (51.7)	.17	.50
Tachypnea‡	144/270 (53.3)	546/875 (62.4)	569/1083 (52.5)	.01	.82
Hypoxia§	138/278 (49.6)	334/926 (36.1)	424/1136 (37.3)	<.01	<.01
Altered mental status	26/266 (9.8)	22/924 (2.4)	10/1129 (0.9)	<.01	<.01
Hypotension¶	9/280 (3.2)	8/931 (0.9)	9/1133 (0.8)	<.01	<.01
Illness onset to hospital admission, d (median, IQR)	3 (1-6)	3 (1-5)	4 (2-6)	.58	<.01

NA, not applicable.

*Other condition includes chronic kidney disease, diabetes mellitus, chronic liver disease, and history of splenectomy.

†Based on verified vaccine information. For all 3 vaccines, vaccination is considered received if given ≥2 wk prior to admission. For *H influenzae* type B vaccine, this was based on 1459/1469 (99%) children ≥19 mo for whom information was available; vaccinated was defined as having received ≥3 doses *H influenzae* type B vaccine. For pneumococcal conjugate vaccine, this was based on 1272/1280 (99%) of children 19 mo to 12 y for whom information was available; vaccinated was defined as having received ≥3 pneumococcal vaccine doses. For influenza vaccine, this was based on 2053/2084 (99%) children ≥6 mo for whom information was available; vaccinated was defined as having received ≥1 influenza vaccine dose during season. An influenza season was defined as September 1 to August 31 of the concurrent year.

‡Tachypnea is defined as ≥60 breaths per min in infants <2 mo; ≥50 breaths per min in infants ≥2 mo to <12 mo; ≥40 breaths per min in children ≥1 y to <5 y; and ≥25 breaths per min in ≥5 y to <18 y.

§Hypoxia is defined as an oxygen saturation <92% on presentation or the receipt of any supplemental oxygen on presentation.

¶Hypotension is defined as a systolic blood pressure <60 mm Hg in infants <1 mo; <70 mm Hg in infants ≥1 mo to <1 y; <70 mm Hg + (2 mm Hg * age in y) in children ≥1 y to <10 y; and <90 in children ≥10 y.

and hypoxia, asthma/RAD and hypoxia, asthma/RAD and tachypnea, neurologic disorder and chronic lung disease, asthma/RAD and chronic lung disease, hypoxia and chronic lung disease, tachypnea and chronic lung disease, and hypoxia and tachypnea; none of the interactions in the age-stratified multivariate models was significant. In the final multivariate models, we found the presence of a neurologic disorder remained significantly associated with ICU admission among children ≥2 years but not among children <2 years (Table VIII).

Discussion

Children with neurologic disorders hospitalized with CAP were older and more likely to have congenital heart or lung

Table III. Detection of pathogens* among children hospitalized with CAP comparing children with and without neurologic disorders among those with samples available for pathogen detection

Microbiologic organisms	Group 1 Any neurologic disorder (n = 261) No. (%)	Group 2 Non-neurologic underlying condition (n = 886) No. (%)	Group 3 No underlying condition (n = 1075) No. (%)	*P* value Group 1 vs 2	*P* value Group 1 vs 3
Any pathogen detection	181 (69.4)	748 (84.4)	875 (81.4)†	<.01	<.01
Single viral detection	108 (41.4)	455 (51.4)	448 (41.7)	<.01	.93
Viral-viral co-detection	38 (14.6)	195 (22.0)	228 (21.2)	<.01	.02
Single bacterial detection	21 (8.0)	43 (4.9)	99 (9.2)	.05	.06
Bacterial-viral co-detection	14 (5.4)	48 (5.4)	93 (8.7)	.97	.08
Bacterial-bacterial co-detection	0 (0)	7 (0.8)	5 (0.5)	NA	NA
Specific viral detections					
Human rhinovirus	63/254 (24.8)	309/871 (35.5)	234/1054 (22.2)	<.01	.37
RSV	46 (17.6)	246 (27.8)	330 (30.7)	<.01	<.01
Human metapneumovirus	40 (15.3)	107 (12.1)	138 (12.8)	.17	.29
Parainfluenza 1, 2, 3 viruses	15 (5.8)	49 (5.5)	87 (8.1)	.89	.20
Adenovirus	14 (5.4)	114 (12.9)	120 (11.2)	<.01	<.01
Influenza A/B viruses	14 (5.4)	54 (6.1)	81 (7.5)	.66	.22
Coronaviruses‡	11/254 (4.3)	52/871 (6.0)	47/1054 (4.5)	.32	.93
Specific bacterial detections					
Mycoplasma pneumoniae	24/254 (9.5)	58/871 (6.7)	96/1054 (9.1)	.13	.87
S pneumoniae	5 (1.9)	19 (2.1)	55 (5.1)	.82	.03
Viridans *streptococcus*	2/248 (0.8)	5/825 (0.6)	7/1026 (0.7)	.67	.69
Streptococcus pyogenes	1 (0.4)	5 (0.6)	10 (0.9)	1.00	.70
Chlamydophila pneumoniae	1/254 (0.4)	5/871 (0.6)	6/1054 (0.6)	1.00	1.00
Haemophilus influenzae	1/248 (0.4)	2/825 (0.2)	6/1026 (0.6)	NA	NA
Methicillin-susceptible *Staphylococcus aureus*	1/248 (0.4)	2/825 (0.2)	2/1026 (0.2)	NA	NA
Methicillin-resistant *Staphylococcus aureus*	0/248 (0)	3/825 (0.4)	14/1026 (1.4)	NA	NA
Other Gram-negative organisms	0/248 (0)	4/825 (0.5)	5/1026 (0.5)	NA	NA

