Continuous Neuromuscular Blockade for Bronchopulmonary Dysplasia

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Am J Perinatol

Abstract

Objective Bronchopulmonary dysplasia (BPD) is the most common late morbidity for premature infants. Continuous neuromuscular blockade (CNMB) is suggested for the most unstable phase of BPD, despite no outcome data. We explored the association between duration of CNMB for severe BPD and mortality.

Design Medical record review of children <5 years old admitted from 2016 to 2022 with BPD and one or more course of CNMB for ≥14 days.

Results Twelve children received a total of 20 episodes of CNMB for ≥14 days (range 14–173 d) during their hospitalization. Most (10/12) were born at <28 weeks' gestation and most (11/12) with birth weight <1,000 g; 7/12 were of Black race/ethnicity. All were hospitalized since birth. Most (10/12) were initially transferred from an outside neonatal intensive care unit (ICU), typically after a >60-day hospitalization (9/12). Half (6/12) of them had a ≥60-day stay in our neonatal ICU before transferring to our pediatric ICU for, generally, ≥90 days (8/12). The primary study outcome was survival to discharge: 2/12 survived. Both had shorter courses of CNMB (19 and 25 d); only one child who died had a course ≤25 days. Just two infants had increasing length Z-scores during hospitalization; only one infant had a final length Z-score > -2.

Conclusion In this case series of infants with severe BPD, there were no survivors among those receiving ≥25 days of CNMB. Linear growth, an essential growth parameter for infants with BPD, decreased in most patients. These data do not support the use of ≥25 days of CNMB to prevent mortality in infants with severe BPD.

Keywords
- bronchopulmonary dysplasia
- paralytic
- pediatric
- mortality

Key Points

- This is a case series of neuromuscular blockade for severe BPD.
- Neuromuscular blockade did not improve linear growth.
- Ten out of 12 infants who were on prolonged neuromuscular blockade died.

received
November 1, 2023
accepted after revision
February 12, 2024

DOI https://doi.org/10.1055/s-0044-1782180.
ISSN 0735-1631.

Perinatal care advances continue to improve survival of premature infants, yet bronchopulmonary dysplasia (BPD) remains the most common late morbidity.[1–5] Management strategies for the most severe forms of BPD are evolving, with wide variances between institutions.[6,7]

Neuromuscular blocking agents (NMBAs), also known as paralytics, are primarily used as adjunctive therapies to optimize mechanical ventilation, reduce oxygen consumption, and prevent unintended medical device removal in critically ill patients.[8–10] The role and utility of NMBAs in the BPD population is not well-described, though a 2019 report by Logan et al references their use as expected practice during the most unstable phase of BPD management.[11] A putative advantage of continuous neuromuscular blockade (CNMB) in BPD is that it stabilizes acute respiratory decompensations long enough that both time and nutrition will improve the underlying lung disease. But CNMB brings its own risks. In other clinical scenarios, these medications, combined with sedative infusions, are associated with serious critical care complications, including ventilator-associated complications, withdrawal, delirium, immobility, and myopathy.[8,9,12,13] CNMB in infants also limits interaction with the environment, potentially compounding the neurodevelopmental risks of prematurity.

Here we report a case series of infants with BPD who received prolonged CNMB. We hypothesized that there would be an association between duration of CNMB and mortality. By describing the characteristics and outcomes of this cohort, we aim to expand the evidence base related to this practice and generate hypotheses for larger scale investigation.

Materials and Methods

This case series represents patients at our academic, tertiary pediatric care center. We queried Epic for children 0 to 5 years old who were admitted between 2016 and 2022, had a diagnosis of BPD, and received one or more course of CNMB infusion for $\geq$14 days. Because there is no standard definition of prolonged CNMB, we chose $\geq$14 days as the definition of a prolonged CNMB episode because it is twice the duration of a typical CNMB course in our institution for children undergoing surgical procedures, such as tracheostomy. The study was determined to be exempt by our local Institutional Review Board (IRB00273809, approval July 6, 2022).

