

Factors that May Predict the Need for Invasive Mechanical Ventilation in Severe Acute Bronchiolitis

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ABSTRACT

Objective: Severe acute bronchiolitis patients may require mechanical ventilation despite other non-invasive respiratory support modalities in the intensive care unit. Referral of the patients who may require intubation to experienced centers, may reduce invasive ventilation associated complications. The objective of this study is to determine the risk factors at PICU admission that may predict the mechanical ventilation requirement in severe acute bronchiolitis patients.

Methods: Retrospective chart review of patients admitted to the PICU due to severe acute bronchiolitis between 01.08.2018-01.11.2019 were included in to the study.

Results: One hundred and five patients were enrolled. High flow nasal cannula was used in 70 patients (66.6%), non-invasive ventilation (spontaneous/time mode) was used in 19 (18.1%) patients and invasive mechanical ventilation was used in 16 (15.3%) patients. Birth weight (Odds Ratio [OR]:0.99), admission weight (OR:0.749), age in months (OR:0.763), history of prematurity (OR:3.06), presence of chronic respiratory diseases (OR:4.61), presence of chronic cardiac diseases (OR:3.23) and respiratory syncytial virus infection (OR:4.37) were significant for intubation requirement in logistic regression analysis. Age \leq 4 months (sensitivity: 50% specificity: 85.3%) and birth weight \leq 3000 g (sensitivity: 75% specificity: 75.8%) were found significant in receiver operating characteristics curve analysis.

Conclusion: Invasive mechanical ventilation in severe acute bronchiolitis is a challenging process that requires experience. History of prematurity without chronic lung disease appears not to be a significant risk factor for intubation. Patients with chronic lung disease, low birth weight, history of prematurity especially when these are complicated with RSV infection should be transferred to experienced centers in the early period.

Keywords: Bronchiolitis, artificial respiration, infant, critical care

Introduction

The clinical picture that starts with viral prodrome and progresses with wheezing and respiratory distress in children under two years of age is defined as acute bronchiolitis (AB) (1). It is known that it can be seen as often as 20%, especially in the first year of life. (2). More than half of the cases can be treated without hospitalization (3). On the other hand, 0.13-0.16% of the cases may require intensive care admission (4). Risk factors associated with severe clinical course in AB patients have been investigated in different studies and younger age ($<$ 12 month), prematurity, presence of congenital heart or chronic lung diseases, and immunodeficiency have been found more risky

for severe disease (1). The mortality rate was reported around 5% in the patients followed up in the pediatric intensive care unit (PICU) (5). Although risk factors for the severe clinical course have been defined in acute bronchiolitis, there are no sufficient studies for factors predicting the intubation risk in acute bronchiolitis. Management of IMV in AB is difficult even for pediatric critical care specialists, it is inevitable to see serious complications such as pneumothorax or pneumomediastinum for inexperienced physicians. Therefore, it is important to know the factors that can predict a severe clinical course. Our study aims to reveal the risk factors in terms of the need for intubation in patients admitted to the PICU due to severe AB.



