Risk Factors for Extubation Failure in Infants With Severe Acute Bronchiolitis

Cíntia Johnston RRT PhD, Werther Brunow de Carvalho MD PhD, Jefferson Piva MD PhD, Pedro Celiny R Garcia MD PhD, and Marcelo Cunio Fonseca MD

OBJECTIVE: To evaluate demographic characteristics, mechanical-ventilation parameters, blood gas values, and ventilatory indexes as predictors of extubation failure in infants with severe acute bronchiolitis. METHODS: We conducted a prospective observational study from March 2004 to September 2005 with consecutive infants (ages 1–12 months) with severe acute bronchiolitis and considered ready to be extubated. We calculated mean airway pressure and oxygenation index. Before extubation we measured respiratory rate, tidal volume, rapid shallow breathing index, maximal inspiratory pressure, and load/force balance. Arterial blood gases were measured 1 hour before extubation. Extubation was classified as a failure if the infant needed re-intubation within 48 hours. RESULTS: Extubation failure occurred in 6 (15%) of the 40 extubated infants. The respective median (and interquartile range) age, weight, and days of mechanical ventilation for the extubation-failure and extubation-success groups were: age 5 (3–8) months versus 4 (4–6) months ($P = .87$), weight 4 (3–5) kg versus 6 (5–7) kg ($P < .001$), and mechanical ventilation days 8 (6–23) d versus 6 (5–12) d ($P = .52$). There were no significant differences in arterial blood gas values or mechanical-ventilation parameters between the extubation-success and extubation-failure groups. There were statistically significant differences between the extubation-failure and extubation-success groups for 2 risk factors, weight ≤ 4 kg and tidal volume ≤ 4 mL/kg, when those risk factors had a large area under the curve of the receiver operating characteristic. Variables that had a large area under the curve were minute volume ≤ 0.8 mL/kg/min and maximal inspiratory pressure ≤ 50 cm H_2O. Variables that had a small area under the curve were load/force balance ≥ 5 and rapid shallow breathing index ≥ 6.7. CONCLUSIONS: In infants with severe acute bronchiolitis the extubation process is complex because of the combined features of this disease. Pediatric studies have not definitely determined predictive factors, weaning protocols, or ventilatory predictive indexes of extubation failure risk in infants with severe acute bronchiolitis. Lower minute volume and lower maximal inspiratory pressure had large areas under the curve of the receiver operating characteristic for extubation-failure risk in infants with severe acute bronchiolitis. *Key words: mechanical ventilation; extubation; bronchiolitis; pediatric critical care; weaning*. [Respir Care 2010; 55(3):328–333. © 2010 Daedalus Enterprises]

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Introduction

Acute bronchiolitis is the most common lower-airway viral infection in infants. The most serious forms occur in infants younger than 6 months, born prematurely, and who have underlying diseases, such as bronchopulmonary dysplasia, immunodeficiency, or congenital heart disease.[1-4]

Respiratory syncytial virus is the main cause of acute bronchiolitis, but other agents are also important: adenovirus; para-influenza 1, 2, and 3; influenza A and B; rhinovirus; mycoplasm; human metapneumovirus; and coronavirus.[2-5]

Acute bronchiolitis is a mild disease in most infants, but 1–3% of these patients require hospital admission, and 15% of those are transferred to a pediatric intensive care unit (ICU).[1,4] Mechanical ventilation may be needed by 5–15% of the hospitalized patients because of fatigue, apnea, or hypoxemia.[1] The mean duration of mechanical ventilation is about 7 days, and the weaning course is slow. Children with severe acute bronchiolitis are ready to be extubated when the fraction of inspired oxygen (F_{IO_2}) is < 0.40, inspiratory pressure is low, and respiratory rate is 8–10 breaths/min.[6]

Inappropriate extubation timing increases morbidity and mortality, ICU stay,[7] and mechanical ventilation duration,[8] which increases the probability of airway trauma associated with re-intubation and the risk of nosocomial infection.[8]

Extubation failure is defined as the need to reintubate and restore mechanical ventilation < 48 hours after extubation.[7-9] Extubation failure occurs in about 15–20% of children[7,9,10] and in 22–28% of premature babies.[7] In a fourth of the cases the extubation failure is a consequence of upper-airway obstruction (post-extubation edema), whereas the other 75% of cases are caused by events such as deterioration of pulmonary conditions, alterations of the ventilatory muscles, and residual effects of sedatives or neuromuscular blockers.[6,9,11] Several variables are associated with extubation failure in pediatric patients, but the available data do not specifically address extubation failure in infants with severe acute bronchiolitis, and most of the weaning indexes are not established for this population.