For patients with a qualifying hospitalization, we reviewed medical records from hospital admission to final disposition and author archives regarding weekly intensive care unit (ICU) goals-of-care meetings and interdisciplinary team care conferences. For children originally transferred to our hospital from another center, we included all available data from the referring hospital and treated both hospital courses as a single hospitalization. For children whose hospitalization included transfer from our hospital to a step-down unit and then readmission to our hospital from that step-down unit, all available data were reviewed and treated as a single hospitalization. All CNMB episodes occurred in our hospital.

Data extraction targeted patient demographics and medical complexity; BPD management before, during, and after CNMB; characteristics of CNMB episodes (agents, doses, duration); evidence regarding any intrateam, team-family, or intrafamily decision-making or conflict regarding CNMB; length of stay, final disposition, and where relevant, end-of-life management. When reporting ventilator settings, peak inspiratory pressures (PIPs) were used for patients receiving pressure control modes and peak airway pressures for those receiving volume control modes of ventilation. All positive microbiology cultures were reviewed and only counted as clinically significant if accompanied by clinical status changes and confirmatory attending documentation.

Descriptive analysis was applied (proportions, percents, etc.) for primary and secondary outcomes. Two-tailed *t*-tests were used to compare the cohort's median final ventilator settings with those reported by McKinney et al for the Bronchopulmonary Dysplasia Collaborative.[14]

Results

Twelve children met the eligibility criteria (►**Table 1**). Most (10/12) were born at $<28^{0/7}$ weeks' gestation and most (11/12) with birth weight $<$1,000 g; 7/12 were of Black race/ethnicity. All were hospitalized since birth. All had multiorgan medical conditions and pulmonary hypertension. One patient had normal brain imaging (ultrasound or MRI); all had delayed neurodevelopment documented by a physical or occupational therapist prior to receiving any CNMB. Most (10/12) had one or more surgical procedure. All had three or more positive cultures (median 8) during the hospitalization; all had clinically significant infections with more than one organism (median 5 organisms). Pathogenic respiratory colonizers accounted for 5/9 systemic infections. Median total days of invasive ventilation were 258 (range 63–541 d). Two children were never extubated, 1 was extubated for 3 days, while 5/12 were extubated for $>$100 days (not necessarily continuously) during the hospitalization. Half had a tracheostomy. Three received extracorporeal membrane oxygenation (ECMO). Infant weight increased for most (8/12) during the hospitalization, 4/12 had increasing head circumference, 2/12 had increasing length with only 1/12 having a length Z-score > -2 (►**Fig. 1**). The only infant discharged on noninvasive ventilation had increasing Z-scores in all csategories.

Hospitalization characteristics had several similarities (►**Table 1**). Most infants were initially transferred to our center from other neonatal ICUs, typically after a $>$60-day hospitalization at the referring hospital. Most then had a $\geq$60-day stay in our neonatal ICU, before transferring to our pediatric ICU for, generally, $\geq$90 days. Three children spent some part of the hospitalization in a step-down facility; for the two survivors, the final discharge was to a step-down facility.

The 12 patients received 20 episodes of prolonged ($\geq$14 d) CNMB (►**Table 2**); 3 children received more than one episode. One CNMB episode was started in the neonatal ICU, the remainder in the pediatric ICU. In total, 4/12 children