PCR, polymerase chain reaction.
*Results reflect pathogen detection based on sampling and pathogen definitions previously described.[3] Proper sampling methodology was defined for bacterial detections as blood culture or whole blood PCR or pleural fluid culture or PCR or endotracheal aspirate culture or bronchoalveolar lavage culture results and for viral detections as a nasopharyngeal/oropharyngeal swab PCR or viral serology results.
†*Histoplasma capsulatum* was detected in 2 patients.
‡Includes coronaviruses 229E, HKU1, NL63, and OC43.

disease than children without neurologic disorders. Children with neurologic disorders were more likely to have hospital LOS >3 days and require ICU admission than those without neurologic disorders but were similarly likely to require invasive mechanical ventilation or vasopressors within 72 hours of ICU admission. On multivariate age-stratified analysis controlling for congenital heart disease, asthma/RAD, tachypnea and hypoxia, having a neurologic disorder remained associated with ICU admission among children ≥2 years old. Overall, differences in pathogen detection in children with neurologic disorders were largely age-specific but a lower proportion of children with neurologic disorders had a respiratory pathogen detected compared with those without neurologic disorders.

In our study population of 2358 children hospitalized with CAP, 11.9% had a neurologic disorder. Children with neurologic disorders comprise a small proportion of the US pediatric population, but the heterogeneity of the disorders limit a single prevalence estimate. The estimated prevalence of epilepsy is 390 per 100 000 children and cerebral palsy is 240 per

Table V. Clinical outcomes among children hospitalized with CAP with and without neurologic disorders

Outcomes	Group 1 Neurologic disorder (n = 280) No. (%)	Group 2 Non-neurologic underlying condition (n = 934) No. (%)	Group 3 No underlying condition (n = 1144) No. (%)	*P* value Group 1 vs 2	*P* value Group 1 vs 3
Hospital LOS (d, median, IQR)	4 (2-7)	3 (2-4)	4 (2-4)	<.01	<.01
Hospital LOS >3 d	154 (55.0)	304 (32.6)	368 (32.2)	<.01	<.01
ICU admission	102 (36.4)	185 (19.8)	210 (18.4)	<.01	<.01
ICU LOS (d, median, IQR)	3 (2-7)	2 (1-5)	2 (1-5)	.04	.04
ICU LOS >3 d	49/102 (48.0)	66/185 (35.7)	86/210 (41.0)	.04	.24
Invasive mechanical ventilation	34/102 (33.3)	52/185 (28.1)	80/210 (38.1)	.36	.41
Ventilator (d, median, IQR)	3 (1-8)	4 (1-8)	4 (2-7)	.79	.52
Ventilator >4 d	13/34 (38.2)	25/52 (48.1)	36/80 (45.0)	.10	.22
Documented receipt of vasopressors within 72 h of ICU admission	7/102 (6.9%)	10/185 (5.4%)	20/210 (9.5)	.62	.43
Death	1 (0.4)	0 (0)	2 (0.2)	NA	NA

Table VIII. Age-stratified multivariate models of select clinical characteristics among children hospitalized with CAP with ICU admission as the outcome

	aOR (95%) CI		
Clinical characteristics	**Age <2 y (n = 963)**	**Age 2-4 y (n = 523)**	**Age 5-17 y (n = 687)**
Neurologic disorder	1.0 (0.5-1.8)	2.8 (1.4-5.5)	3.6 (2.2-5.9)
Asthma/RAD	NA*	1.9 (1.2-3.0)	1.4 (0.9-2.1)
Congenital heart disease	1.5 (0.8-2.8)	0.9 (0.4-2.3)	1.0 (0.5-2.1)
Chronic lung disease	2.3 (1.1-4.7)	2.0 (0.8-4.6)	0.8 (0.3-2.6)
Hypoxia†	2.9 (2.2-4.0)	3.6 (2.2-5.8)	4.2 (2.7-6.4)
Tachypnea‡	0.9 (0.7-1.3)	1.9 (1.1-3.1)	2.0 (1.2-3.2)