In the present study we evaluated demographic characteristics, mechanical-ventilation parameters, blood gas values, and ventilatory indexes as risk factors for extubation failure in infants with severe acute bronchiolitis on mechanical ventilation.

Methods

From March 2004 to September 2005 we conducted a prospective observational study in the pediatric ICU of Hospital São Lucas, Porto Alegre, Brazil. This pediatric ICU is a 13-bed tertiary-care unit that admits an average of 500 children each year.

The inclusion criteria were: infants (≤ 12 months of age), on mechanical ventilation, with a clinical diagnosis of severe acute bronchiolitis (history of upper-airway infection, thoracic retractions, nasal flaring, first wheezing crisis), radiologic findings suggestive of hyperinflation (with or without interstitial infiltrates, or alveolar collapse, or both), and who were ready to be weaned from mechanical ventilation.

This study was approved by our institutional ethics committee, and all parents or guardians provided written informed consent.

There was no formal protocol for weaning patients from mechanical ventilation, but the attending physician weaned the patients with following parameters: $F_{IO_2} \leq 0.40$, peak inspiratory pressure (PIP) ≤ 25 cm H_2O, positive end-expiratory pressure (PEEP) ≤ 5 cm H_2O, and respiratory rate ≤ 8 breaths/min.[6] We also evaluated resolution of the primary disease, hemodynamic stability, electrolyte changes, and hemoglobin level.

We used 3 ventilator models: Servo 300 (Siemens, Siemens/Maquet, Bridgewater, New Jersey), Sechrist IV 100B (Sechrist, Anaheim, California), and Sechrist IV 200. The infants were usually ventilated on intermittent mandatory ventilation or synchronized intermittent mandatory ventilation, in pressure-control mode.

The extubation time was determined exclusively by the medical team in charge in the pediatric ICU. The respiratory therapists recorded the following variables before extubation: mechanical-ventilation parameters; respiratory rate during spontaneous breathing; minute volume ($\dot{V}_E$), measured with an infant spirometer (Wright infant spirometer, Ferraris Medical, London, United Kingdom) during 1 min of spontaneous breathing; tidal volume (V_T), calculated by dividing $\dot{V}_E$ by respiratory rate; rapid shallow breathing index (RSBI), which is respiratory rate/V_T/weight);[12] maximal inspiratory pressure (PI_{max}), measured with a manovacuometer (MPG, Marshalltown, Iowa) connected to the endotracheal tube, at 20 s, by occluding the airway with a one-way valve and selecting the most negative value of 3 efforts during spontaneous breathing;[13] and the load/force balance,[14] calculated as:

$$\text{Load/force balance} = 15 \times \text{mean airway pressure}/PI_{max} + 0.03 \times \text{RSBI} - 5$$

Arterial blood gases were measured 1 hour before extubation. Extubation failure was defined as the need for tracheal intubation within 48 hours after extubation.

Statistical Analysis

We used the Fisher exact test to compare categorical data, and the Kruskal-Wallis test for variables with nonnormal distribution to compare the extubation-failure and extubation-success groups.

The cut-off points were selected with better sensitivity and specificity in the receiver operating characteristic curve with the data from Farias et al[12] for PI_{max} and RSBI. Other values and variables do not have cut points from previous studies[7-9]; this is the first study that measured these respiratory indexes in infants with severe bronchiolitis and on mechanical ventilation.

We used standard equations to calculate sensitivity, specificity, positive predictive values, and negative predictive values only for the variables that reached significance ($P \leq .05$) in the comparisons of the extubation-failure and extubation-success groups. A true positive result was recorded when a test predicted extubation failure and extubation failed. A false positive result was recorded when a test predicted extubation failure but extubation was successful. A true negative result was recorded when a test predicted extubation success and extubation succeeded. A false negative result was recorded when a test predicted extubation success but extubation failed.