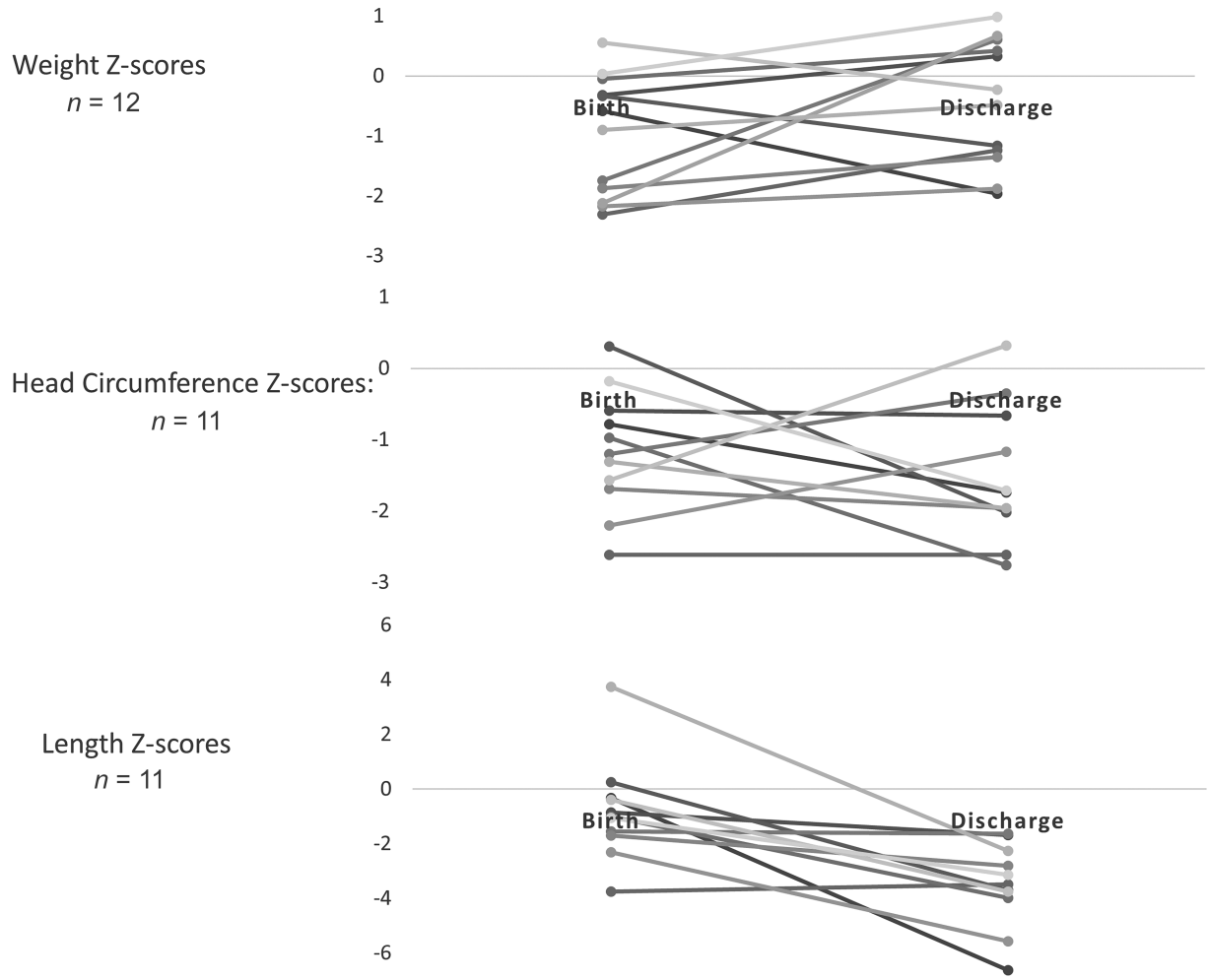

Fig. 1 Growth paraments, admission to discharge.

received 14 to 29 total days of CNMB, 1/12 child received 30 to 59 days, and 7/12 children received ≥60 days (maximum 210 d). Nineteen out of 20 courses included vecuronium. Dosing varied for each CNMB agent, both between patients and within patients. A goal of full paralysis was documented for 8/20 episodes; 12/20 episodes included at least some days with a documented goal of weakening (e.g., to improve ventilator synchrony or increase tolerance of interventions). To monitor degree of neuromuscular blockade, train of four was routinely used when infant required full paralysis. Weakening doses of CNMB allowed for a degree of spontaneous movement, eye opening, and extremities. All infants received multiagent sedative infusions concurrently with all CNMB infusions. Seven of the 12 patients received additional days of CNMB for durations shorter than 14 days, contributing to a range of 8 to 38 days of additional CNMB (►**Table 2**).

Most children (9/12) were on conventional ventilators only during CNMB episodes, typically in pressure control modes (7/11). Final ventilator orders for the 11/12 children on invasive ventilation at hospital disposition revealed a median PIP 44 (range 32–54), median positive end expiratory pressure 11 (range 5–14), median rate 26 (range 16–40) and median fraction inspired oxygen 1.0 (was 1.0 in 10/11). Mean airway pressures ranged from 17 to 26 (median 23). ►**Table 3** compares these settings to a BPD point-prevalence study by McKinney et al[14] All CNMB courses involved concomitant systemic steroids and pulmonary hypertension treatment (usually three or more simultaneous agents). Many involved 10 or more daily respiratory medications (►**Table 2**). Nine of the 12 children had clinically significant infections while receiving CNMB; half (6/12) had a positive culture within 24 hours of initiating CNMB. Respiratory infections accounted for 75% of infections. Of these infections, gram-negative organisms were the primary pathogens. The majority of respiratory cultures resulted from endotracheal/tracheotomy tube aspirates; 3/12 children had positive respiratory viral panels. Nine of the 12 children had two or more infection sources; 2/3 bloodstream infections and 3/6 urinary tract infections involved a pathogenic organism found in prior respiratory cultures.