*Asthma/RAD excluded from the <2 year age group because of the uncertainty of accurate diagnosis at that age.
†Hypoxia is defined as an oxygen saturation <92% on presentation or the receipt of any supplemental oxygen on presentation.
‡Tachypnea is defined as ≥60 breaths per min in infants <2 mo; ≥50 breaths per min in infants ≥2 mo to <12 mo; ≥40 breaths per min in children ≥1 y to <5 y; and ≥25 breaths per minute in ≥5 y to <18 y.

100 000 children.[4] The estimated prevalence of birth defects range from a prevalence of 0.8-3.5 per 100 000 live births for disorders such anencephaly, spina bifida, encephalocele, and chromosomal abnormalities except for Down syndrome, which is more common (14.5 per 100 000 live births).[6] Despite being uncommon in the general population, children with neurologic disorders have been reported to account for 5.3% of all pediatric hospitalizations.[13] In a study using US claims data, investigators found that 11% of children hospitalized with respiratory infections had neurologic disorders.[22] This is nearly identical to the proportion of children with neurologic disorders seen in our study.

Compared with children with non-neurologic underlying conditions and children with no underlying conditions, children with neurologic disorders in our study were older and more often had coexisting congenital heart disease (30.4%) and chronic lung disease (12.5%). This reflects the burden of chronic disease and medical complexity in this population.[8-10]

Overall, children with neurologic disorders were more likely to require ICU admission, our primary outcome of severe illness. However, on multivariate analysis the association between neurologic disorder and ICU admission remained only for children ≥2 years of age. The reasons for this finding are not entirely clear and the EPIC dataset did not include reason for ICU admission. However, there are several possible reasons for this finding. First, it is possible that there was increased disability with increasing age or related to specific neurologic disorders, but we do not have detailed neurologic or functionality information in the EPIC dataset to assess this hypothesis. Second, it is possible that younger children with certain neurologic disorders, which were included in the case definition (such as epilepsy or developmental delay), may not have been fully diagnosed and, therefore, were not formally classified as having a neurologic disorder. Third, it is possible that children with neurologic disorders may have increasing disability with age because of their neurologic disorder alone (eg, impaired cough reflex) such that they were admitted to the ICU for aspiration risk and increased monitoring or treatment such as suctioning. Lastly, clinicians may have been more likely to admit all children younger than 2 years regardless of any underlying medical condition to the ICU for a respiratory admission for increased monitoring or treatment, thus, the effect of having a neurologic disorder would be decreased in this younger age group.

Although ICU admission has not previously been specifically evaluated among children hospitalized with CAP, the increased risk of ICU admission has previously been reported among children with neuromuscular disorders but hospitalized with specific viral infections. Wilkesmann et al[20] reported that children with neuromuscular conditions hospitalized with RSV were more likely to require ICU admission than those without neuromuscular conditions (45% vs 10%). Chaves et al[23] found that among children hospitalized with influenza, children with neuromuscular disorders were more likely to have ICU admissions or death compared with those without neuromuscular conditions (11% vs 3%). Previous studies have highlighted the disproportionate number of episodes of respiratory failure and deaths in children with neurologic disorders hospitalized with influenza or RSV infections.[16,18,20,24,25] We found that children with neurologic disorders required invasive mechanical ventilation with the same frequency as children with non-neurologic underlying conditions and children with no underlying conditions. Because we comprehensively and prospectively evaluated children hospitalized with CAP directly, we did not identify cases through preferential testing or severity criteria which may have contributed to the differences between our study and the various previously published studies.

Overall, in each age group, respiratory pathogens were significantly less frequently detected in children with neurologic disorders compared with children with non-neurologic underlying conditions. Although the reasons for these differences are unclear and warrant further investigation, there are several possible explanations. More frequent aspiration without a discernible pathogen but still with clinical and radiographic pneumonia, may have contributed to the lower frequency of pathogen detection among children with neurologic disorders; the EPIC study did not systematically collect sputum or endotracheal aspirate specimens in the children to further assess this possibility.[9,11,14,15] It is also possible that because pathogens were less frequently detected in older

children overall,[3] that the finding of fewer pathogens detected in children with neurologic disorders may be related to their older age compared with children with non-neurologic underlying conditions and no underlying conditions. Interestingly and specifically rhinovirus, adenovirus, and RSV were all less frequently detected in children with neurologic disorders compared with children with non-neurologic medical conditions, of which asthma/RAD was most common; although we did not further stratify by underlying medical condition, these viruses have been associated with asthma and RAD in previous studies.[26,27] Importantly, respiratory virus detections were more common than bacterial detections among children with neurologic disorders, as was also true for all other children hospitalized with CAP. In addition, the frequency of co-detections and specific pathogens detected were generally similar in all 3 groups.