We assessed the general performance of each index with positive and negative likelihood ratios,[15-18] calculated for each index[19,20] after discretization into dichotomous variables. Indexes were predictive (positive likelihood ratio > 2, negative likelihood ratio < 0.5, or ratio of positive likelihood ratio to negative likelihood ratio > 4), well predictive (positive likelihood ratio > 5, negative likelihood ratio < 0.2, or ratio of positive likelihood ratio to negative likelihood ratio > 10), or very well predictive (positive likelihood ratio > 10, negative likelihood ratio < 0.1, or ratio of positive likelihood ratio to negative likelihood ratio > 100).[15,16]

The area under the curve (AUC) of the receiver operating characteristic was calculated with a nonparametric method,[20-22] and the 95% confidence intervals were calculated with the Wilcoxon test. Results were classified as uninformative (AUC = 0.5), poorly accurate (0.5 < AUC = 0.7), moderately accurate (0.7 < AUC = 0.9), highly accurate (0.9 < AUC = 1), or perfect (AUC = 1). Statistical significance was set at $P < .05$.

Results

Five hundred eighty-nine infants were admitted to the pediatric ICU from March 2004 to September 2005. Forty-one received mechanical ventilation because of severe acute bronchiolitis. One of them died because of sepsis, and we excluded that data from the analysis.

The median and IQR values of patient characteristics were: age 4 (3–7) months, weight 5 (4–8) kg; mean airway pressure 17 (16–19) cm H_2O; oxygenation index 6 (5–8); mechanical ventilation time 6 (3–10) d; Pediatric Risk of Mortality II score 17 (12–20); Ramsay score 3 (3–4).

Table 1. Characteristics of 40 Extubated Infants With Severe Acute Bronchiolitis

	Extubation Failure (n = 6) (15%)	Extubation Success (n = 34) (85%)	P
Age (median and IQR months)	5 (3–8)	4 (4–6)	.87
Weight (median and IQR kg)	4 (3–5)	6 (5–7)	< .001
Sex (M/F)	3/3	21/13	.66
Comorbidities (n)			
Prematurity	2	15	> .99
Congenital heart disease	2	5	> .99
Hydrocephalus	1	4	> .99
Sepsis	0	4	> .99
Cystic fibrosis	0	1	> .99
None	1	5	> .99
Duration of mechanical ventilation (median and IQR d)	8 (6–23)	6 (5–12)	.52

IQR = interquartile range

An associated condition was found in 85% (34/40) of the patients: prematurity (43%), congenital heart diseases (13%), and hydrocephalus (13%) (Table 1).

Extubation failure occurred in 15% (6/40) of the infants. All had associated morbidities, and the most frequent were prematurity and congenital heart disease (see Table 1). None of the patients received noninvasive ventilation. The demographic characteristics of the groups were similar, but the mean weight of infants in the extubation-failure group was lower ($P < .001$). The duration of mechanical ventilation (see Table 1), PIP, PEEP, RSBI, oxygenation index, and arterial blood gases were not different between the groups (Table 2).

The respiratory parameters before extubation are shown in Table 2. During the pre-extubation spontaneous breathing test the mean V_T and $\dot{V}_E$ were greater in the extubation-success group. The other parameters (respiratory rate and F_{IO_2}), measured 1 hour before extubation, were not significantly different between the groups.

We calculated the AUC for the prediction of extubation failure, the sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values for the following variables, when they reached $P \leq .05$ in the comparison of the extubation-success and extubation-failure groups: weight $\leq$ 4 kg, $V_T \leq$ 4 mL/kg, $\dot{V}_E \leq$ 0.8 mL/kg/min, $PI_{max} \leq$ 50 cm H_2O, load/force balance $\geq$ 5, RSBI $\geq$ 6.7 (Table 3).

Discussion

Pediatric studies have not definitely determined predictive factors, weaning protocols, or ventilatory predictive indexes of extubation-failure risk in groups of infants with

Table 2. Pre-extubation Mechanical Ventilation Parameters, Arterial Blood Gas Values, and Respiratory Indexes

	Extubation Failure (n = 6) (15%)	Extubation Success* (n = 34) (85%)	P
PIP (mean ± SD cm H_2O)	20 ± 8	27 ± 5	.08
PEEP (mean ± SD cm H_2O)	7 ± 3	5 ± 2	.08
Spontaneous respiratory rate (mean ± SD breaths/min)	38.2 ± 10.7	38.6 ± 11.4	.93
F_{IO_2} (mean ± SD)	0.3 ± 0.1	0.3 ± 0.1	.30
Inspiratory time (mean ± SD s)	0.8 ± 0.1	0.8 ± .1	.29
V_T (mean ± SD mL/kg)	5 ± 2	10 ± 5	.003
$\dot{V}_E$ (mean ± SD mL/kg/min)	0.8 ± 0.5	2 ± 4	.01
pH (mean ± SD)	7.37 ± 0.1	7.41 ± 0.1	.21
P_{aCO_2} (mean ± SD mm Hg)	39 ± 11	43 ± 9	.31
P_{aO_2} (mean ± SD mm Hg)	75 ± 21	86 ± 26	.32
Rapid shallow breathing index (median and IQR)	9.4 (5–12)	4.4 (4–7)	.12
PI_{max} (median and IQR cm H_2O)	40 (34–50)	65 (64–72)	.001
Load/force balance (median and IQR)	5 (4–6)	4 (3.6–4.3)	.008
Mean airway pressure (median and IQR)	14 (10–18)	17 (16–19)	.048
Oxygenation index (median and IQR)	6 (2–10)	6 (6–9)	.55