Many hospitalizations (8/12) were characterized by some degree of intrateam and/or team-family conflict about indications, duration, or benefits of CNMB. Of the eight instances of intrateam conflict, seven included conflicting perspectives among prescribing providers and six included conflict between prescribing providers and bedside staff. Two cases involved team-family conflict regarding CNMB (in both cases families felt the child did not need the CNMB). For the

Table 1 Patient and hospitalization characteristics

Child	$N = 12$ Number (%)
Race/Ethnicity	
White	2 (17%)
Black	7 (58%)
Asian	2 (17%)
Mixed	1 (8%)
Sex	
Female	7 (58%)
Male	5 (42%)
Gestational age at birth (weeks)	
$23^{0/7}$–$24^{6/7}$	4 (33%)
$25^{0/7}$–$27^{6/7}$	6 (50%)
$28^{0/7}$–$33^{6/7}$	2 (17%)
Birth weight (g)	
< 500	2 (17%)
500–999	9 (75%)
1,000–1,499	1 (8%)
Documented organ involvement prior to paralytic	
Cardiac	9 (75%)
Gastrointestinal	11 (92%)
Neurologic	6 (50%)
Genetic	2 (17%)
Infection	8 (67%)
Other	12 (100%)
Brain imaging prior to paralytic	
Normal	0 (0%)
Mild/Nonspecific	9 (75%)
Moderate/Severe	3 (25%)
Neurodevelopment prior to paralytic	
Normal for gestational age	0 (0%)
Delayed for gestational age	12 (100%)
Hospitalization	**$N = 12$ Number (%)**
Birth location	
Inborn	2 (17%)
Outborn	10 (83%)
Length of stay prior to transfer for outborn infants ($n = 10$)	
< 28 days	1 (10%)
28–59 days	0 (0%)
60–89 days	4 (40%)
90–120 days	1 (10%)
> 120 days	4 (40%)
Length of stay in our neonatal intensive care unit ($n = 9$)	
< 28 days	3 (33%)
28–59 days	0 (0%)
60–89 days	1 (11%)
90–120 days	1 (11%)
> 120 days	4 (44%)
Length of stay in our pediatric intensive care unit ($n = 11$)	
< 28 days	1 (9%)
28–59 days	1 (9%)
60–89 days	1 (9%)
90–120 days	2 (18%)
> 120 days	6 (55%)
Surgeries	
Tracheostomy	
Prior to paralytic	3 (25%)
After paralytic	3 (25%)
Ever extubated	
No	2 (17%)
Yes	10 (83%)
Median days of extubation	65 days (0–295)

four families described as "mostly" or "always present" at the bedside (defined as visiting ≥75% of hospital days), no team or team-family conflict was reported. For the four families "rarely present" at the bedside (defined as visiting <30% of hospital days), three involved intrateam conflict. Nearly half (5/12) of families expressed regrets about CNMB, usually because it interfered with their interactions with their child ("I feel like I am holding a lifeless body" Parent 3) and/or because it interfered with neurodevelopment. All children had a Pediatric Palliative Care consult. None had an Ethics Consult.

Ten out of 12 infants died before discharge (1/10 in neonatal ICU, 9/10 in pediatric ICU). Five out of 10 received one or more episode of cardiopulmonary resuscitation (CPR), though none in the final week of life. All nonsurvivors had "No CPR" orders in place prior to death. Within this limitation, family values dictated the degree of de-escalation, which contributed to variance in the types of ICU therapies continued at end-of-life. Although CNMB infusions were discontinued prior to death for all infants, 4/10 infants remained on CNMB until a few hours before death. Hypercarbic and hypoxic respiratory failure was cause of death for all, most progressed to multisystem failure (kidney or intestinal). Eight out of 10 deaths were documented as withdrawal of therapies, though half of infants remained on invasive mechanical ventilation at the time of death. CNMB infusions were discontinued for most infants (►Table 4).