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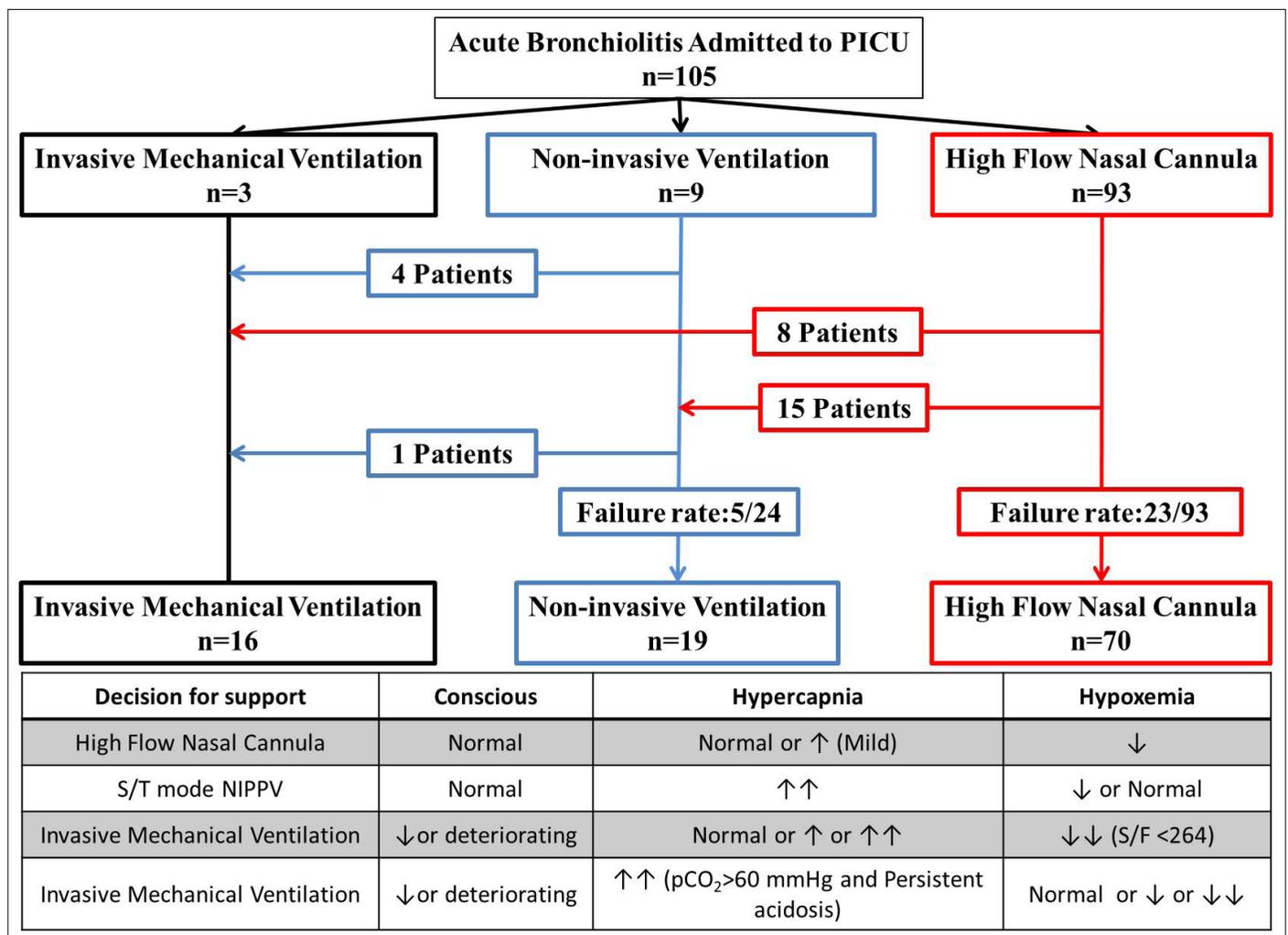


Figure 1. Decision algorithm for respiratory support in admission or any time during intensive care unit stay.

Materials and Methods

The patients aged between 1 and 24 months and admitted to the PICU due to severe AB between 01.08.2018-01.11.2019 were retrospectively evaluated. Patients with cyanotic heart disease (decision algorithm not applicable) and patients with tracheostomy were not included in the study. Signs and symptoms associated with poor feeding and respiratory distress characterized by tachypnea, nasal flaring, and hypoxemia ($SpO_2 < 94\%$ in room air) or hypercapnia ($pCO_2 > 60$ mmHg) were defined as severe AB (1). High-flow nasal cannula (HFNC), spontaneous/time (S/T) mode non-invasive positive pressure ventilation (NIPPV) with oro-nasal or full face mask, or IMV were applied to the patients according to their clinical needs. Our clinical algorithm for the management of severe AB is as follows (Figure 1). Conscious patients with mild hypoxemia ($SpO_2 < 94\%$ in room air, that can be normalized with $FiO_2 < 40\%$) and normocapnia (or mild hypercapnia $pCO_2 < 60$ mmHg) at admission were followed up with HFNC. Conscious patients with hypercapnia ($pCO_2 > 60$ mmHg), and with or without mild hypoxemia in admission or any time during PICU stay were followed up with S/T mode NIPPV. Unconscious patients (without sedation) or persistent severe hypoxemia ($sPO_2/FiO_2 < 264$ or $FiO_2 > 40\%$ for $SpO_2 > 94\%$) or persistent respiratory acidosis with severe hypercapnia ($pCO_2 > 60$ mmHg with abnormal