* The difference between the extubation-success and extubation-failure groups was statistically significant.
PIP = peak inspiratory pressure
PEEP = positive end-expiratory pressure
F_{IO_2} = fraction of inspired oxygen
V_T = tidal volume
$\dot{V}_E$ = minute volume
PI_{max} = maximal inspiratory pressure

Table 3. Analysis of Risk Factors for Extubation Failure in Infants With Severe Acute Bronchiolitis

	Value and 95% Confidence Interval							
Risk Factor	Sensitivity (%)	Specificity (%)	AUC-ROC (%)	Positive Likelihood Ratio	Negative Likelihood Ratio	Odds Ratio	Positive Predictive Value (%)	Negative Predictive Value (%)
Weight ≤ 4 kg	50 (11.8–88.2)	76.5 (58.8–89.3)	63.2 (40.2–86.3)	2.13 (0.78–5.8)	0.65 (0.29–1.49)	3.25 (0.62–17.4)	27.3 (6.0–61)	89.7 (72.6–97.8)
V_T ≤ 4 mL/kg	33.3 (4.33–77.7)	88.2 (72.5–96.7)	60.8 (39.4–82.2)	2.83 (0.66–12.2)	0.76 (0.42–1.35)	3.75 (0.61–24.6)	33.3 (4.3–77.7)	88.2 (72.5–96.7)
$\dot{V}_E$ ≤ 0.8 mL/kg/min	83.3 (35.9–99.6)	97.1 (84.7–99.9)	90.2 (73.6–100)	28.3 (4.0–202)	0.17 (0.03–1.03)	165 (*)	83.3 (35.9–99.6)	97.1 (84.7–99.9)
PI_{max} ≤ 50 cm H_2O	100 (54.1–100)	94.1 (80.3–99.3)	97.1 (93–100)	17 (4.43–65.2)	0 (*)	(*)	75 (34.9–96.8)	100 (89.1–100)
Load/force balance ≥ 5	33.3 (4.33–77.7)	11.8 (3.3–27.5)	22.5 (1.2–43.9)	0.38 (0.12–1.18)	5.67 (1.92–16.70)	0.07 (0.01–0.43)	6.25 (0.77–20.8)	50 (15.7–84.3)
RSBI ≥ 6.7	33.3 (4.33–77.7)	11.8 (3.3–27.5)	22.5 (1.2–43.9)	0.38 (0.12–1.18)	5.67 (1.92–16.70)	0.07 (0.01–0.43)	6.25 (0.77–20.8)	50 (15.7–84.3)

* = Impossible to calculate because of insufficient number of cases.
AUC-ROC = area under the curve of the receiver operating characteristic
V_T = tidal volume
$\dot{V}_E$ = minute volume
PI_{max} = maximal inspiratory pressure
RSBI = rapid shallow breathing index

severe acute bronchiolitis.[6-12,23,24] Those studies found that protocols reduced mechanical ventilation duration, but they did not accurately identify which patients would fail extubation.[10] We believe that the analysis of extubation-failure risk factors should be conducted for populations that are as homogeneous as possible (in our case, infants up to 12 months of age) and with similar diseases (in this case, severe acute bronchiolitis). Previous studies included children with various ages and diseases.

The present study with ventilated infants with severe acute bronchiolitis found that the extubation failure rate in this population (15%) was similar to that in the general ventilated pediatric population. The pre-extubation measurement of the variables (demographic characteristics, arterial blood gas values, and mechanical-ventilation parameters) revealed no differences between the 2 groups (extubation failure vs extubation-success), except weight (P < .001), which was lower in the extubation-failure group. With the cut-off point of ≤ 4 kg, the results showed low sensitivity, good specificity, and a large AUC.