When comparing the 2 survivors to the 10 children who died, it is notable that both survivors had short courses of CNMB (19 and 25 d); only one child who died had a course of ≤25 days. Each survivor only had one course of CNMB and no clinically significant infections during CNMB. One survivor had received ECMO, had a tracheostomy, and was discharged to a step-down facility on invasive chronic ventilation. The other survivor was discharged to a step-down facility on noninvasive ventilation.

Table 2 Continuous neuromuscular blockade episodes and concurrent respiratory support

Pt	CNMB episode	Days of CNMB	CNMB type	Minimum dose (mg/kg/h)	Maximum dose (mg/kg/h)	Proportion of LOS on any paralytic (%, days)	Ventilator type during CNMB	Respiratory medications	Pulmonary hypertension medications
1	1	38	cis	0.03	0.5	69% (38/55)	SIMV	albuterol, budesonide, chlorothiazide, furosemide hydrocortisone	bosentan, epoprostenol, iNO, sildenafil
			vec	0.02	0.14				
2	1	29	vec	0.1	0.25	12% (29/246)	HFOV, SIMV	chlorothiazide, furosemide, hydrocortisone, ipratropium, levalbuterol, methylprednisolone sodium succinate, spironolactone	epoprostenol, iNO, sildenafil
3	1	66	cis	0.05	0.22	97% (66/68)	SIMV	acetylcysteine, albuterol, budesonide, fluticasone, furosemide, hydrochlorothiazide, methylprednisolone sodium succinate, prednisone, prednisolone sodium phosphate, spironolactone	epoprostenol, iNO, milrinone, sildenafil
			vec	0.04	0.2				
4[a]	1	25	cis	0.1	0.24	25% (25/102)	SIMV	budesonide, chlorothiazide, fluticasone, furosemide, levalbuterol, methylprednisolone sodium succinate, spironolactone	epoprostenol, iNO, sildenafil, treprostinil
			vec	0.1	0.2				
5[b,c]	1	15	vec	0.04	0.12	42% (114/269)	SIMV	acetylcysteine, budesonide, chlorothiazide, furosemide, hydromorphone, levalbuterol, methylprednisolone sodium succinate, spironolactone	bosentan, epoprostenol, sildenafil
	2	30	vec	0.03	0.16		SIMV	acetylcysteine, budesonide, chlorothiazide, furosemide, hydrocortisone, levalbuterol, methylprednisolone sodium succinate, spironolactone	bosentan, epoprostenol, iNO, sildenafil, treprostinil
	3	31	cis	0.1	0.25		MMV, SIMV	budesonide, chlorothiazide, furosemide, hydrocortisone, levalbuterol, spironolactone	bosentan, epoprostenol, treprostinil
			vec	0.04	0.08				
6[b,c]	1	16	vec	0.06	0.16	65% (210/325)	SIMV	budesonide, hydrochlorothiazide, levalbuterol, prednisolone sodium phosphate, spironolactone	iNO
	2	20	vec	0.04	0.08		SIMV	acetylcysteine, budesonide, chlorothiazide, furosemide, hydrocortisone, levalbuterol, spironolactone	iNO
	3	157	vec	0.02	0.16		SIMV	budesonide, chlorothiazide, fluticasone propionate, furosemide, ipratropium, levalbuterol, methylprednisolone sodium succinate, prednisolone sodium phosphate, spironolactone	iNO, sildenafil
7[a,b]	1	19	vec	0.021	0.11	12% (27/224)	SIMV	acetylcysteine, albuterol, chlorothiazide, furosemide, hydrocortisone	epoprostenol, iNO

(*Continued*)

Table 2 (*Continued*)