Per the Advisory Committee on Immunization Practices guidelines, all children >6 months of age and older should receive an annual influenza vaccination.[28] Although our analysis demonstrated that children with neurologic disorders were more likely to have received influenza vaccination compared with children with no underlying condition (41.7% vs 28.7%), this is well below the Healthy People 2020 target (70%) for annual pediatric influenza vaccination.[29-31] This finding highlights that clinicians should strongly support influenza vaccination in these children. The Advisory Committee on Immunization Practices also recommends pneumococcal vaccination in children,[32] coverage of which was high in our study, including among children with neurologic disorders.

These findings are subject to several limitations. First, data on the functional status of children enrolled in the EPIC study were not collected. Thus, we were unable to classify the degree of disability or ability to manage secretions caused by different neurologic disorders and the potential impact on outcomes. Similarly, we acknowledge that the neurologic disorders group is heterogeneous, but we used definitions that have been reported previously. In addition, in the assessment of specific disorders, although our numbers were small in any 1 group, the clinical outcomes of the overall population of children with neurologic disorders and those of the subset of children with neurologic disorders and no other comorbidities were similar. Second, children with preexisting tracheostomy were excluded from this study, which may have excluded some of the children who are most severely neurologically compromised who have the highest risk for pneumonia. Third, aspiration can occur frequently in children with neurologic disorders,[14,15,33] and it is possible that the lower proportion of pathogens detected in children with neurologic disorders was related to aspiration pneumonia when an etiologic agent was not detected. Sputum samples were not collected routinely in the children, and very few endotracheal aspirates were obtained in our study. Fourth, although we used a comprehensive array of diagnostic methods, detection of a pathogen does not necessarily denote causation.[3] Fifth, we did not have data on the use of noninvasive positive pressure ventilation, thus, we are unable to describe all potential forms of respiratory support that may have been used during hospitalization. Sixth, the threshold and reasons for ICU admission vary among clinicians and institutions and, thus, have limitations as a marker for severity. Although we did not collect information on reason for ICU admission, we did find that most children admitted to the ICU had tachypnea, hypoxia, or altered mental status; however, there may be other factors, including clinician preferences or other nonclinical factors, for which we did not account. Finally, our study sites were tertiary care children's hospitals, and the array of neurologic disorders and overall medical complexity in these patients may differ from those seen in nonreferral centers. This may have had a limited effect, however, because patients with more complex neurologic disorders would likely be referred to specialty centers regardless of the acute illness.[13]

We demonstrated that children ≥2 years old with neurologic disorders were more likely to require ICU admission after controlling for asthma/RAD, congenital heart disease, hypoxia, and tachypnea. Overall, when stratified by age, the proportion of children with a detected pathogen was lower among children with neurologic disorders compared to children without neurologic disorders. Given the high proportion of and increased risk of severe illness among children with neurologic conditions hospitalized with CAP in our study, our findings underscore the vulnerable nature of children, the need for immunization in this population, and the requirement for comprehensive respiratory care in this vulnerable population. ■

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References

1. Michelow IC, Olsen K, Lozano J, Rollins NK, Duffy LB, Ziegler T, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics 2004;113:701-7.
2. Lee GE, Lorch SA, Sheffler-Collins S, Kronman MP, Shah SS. National hospitalization trends for pediatric pneumonia and associated complications. Pediatrics 2010;126:204-13.
3. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al. Community-acquired pneumonia requiring hospitalization among US children. N Engl J Med 2015;372:835-45.
4. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? Neurology 2007;68:326-37.
5. Kirby RS, Wingate MS, Van Naarden Braun K, Doernberg NS, Arneson CL, Benedict RE, et al. Prevalence and functioning of children with cerebral palsy in four areas of the United States in 2006: a report from the Autism and Developmental Disabilities Monitoring Network. Res Dev Disabil 2011;32:462-9.
6. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, et al. Updated national birth prevalence estimates for selected birth defects