Age, particularly less than 3 months, is an independent factor associated with extubation failure.[9,24] However, the extubation failure rate in patients with acute bronchiolitis in our study (15%) did not differ from the extubation failure rates in groups of older children with other diseases.[6-12]

In our results, mean airway pressure, V_T, and $\dot{V}_E$ were significantly greater in the extubation-success group. However, mean airway pressure was measured during mechanical ventilation, and it is dependent on PIP, PEEP, and respiratory cycle time. The reason for the high risk of extubation failure may be ineffective spontaneous efforts, as suggested by a spontaneous V_T of 4 mL/kg. This study found low sensitivity and high specificity when the AUC was large for V_T. And specificity and sensitivity were high and AUC was large for $\dot{V}_E \leq 0.8$ mL/kg/min. This result was very similar to those reported by other studies.[7,9] Bedside measurements can be easily made with minimum handling of the child.

In previous pediatric studies[12,23-26] PI_{max} was used as an extubation predictor. Those studies included children of various ages and diseases, and positive predictive value of extubation success was obtained when PI_{max} was ≥ 45 cm H_2O. In at least one study,[13] $PI_{max} \geq 65$ (IQR 47–84) cm H_2O was found to be a valuable predictor of successful extubation. That value is very similar to the one we found in our study: $PI_{max} \geq 65$ (IQR 64–72) cm H_2O. To overcome the resistance caused by the obstruction of the small airways it is necessary to generate a larger pressure difference and, therefore, to have better inspiratory and expiratory muscle forces. Therefore, in infants with severe acute bronchiolitis, the predictive PI_{max} values for successful extubation should be higher. In our study, PI_{max} measured immediately before extubation was lower in the extubation-failure group; moreover, it had good sensitivity and specificity and very good accuracy as a risk factor of extubation failure (see Table 3). The lower PI_{max} in the infants who failed extubation (see Table 2) may be explained by a poorer respiratory drive,[27] lower inspiratory muscle strength, hyperinflation, or a combination of these factors.[28]

The load/force balance proposed by Vassilakopoulos et al[14] in 2006 was only evaluated in adult patients, and load/force balance = 1 was defined as the ideal cut-off point for successful extubation. This index is considered more complete because the load/force balance equation (given earlier) includes mean airway pressure, PIP, and RSBI, which makes it a more sensitive indicator for pre-extubation evaluation. In our study, the load/force balance values were significantly lower ($P = .008$) in the extubation-success group (4 [3.6–4.3]) than in the extubation-failure group (5 [4–6]), but sensitivity, specificity, and accuracy for extubation failure were lower. This is the first study to use the load/force balance to predict extubation failure in pediatric patients, and, specifically, in infants with severe acute bronchiolitis. The higher load/force balance in these infants may be assigned to the fact that some of their physiologic parameters are higher and have a wider range of variation than in adults.

Extubation failure may result from an inadequate drive, dysfunction of the respiratory muscles, excessive inspiratory load, or a combination of these factors. Therefore, evaluation of the drive and of respiratory muscle functioning might more accurately detect infants at risk of extubation failure.[28] The load/force balance value combines physiologic data and may therefore be a good index for pediatric patients. However, pediatric patients with other diseases should be studied to establish a reliable cut-off point for risk of extubation failure.

Farias et al studied pediatric patients who received mechanical ventilation because of several distinct etiologies.[12,24,25] They found that RSBI > 6.5 can poorly predict extubation failure. In our study with infants with severe acute bronchiolitis, an RSBI of 6.7 had low sensitivity and specificity and a small AUC, and these results are very close to those described by Farias. The variability of physiologic parameters is higher among children, and this is true of weight, respiratory rate, and V_T, which are directly involved in RSBI. This fact makes it difficult to use RSBI as a reliable index for all pediatric patients.

Some limiting factors in our study restrict the extrapolation of our data. We used only one ventilation mode, so the effect of other ventilation modes on extubation failure was not evaluated. There was no predefined protocol for weaning. There was a limited number of extubation failures. And previous studies did not analyze the cut-off points found in this research, so further studies are needed.

Conclusions

In infants with severe acute bronchiolitis the extubation process is complex because of the combined features of this disease. Pediatric studies have not definitely determined predictive factors, weaning protocols, or ventilatory predictive indexes of extubation-failure risk in infants with severe acute bronchiolitis. This study showed that lower $\dot{V}_E$ and PI_{max} values had large AUC of extubation-failure risk in infants with severe acute bronchiolitis.

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