Pt	CNMB episode	Days of CNMB	CNMB type	Minimum dose (mg/kg/h)	Maximum dose (mg/kg/h)	Proportion of LOS on any paralytic (%, days)	Ventilator type during CNMB	Respiratory medications	Pulmonary hypertension medications
8[b]	1	70	vec	0.03	0.12	36% (81/227)	SIMV	acetylcysteine, budesonide, chlorothiazide, furosemide, levalbuterol, prednisolone sodium phosphate, spironolactone	epoprostenol, iNO, sildenafil
9[b,c]	1	112	cis	0.03	0.16	46% (178/388)	APRV, SIMV	acetylcysteine, albuterol, aminophylline, budesonide, chlorothiazide, fluticasone, furosemide, ipratropium, levalbuterol, methylprednisolone sodium succinate	bosentan, epoprostenol, iNO, sildenafil, treprostinil
			vec	0.01	0.1				
	2	20	vec	0.02	0.05		SIMV	acetylcysteine, budesonide, chlorothiazide, furosemide, hydromorphone, levalbuterol	bosentan, epoprosentol, sildenafil, treprostinil
	3	19	cis	0.03	0.3		SIMV	acetylcysteine, albuterol, budesonide, chlorothiazide, furosemide, methylprednisolone sodium succinate, spironolactone	bosentan, sildenafil, treprostinil
10[b]	1	60	vec	0.04	0.12	62% (75/121)	SIMV	budesonide, chlorothiazide, furosemide, hydrocortisone, levalbuterol, methylprednisolone sodium succinate, spironolactone	epoprostenol, iNO, sildenafil, treprostinil
11	1	17	vec	0.05	0.1	13% (17/128)	HFOV, SIMV	acetylcysteine, albuterol, budesonide, hydrocortisone, levalbuterol, methylprednisolone sodium succinate	iNO, sildenafil
12[b]	1	14	vec	0.06	0.15	27% (69/252)	SIMV	budesonide, chlorothiazide, dexamethasone, furosemide, levalbuterol	bosentan, epoprostenol, iNO, sildenafil
	2	31	vec	0.03	0.06		SIMV	azithromycin, budesonide, chlorothiazide, furosemide, levalbuterol, methylprednisolone	bosentan, epoprostenol, iNO, sildenafil, treprostinil
	3	14	vec	0.05	0.14		SIMV	acetylcysteine, azithromycin, budesonide, chlorothiazide, furosemide, ipratropium, levalbuterol, spironolactone	bosentan, epoprostenol, iNO, sildenafil, treprostinil, milrinone

Abbreviations: APRV, airway pressure release ventilation; cis, cisatracurium; CNMB, continuous neuromuscular blockade; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; LOS, length of stay; MMV, mandatory minute ventilation; Pt, patient; SIMV, synchronized intermittent mandatory ventilation; vec, vecuronium.

[a]Patients 4 and 7 were alive at time of data collection and had at least one hospital readmission prior to the age of 5.

[b]Patients had additional courses of CNMB shorter than 14 days.

[c]Patient received extracorporeal membrane oxygenation.

Table 3 Invasive ventilator settings at disposition, compared with Bronchopulmonary Dysplasia Collaborative[14]

Invasive ventilator setting	Cohort median ($n = 11$)	BPD Collaborative median	*p*-Value	BPD Collaborative IQR (cm H_2O)
MAP (cm H_2O)	23	17	0.005	13.8–20
PIP (cm H_2O)	44	32	0.004	25.5–50.5
PEEP (cm H_2O)	11	10	0.07	8–11
Rate (breaths/min)	26	20	0.02	Not reported
FIO_2 (cm H_2O)	1.0	0.33	0.002	0.29–0.4

Abbreviations: BPD, bronchopulmonary dysplasia; FIO2, fraction inspired oxygen; IQR, InterQuartile Range; MAP, mean airway pressure; PEEP, peak end expiratory pressure; PIP, peak inspiratory pressure.

Table 4 Invasive ventilator settings at disposition

Pt	Mode	MAP (cm H_2O)	PIP/PAP (cm H_2O)	PEEP (cm H_2O)	Rate (breaths/min)	FIO_2 (cm H_2O)	Time between stopping CNMB and disposition (days)	Alive at disposition
1	PC	17	38	5	35	1.0	0	No
2	PC	24	35	12	40	1.0	2	No
3	VC	26	50	10	45	1.0	0	No
5	VC	24	54	11	30	1.0	19	No
6	PC	23	50	10	26	1.0	0	No
7	VC	17	32	11	20	0.3	28	Yes
8	VC	23	53	12	20	1.0	64	No
9	PC	22	46	12	25	1.0	41	No
10	PC	20	40	11	40	1.0	5	No
11	PC	19	33	13	16	1.0	103	No
12	PC	24	44	14	20	1.0	0	No

Abbreviations: CNMB, continuous neuromuscular blockade; FIO_2, fraction inspired oxygen; MAP, mean airway pressure; PC, pressure control; PEEP, peak end expiratory pressure; PIP/PAP, peak inspiratory pressure/peak airway pressure; Pt, patient; VC, volume control.