in the United States, 2004-2006. Birth Defects Res A Clin Mol Teratol 2010;88:1008-16.
7. Evans PM, Alberman E. Certified cause of death in children and young adults with cerebral palsy. Arch Dis Child 1991;66:325-9.
8. Cohen E, Kuo DZ, Agrawal R, Berry JG, Bhagat SK, Simon TD, et al. Children with medical complexity: an emerging population for clinical and research initiatives. Pediatrics 2011;127:529-38.
9. Healy FM, Panitch HB. Pulmonary complications of pediatric neurological diseases. Pediatr Ann 2010;39:216-24.
10. Dodge NN. Cerebral palsy: medical aspects. Pediatr Clin North Am 2008;55:1189-207. ix.
11. Seddon PC, Khan Y. Respiratory problems in children with neurological impairment. Arch Dis Child 2003;88:75-8.
12. Plioplys AV, Kasnicka I, Lewis S, Moller D. Survival rates among children with severe neurologic disabilities. South Med J 1998;91:161-72.
13. Berry JG, Poduri A, Bonkowsky JL, Zhou J, Graham DA, Welch C, et al. Trends in resource utilization by children with neurological impairment in the United States inpatient health care system: a repeat cross-sectional study. PLoS Med 2012;9:e1001158.
14. Weir K, McMahon S, Barry L, Ware R, Masters IB, Chang AB. Oropharyngeal aspiration and pneumonia in children. Pediatr Pulmonol 2007; 42:1024-31.
15. Weir KA, McMahon S, Taylor S, Chang AB. Oropharyngeal aspiration and silent aspiration in children. Chest 2011;140:589-97.
16. Blanton L, Peacock G, Cox C, Jhung M, Finelli L, Moore C. Neurologic disorders among pediatric deaths associated with the 2009 pandemic influenza. Pediatrics 2012;130:390-6.
17. Cox CM, Blanton L, Dhara R, Brammer L, Finelli L. 2009 Pandemic Influenza A (H1N1) Deaths among Children—United States, 2009–2010. Clin Infect Dis 2011;52:S69-74.
18. Louie JK, Gavali S, Acosta M, Samuel MC, Winter K, Jean C, et al. Children hospitalized with 2009 novel influenza A(H1N1) in California. Arch Pediatr Adolesc Med 2010;164:1023-31.
19. Tran D, Vaudry W, Moore DL, Bettinger JA, Halperin SA, Scheifele DW, et al. Comparison of children hospitalized with seasonal versus pandemic Influenza A, 2004–2009. Pediatrics 2012;130:397-406.
20. Wilkesmann A, Ammann RA, Schildgen O, Eis-Hubinger AM, Muller A, Seidenberg J, et al. Hospitalized children with respiratory syncytial virus infection and neuromuscular impairment face an increased risk of a complicated course. Pediatr Infect Dis J 2007;26:485-91.
21. Yi H, Lanctot KL, Bont L, Bloemers BL, Weijerman M, Broers C, et al. Respiratory syncytial virus prophylaxis in Down syndrome: a prospective cohort study. Pediatrics 2014;133:1031-7.
22. Havers FA, Chen J, Christensen D, Moore C, Peacock G, Finelli L, et al. Respiratory infection hospitalizations among children with neurologic disorders United States, July 2009 to June 2010. San Francisco, CA: IDWeek 2013; 2013.
23. Chaves SS, Aragon D, Bennett N, Cooper T, D'Mello T, Farley M, et al. Patients hospitalized with laboratory-confirmed influenza during the 2010-2011 influenza season: exploring disease severity by virus type and subtype. J Infect Dis 2013;208:1305-14.
24. Keren R, Zaoutis TE, Bridges CB, Herrera G, Watson BM, Wheeler AB, et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalized with influenza infection. JAMA 2005;294:2188-94.
25. Bhat N, Wright JG, Broder KR, Murray EL, Greenberg ME, Glover MJ, et al. Influenza-associated deaths among children in the United States, 2003-2004. N Engl J Med 2005;353:2559-67.
26. Gern JE. The ABCs of rhinoviruses, wheezing, and asthma. J Virol 2010; 84:7418-26.
27. Lynch JP, Fishbein M, Echavarria M. Adenovirus. Semi Respir Crit Care Med 2011;32:494-511.
28. Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices—United States, 2013-2014. MMWR Recomm Rep 2013;62:1-43.
29. Grohskopf LA, Olsen SJ, Sokolow LZ, Bresee JS, Cox NJ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2014-2015 Influenza Season. MMWR Morb Mortal Wkly Rep 2014;63:691-7.
30. Lu PJ, Santibanez TA, Williams WW, Zhang J, Ding H, Bryan L, et al. Surveillance of influenza vaccination coverage—United States, 2007-2008 through 2011-2012 influenza seasons. MMWR Surveill Summ 2013;62:1-28.
31. Immunization and Infectious Diseases. 2014. http://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives. Accessed October 24, 2014.
32. Nuorti JP, Whitney CG. Prevention of pneumococcal disease among infants and children—use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine— recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2010;59:1-18.
33. Srivastava R, Jackson WD, Barnhart DC. Dysphagia and gastroesophageal reflux disease: dilemmas in diagnosis and management in children with neurological impairment. Pediatr Ann 2010;39: 225-31.