or deteriorating consciousness) in admission or any time during PICU stay were followed up with IMV. Pressure regulated volume control-assist/control (PRVC-A/C) mode has been used in the initial mechanical ventilation management and synchronized intermittent mandatory ventilation (SIMV) modes (pressure control or PRVC) have been used in the weaning period. Intubated patients has been followed up with deep sedation, analgesia and neuromuscular blocking agents (rocuronium or vecuronium) until the lung dynamics improve. Patients were adequately been sedated at a level that will not interfere with spontaneous breathing during the weaning period. In cases more than one respiratory support method were used, the most advanced (IMV>NIPPV>HFNC) method was taken into consideration. A crowded home environment was defined as five or more people living at the same home. Patient datas such as age, gender, admission weight, prematurity, birth weight, onset time of complaints, previous hospital admissions, chronic diseases, modified Wood's Clinical Asthma score (mWCAS) (6), and nasal swab polymerase chain reaction (PCR) results (influenza A, B, and respiratory syncytial virus) were collected.

Categorical variables were expressed as n (%) and continuous variables were expressed as the median and interquartile range (25p-75p) or mean and standart deviation (SD) according to

normality. The Kolmogorov–Smirnov test was used for *normality analysis*. Logistic regression analysis was used for risk factor analysis for intubation requirement and results were presented as odds ratio (OR), 95% confidence interval (95% CI), and p-value. Receiver operating characteristics (ROC) curve analysis was used to investigate the predictive value of significant parameters in logistic regression for intubation requirement. Chi-square test or Fisher's exact test was used according to availability for statistical comparison of categorical variables between two groups. Mann-Whitney U or independent t-test (according to normality) was used for statistical comparison of independent continuous variables between two groups. A p-value <0.05 was considered significant for all statistical analyses. SPSS (statistical package for social sciences) version 23 for Windows and Medcalc 14.8.1 for Windows were used for statistical calculations.

This study was reviewed and approved by the local ethics committee.

Results

One hundred and five patients aged between 2-24 months (mean 7.9 month [SD: 4.3]) months) were included in the study. Thirty-nine (37.1%) of the patients were female. The mean admission weights of the patients were 9.1 kg (SD: 2.18). There was a

history of prematurity in 25 (23.8%) of patients. The median birth weights of patients were 3200 g (2780-3450). Fifty-four (51.9%) patients had a history of previous hospitalizations and 68 (64.8%) patients had a history of chronic diseases. The onset of complaints before PICU was 4 days (2-7). Respiratory syncytial virus (RSV) was detected in 41 (39%), and influenza virus was detected in 7 (6.7%) patients. The median mWCAS of the patients was 5 (4-5). Sixteen (15.3%) patients require IMV (Table 1). HFNC was used in 70 patients (66.6%) and NIPPV was used in 19 (18.1%) patients during the study period. Duration of IMV was median 7.5 days (7-8). Air leak syndromes that may be associated with IMV has not been seen in any patients. The median length of stay in the PICU was 10 days (8-11) while the total hospital stay was 14 days (12-15). The results of logistic regression analysis for the intubation risk of the patients were presented in Table 2. Continuous variables that statistically significant in the logistic regression analysis were also evaluated by ROC curve analysis. Birth weight, age, and admission weight were included in ROC curve analysis for predicting intubation requirement. For birth weight cut off value ≤ 3000 g, sensitivity was 75% and specificity was 75.28% (AUC: 0.768, 95% CI: 0.676-0.845; $p < 0.001$). For age in months cut off value ≤ 4 months, sensitivity was 50% and specificity was 85.3% (AUC: 0.708, 95% CI: 0.611-0.792; $p = 0.002$). ROC curve analysis was found non-significant for admission weight ($p = 0.2$).