Discussion

The most severe BPD phenotype comprises a heterogenous group of premature infants with disrupted alveolar and microvasculature development. The fundamental management strategy for such patients is to promote somatic, lung, and brain growth via adequate oxygenation and ventilation.[11] This often requires prolonged mechanical ventilation, chronic sedation, and treatment of pulmonary hypertension.[11,15–17] Here we report a case series of 12 infants who received prolonged CNMB as an adjuvant therapy. Most infants were transferred to our center for escalating respiratory needs after >60 days at their birth hospital, reflecting both a willingness by accepting clinicians to initiate intensive interventions for severely ill patients and a desire by families to pursue those interventions. Overall for this cohort, prolonged CNMB did not promote growth and 83% died. Notably, the two survivors had two of the shortest courses (≤25 d) of CNMB.

NMBAs are pharmacologic tools to facilitate mechanical ventilation and minimize oxygen consumption and are broadly used as short-term therapies by anesthesiologists, pediatric intensivists, and neonatologists.[8–11] In infants with severe BPD, these medications can be rescue agents during pulmonary hypertension crises and severe dynamic hyperinflation but are not known to have disease-modifying effects.[8,18–20] As supported by our cohort, most children with severe BPD have concurrent parenchymal disease, pulmonary hypertension, and large airway disease (malacia), all of which can be life-threatening.[21] When life-threatening episodes occur repeatedly, CNMB initiated with short-term intentions may become a prolonged therapy, even in the absence of supporting data.

Despite thousands of children receiving CNMB as an adjuvant therapy in ICUs each year, 17% of the sample in Patel et al representing >60,000 children, few reports describe practice standards, duration of use, or outcomes, and no reports address severe BPD.[13] Patel et al describe durations of CNMB use as hours or days, not weeks. We found two large cohort studies, both retrospective and representing heterogenous populations (mechanically ventilated children in Italian ICUs and infants with congenital diaphragmatic hernia) that report increased in-hospital mortality with CNMB use.[22,23] However, a secondary analysis of the prospective Randomized Evaluation of Sedation Titration for Respiratory Failure study demonstrated no increased mortality.[24] Although these CNMB studies provide some insights regarding mortality risk, they cannot be generalized to infants with severe BPD.

Morbidity data related to CNMB are more robust. CNMB use is associated with ventilator-associated complications,

including three-times the risk of infection.[12,25,26] Since NMBAs reduce innate pulmonary clearance mechanisms (cough, diaphragm excursion, mobility), infection risk is difficult to avoid. Chronic mechanical ventilation, steroids, and multimonth ICU hospitalizations also predispose patients to infection. Importantly for infants with BPD, infections can undermine the "progrowth state" needed for survival, where growth and core muscle strength are mediators of large airway disease.[11,12,27,28] In our cohort, somatic growth was not promoted for most infants, with >50% dropping ≥2 standard deviations in length from birth to discharge.

Weakness is another important CNMB morbidity. Patients with tracheostomies and long durations of mechanical ventilation can develop ICU-acquired weakness and myopathy.[29,30] Mechanical ventilation independently contributes to diaphragm atrophy and CNMB exacerbates diaphragm atrophy, especially in pediatric patients whose spontaneous breaths are <50% of ventilator-delivered breaths.[31,32] Prolonged and progressive muscle atrophy diminishes the ability to wean from mechanical ventilation, exacerbating a cycle of escalating respiratory support that propagates further diaphragm and respiratory muscle weakness.[33] No data are published on whether CNMB-associated weakness worsens large airway disease or increases the ventilatory support needed by infants with severe BPD. It is notable that the final ventilator settings of the children who died in our cohort were significantly higher than those described in the BPD collaborative by McKinney et al[14] Since prolonged CNMB offers no disease-modifying benefits, therefore, understanding its short- and long-term impact on pulmonary mechanics is essential before adopting it as an adjuvant therapy in this population.