Table I. Neurologic disorders among children hospitalized with CAP (n = 280)

Neurologic disorders*	No. (%)
Epilepsy	121 (43.2)
Down syndrome	75 (26.8)
Cerebral palsy	57 (20.4)
Developmental delay	43 (15.4)
Chromosomal abnormalities†	34 (12.1)
Spinal cord injury or abnormality	21 (7.5)
Other neurologic disorders*	75 (26.8)
Hydrocephalus	10 (13.3)
Hypotonia	7 (9.3)
Muscular dystrophy	6 (8.0)
Microcephaly	5 (6.7)
Periventricular leukomalacia	5 (6.7)
Metabolic disorders	4 (5.3)
Agenesis of the corpus callosum	4 (5.3)
Ischemic encephalopathy	4 (5.3)
Spinal muscular atrophy type 1 and 2	4 (5.3)
Neurofibromatosis	4 (5.3)
Static encephalopathy	4 (5.3)
Autism	3 (4.0)
Smith-Magenis syndrome	3 (4.0)
Spastic quadriplegia	3 (4.0)
Intraventricular hemorrhage	2 (2.7)
Holoprosencephaly	2 (2.7)
Chiari malformation	2 (2.7)
Fetal alcohol syndrome	1 (1.3)
Ganglioglioma	1 (1.3)
Langerhans cells histiocytosis CNS disease	1 (1.3)
Myasthenia gravis	1 (1.3)
Motor neuron disease	1 (1.3)
Craniosynostosis	1 (1.3)

CNS, central nervous system.
*Disorders are not mutually exclusive, and children may have more than 1 neurologic disorder.
†Excluding Down syndrome.

Table IV. Detection of pathogens[*,†] among children hospitalized with CAP stratified by age in children with and without neurologic disorders among those with samples available for pathogen detection

Microbiologic organisms	Group 1 Any neurologic disorder, No. (%)	Group 2 Non-neurologic underlying condition, No. (%)	Group 3 No underlying condition, No. (%)	*P* value Group 1 vs 2	*P* value Group 1 vs 3
Any pathogen detection					
<2 y	53/71 (74.7)	327/366 (89.3)	482/543 (88.8)	<.01	<.01
2-4 y	50/66 (75.8)	201/232 (86.6)	216/261 (82.8)	.03	.19
5-17 y	78/124 (62.9)	220/288 (76.4)	177/271 (65.3)	<.01	.64
Specific viral detections					
Human rhinovirus					
<2 y	23/69 (33.3)	118/361 (32.7)	146/533 (27.4)	1.0	.30
2-4 y	16/65 (24.6)	74/228 (32.5)	52/258 (20.2)	.29	.43
5-17 y	24/120 (20.0)	117/282 (41.5)	36/263 (13.7)	<.01	.12
RSV					
<2 y	19/71 (26.8)	146/366 (39.9)	242/543 (44.6)	.04	<.01
2-4 y	15/66 (22.7)	77/232 (33.2)	72/261 (27.6)	.10	.42
5-17 y	12/124 (9.7)	23/288 (8.0)	16/271 (5.9)	.57	.18
Human metapneumovirus					
<2 y	14/71 (19.7)	48/366 (13.1)	79/543 (14.6)	.14	.25
2-4 y	12/66 (18.2)	41/232 (17.7)	40/261 (15.3)	.92	.57
5-17 y	14/124 (11.3)	18/288 (6.3)	19/271 (7.0)	.08	.15
Parainfluenza 1, 2, 3 viruses					
<2 y	2/71 (2.8)	22/366 (6.0)	48/543 (8.8)	.40	.08
2-4 y	5/66 (7.6)	13/232 (5.6)	25/261 (9.6)	.56	.61
5-17 y	8/124 (6.5)	14/288 (4.9)	14/271 (5.2)	.51	.61
Adenovirus					
<2 y	5/71 (7.0)	81/366 (22.1)	90/543 (16.6)	<.01	.04
2-4 y	5/66 (7.6)	24/232 (10.3)	23/261 (8.8)	.50	.75
5-17 y	4/124 (3.2)	9/288 (3.1)	7/271 (2.6)	1.0	.75
Influenza A/B viruses					
<2 y	1/71 (1.4)	16/366 (4.4)	39/543 (7.2)	.33	.07
2-4 y	5/66 (7.6)	12/232 (5.2)	12/261 (4.6)	.55	.35
5-17 y	8/124 (6.5)	26/288 (9.0)	30/271 (11.1)	.38	.15
Coronaviruses[‡]					
<2 y	3/69 (4.4)	24/361 (6.7)	27/533 (5.1)	.60	1.0
2-4 y	3/65 (4.6)	17/228 (7.5)	13/258 (5.0)	.58	1.0
5-17 y	5/120 (4.2)	11/282 (3.9)	7/263 (2.7)	1.0	.53
Specific bacterial detections					
Mycoplasma pneumoniae					
<2 y	0/69 (0)	12/361 (3.3)	8/533 (1.5)	.23	.61
2-4 y	2/65 (3.1)	7/228 (3.1)	20/258 (7.8)	1.0	.27
5-17 y	22/120 (18.3)	39/282 (13.8)	68/263 (25.9)	.25	.11
S pneumoniae					
<2 y	1/71 (1.4)	11/366 (3.0)	20/543 (3.7)	.70	.49
2-4 y	0/66 (0)	4/232 (1.7)	19/261 (7.3)	.58	.02
5-17 y	4/124 (3.2)	4/288 (1.4)	16/271 (5.9)	.25	.26
Viridans *streptococcus*					
<2 y	0/68 (0)	3/348 (0.9)	5/525 (1.0)	1.0	1.0
2-4 y	1/63 (1.6)	1/212 (0.5)	1/250 (0.4)	.41	.36
5-17 y	1/117 (0.9)	1/265 (0.4)	1/251 (0.4)	.52	.54
Streptococcus pyogenes					
<2 y	0/71 (0)	3/366 (0.8)	5/543 (0.9)	1.0	1.0
2-4 y	0/66 (0)	1/232 (0.4)	4/261 (1.5)	1.0	.59
5-17 y	1/124 (0.8)	1/288 (0.4)	1/271 (0.4)	.51	.53
Chlamydophila pneumoniae					
<2 y	0/69 (0)	2/361 (0.6)	1/533 (0.2)	1.0	1.0
2-4 y	1/65 (1.5)	1/228 (0.4)	2/258 (0.8)	.40	.49
5-17 y	0/120 (0)	2/282 (0.7)	3/263 (1.1)	1.0	.56
H influenzae					
<2 y	0/68 (0)	2/348 (0.6)	6/525 (1.1)	1.0	1.0
2-4 y	1/63 (1.6)	0/212 (0)	0/250 (0)	.23	.20
5-17 y	0/117 (0)	0/265 (0)	0/251 (0)	1.0	1.0
Methicillin-susceptible *S aureus*					
<2 y	0/68 (0)	1/348 (0.3)	0/525 (0)	1.0	1.0
2-4 y	0/63 (0)	0/212 (0)	1/250 (0.4)	1.0	1.0
5-17 y	1/117 (0.9)	1/265 (0.4)	1/251 (0.4)	.52	.54

(*continued*)

Table IV. Continued

Microbiologic organisms	Group 1 Any neurologic disorder, No. (%)	Group 2 Non-neurologic underlying condition, No. (%)	Group 3 No underlying condition, No. (%)	*P* value Group 1 vs 2	*P* value Group 1 vs 3
Methicillin-resistant *S aureus*					
<2 y	0/68 (0)	2/348 (0.6)	7/525 (1.3)	1.0	1.0
2-4 y	0/63 (0)	1/212 (0.5)	3/250 (1.2)	1.0	1.0
5-17 y	0/117 (0)	0/265 (0)	4/251 (1.6)	1.0	.31

PCR, polymerase chain reaction.
*Results reflect pathogen detection based on sampling and pathogen definitions previously described.[3] Proper sampling methodology was defined for bacterial detections as blood culture or whole blood PCR or pleural fluid culture or PCR or endotracheal aspirate culture or bronchoalveolar lavage culture results and for viral detections as a nasopharyngeal/oropharyngeal swab PCR or viral serology results.
†*Histoplasma capsulatum* was detected in 2 patients.
‡Includes coronaviruses 229E, HKU1, NL63, and OC43.