Among infants in our cohort who died, 3/10 received CNMB for >30% of their hospital days at our center and 4/10 for >60% of their hospital days at our center. Multiple infants were maintained on "low-dose" CNMB with a documented goal of less than full paralysis. A child's lived experience of an awake but chemically weakened state is not well-understood. Adult studies have associated being awake under paralysis with pain, anxiety, and other psychological sequelae.[34,35] To combat this, the use of CNMB often includes concomitant sedative and/or analgesic infusions, medications associated with detrimental effects on the developing brain in animal models and human studies.[36,37] School-aged children with severe BPD show lower cognitive, language, academic, executive, emotional, social, physical functioning, and quality of life scores compared with unaffected and moderately affected peers.[38–40] All children in our cohort had documented neurodevelopmental delay before and after CNMB, highlighting the vulnerability of this population to ongoing neurodevelopmental insults. When evaluating benefits and burdens of therapies, current and future quality of life considerations should not be undervalued.

Parents of very premature infants are often counseled early on about potential mortality. Once an infant survives for months in the hospital, parents may be surprised by the ongoing mortality risk related to BPD. When transferred to a tertiary center for severe BPD management, as many patients in this cohort were, parents may have heightened expectations for an infant's improvement. In our cohort, parental sentiments regarding CNMB included both acceptance and regret: CNMB maintained physiologic stability but prevented interaction with their child. Most were willing to accept this tradeoff if it would help their child survive. Yet even when death was near, CNMB, invasive ventilation, and intensive multimodal therapies were continued for many patients. CNMB was stopped >1 month prior to death for three infants; yet, all infants died of chronic hypoxic and hypercarbic respiratory failure, which progressed to multisystem failure (renal, intestinal) in most. Our data would suggest that if a child is not improving after 30 days of CNMB, teams should revisit with families whether ongoing paralytic is still a priority over meaningful interactions with the child.

Patient care that involves unproven treatments, long lengths of stay, and poor prognosis are associated with conflict and distress within health care teams[41,42] and this was found in our cohort. As has been described in other settings,[43,44] conflict often arose between providers with different roles, such as prescribing clinicians who spend shorter periods with patients and families versus bedside staff who spent longer periods with patients and families. Concerns about patient suffering are known to intensify when patients cannot interact with their loved ones and as treatment benefits become difficult to measure.[42,44–46] Interdisciplinary perspectives likely provide the most comprehensive evaluation of the risk/benefit ratio to a child of innovative therapies like CNMB.

In our cohort, 12 children accounted for >4,000 hospital days, most of those in ICUs, and >3,000 days of invasive ventilation. Going forward, the best way to study CNMB as an adjuvant therapy for severe BPD is via multicenter, prospective, randomized trials that track diverse patient outcomes, short- and long-term family outcomes, and impact on health system and community resources. These data will inform the clinical and ethical questions about whether weeks to months of CNMB to maintain hemodynamic stability is a reasonable goal of care for children with refractory BPD.

We acknowledge the limitations inherent in this small, retrospective, single-center, case series. Additionally in our cohort, CNMB was used as a potential rescue therapy for children with severe and refractory disease at risk for imminent death from BPD. Our results are confounded by this indication and should not be interpreted as proof of causation between CNMB and outcomes. The paucity of evidence regarding CNMB in infants with BPD limits any comparative analysis. Patients receiving CNMB before 2016, when EPIC went live at our center, were excluded. Detail regarding team and family dynamics was not always available; if conflict could not be directly associated with CNMB, it was not included in the analysis.

Conclusion

Published data regarding practice standards and outcomes of CNMB in the management of infants with severe BPD do not

exist. This is a case series describing basic characteristics of 12 infants with severe BPD who received CNMB infusion for ≥14 days at a single center. Two infants survived to hospital discharge; both had shorter courses of CNMB compared with most of the cohort. Our data suggest that ≥25 days of CNMB does not promote growth or survival in infants with severe BPD.

Funding
None.

Conflict of Interest
None declared.

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