Table VI. Characteristics of children hospitalized with CAP with and without neurologic disorders admitted to the ICU

Characteristics	Group 1 Any neurologic disorder (n = 102) No. (%)	Group 2 Non-neurologic underlying condition (n = 185) No. (%)	Group 3 No underlying condition (n = 210) No. (%)	*P* value Group 1 vs 2	*P* value Group 1 vs 3
Male	55 (53.9)	110 (59.5)	114 (54.3)	.36	.95
Race/ethnicity					
Non-Hispanic white	46 (45.1)	74 (40.0)	97 (46.2)	.40	.86
Non-Hispanic black	29 (28.4)	66 (35.7)	32 (15.2)	.21	<.01
Hispanic	20 (19.6)	30 (16.2)	59 (28.1)	.47	.05
Other	7 (6.9)	15 (8.1)	22 (10.5)	.87	.30
Age groups					
<2 y	27 (26.5)	87 (47.0)	140 (66.7)	<.01	<.01
2-4 y	23 (22.6)	43 (23.2)	37 (17.6)	.67	.30
5-17 y	52 (51.0)	55 (29.7)	33 (15.7)	<.01	<.01
Non-neurologic underlying condition					
Any non-neurologic underlying condition	53 (52.0)	185 (100)	NA		
Congenital heart Disease	39 (38.2)	17 (9.2)	NA	<.01	NA
Asthma/RAD	30 (29.4)	130 (70.3)	NA	<.01	NA
Chronic lung disease	15 (14.7)	20 (10.8)	NA	.33	NA
Pre-term birth (<37 wk)	8/27 (29.6)	46/87 (52.9)	NA	.03	NA
Immunosuppressive condition	2 (2.0)	5 (2.7)	NA	1.0	NA
Other condition*	1 (1.0)	8 (4.3)	NA	.12	NA
Reported symptoms					
Cough	90 (88.2)	174 (94.1)	193 (91.9)	.08	.30
Fever	85 (83.3)	161 (87.0)	187 (89.1)	.39	.16
Shortness of breath	79 (77.5)	153 (82.7)	156 (74.3)	.28	.54
Vomiting/nausea	26 (25.5)	97 (52.4)	117 (55.7)	<.01	<.01
Altered mental status	34 (33.3)	46 (24.9)	60 (28.6)	.13	.39
Diarrhea	26 (25.5)	39 (21.1)	65 (31.0)	.39	.32
Seizures	17 (16.7)	3 (1.6)	5 (2.4)	<.01	<.01
Clinical findings					
Chest indrawing	67/101 (66.3)	159/184 (86.4)	155/208 (74.5)	<.01	.13
Tachypnea†	65/99 (65.7)	121/178 (68.0)	118/197 (59.9)	.69	.34
Hypoxia‡	68/101 (67.3)	111/185 (60.0)	131/210 (62.4)	.22	.39
Altered mental status	15/93 (16.1)	15/180 (8.3)	7/202 (3.5)	.05	<.01
Hypotension§	7/102 (6.9)	5/183 (2.7)	5/208 (2.4)	.12	.07
Illness onset to hospital admission, d (median, IQR)	2 (1-5)	2 (1-4)	3 (2-5)	.98	.09

NA, not applicable.
*Other condition includes chronic kidney disease, diabetes mellitus, chronic liver disease, and history of splenectomy.
†Tachypnea is defined as ≥60 breaths per min in infants <2 mo; ≥50 breaths per min in infants ≥2 mo to <12 mo; ≥40 breaths per min in children ≥1 y to <5 y; and ≥25 breaths per min in ≥5 y to <18 y.
‡Hypoxia is defined as an oxygen saturation <92% on presentation or the receipt of any supplemental oxygen on presentation.
§Hypotension is defined as a systolic blood pressure <60 mm Hg in infants <1 mo; <70 mm Hg in infants ≥1 mo to <1 y; <70 mm Hg + (2 mm Hg * age in y) in children ≥1 y to <10 y; and <90 in children ≥10 y.

Table VII. Subgroup analysis of clinical outcomes among children hospitalized with CAP with neurologic disorders with no other non-neurologic underlying conditions compared with children without neurologic disorders

Outcomes	Group 1A Neurologic disorder and no other underlying condition, n = 134	Group 2 Non-neurologic underlying condition, n = 934	Group 3 No underlying condition, n = 1144	*P* value Group 1A vs 2	*P* value Group 1A vs 3
Hospital LOS >3 d	70 (52.2)	304 (33.6)	368 (32.2)	<.01	<.01
ICU admission	49 (36.6)	185 (19)	210 (18.4)	<.01	<.01
ICU LOS >3 d	23/49 (46.9)	66/185 (35)	80/210 (41)	.15	.44
Invasive mechanical ventilation	21/49 (42.9)	52/185 (28)	80/210 (38.1)	.05	.54
Ventilator LOS >4 d	7/21 (33.3)	25/52 (48.1)	36/80 (45.0)	.25	.34