Table 1. General characteristics of intubated and non-intubated acute bronchiolitis patients.

	Non-Intubated (n=86)	Intubated (n=16)	p	
Age (month) *	8.3±4.4	5.1±2.5	<0.001	
Gender (female)**	33 (37.1%)	6 (37.5%)	0.9	
Birth Weight (g)**	3300 (3020-3600)	2800 (1240-3075)	0.001	
Admission Weight (kg)*	9.4±1.89	7.9±3.15	0.08	
Peripherally Oxygen Saturation (%)*	92.1±2.5	90.7±3.7	0.3	
Heart Rate (/min)*	146.5±17.8	154±25.	0.28	
Respiratory Rate (/min)**	52 (48-60)	53 (48-60)	0.97	
RSV positive*	30 (33.7%)	11 (68.8%)	0.008	
Influenza Positive*	5 (5.6%)	2 (12.5%)	0.31	
History of Prematurity+	18 (20.2%)	7 (43.8%)	0.04	
Weeks of Pregnancy+	≤ 28 Week	5 (5.6%)	2 (12.5%)	
	29 to ≤32 Week	7 (7.9%)	2 (12.5%)	
	32 to ≤35 Week	0 (0%)	2 (12.5%)	0.009
	35 to ≤37 Week	6 (6.7%)	1 (6.3%)	
	≥ 38 Week (Term)	71 (79.8%)	9 (56.3%)	
Previous Hospitalizations for Acute Bronchiolitis*	43 (48.9%)	11 (69.8%)	0.143	
Chronic Heart Disease*	21 (23.6%)	8 (50%)	0.03	
Chronic Respiratory Disease*	6 (6.7%)	4 (25%)	0.02	
Chronic Neurologic Disease*	7 (7.9%)	2 (12.5%)	0.54	
Passive Smoke exposure*	37 (41.6%)	10 (62.5%)	0.12	
Crowded home environment*	20 (22.2%)	5 (31.3%)	0.44	
Modified Wood's Clinical Asthma score**	5 (4-5)	5 (4-6.5)	0.07	
Intensive Care Length of Stay (day)**	9 (8-10)	11 (10-13.5)	<0.001	
Hospital Length of Stay (day)**	13 (12-14)	15 (14.5-20.5)	<0.001	

*Expressed as mean±standard deviation. Statistical calculation (p-value) was performed by t-test.

**Expressed as median and interquartile range (25p-75p). Statistical calculation (p-value) was performed by Mann Whitney U test.

+Expressed as n (%). Statistical calculation (p-value) was performed by Chi-square or Fisher's exact test.

Table 2. Logistic regression analysis of independent parameters for mechanical ventilation.

Independent Parameters	OR*	95% Confidence Interval for OR		p
Birth weight (g)	0,9993	0,9988	0,9998	0,008
Age (month)	0,763	0,618	0,941	0,01
Prematurity (yes/no)	3,068	1,006	9,355	0,049
Chronic Respiratory Diseases (yes/no)	4,611	1,134	18,746	0,03
Chronic Heart Disease (yes/no)	3,23	1,083	9,683	0,03
RSV** positive (yes/no)	4,327	1,377	13,594	0,012
Admission Weight (kg)	0,749	0,593	0,947	0,01
Independent Parameters*	OR*	95% Confidence Interval for OR		p
Birth weight (g)	0,9993	0,9986	0,9999	0,03
Age (month)	0,819	0,648	1,034	0,09
Prematurity (yes/no)	1,97	0,46	8,34	0,37
Chronic Heart Disease (yes/no)	2,57	0,73	9,1	0,15
RSV** positive (yes/no)	2,9	0,84	9,99	0,08
Admission Weight (kg)	0,8	0,62	1,07	0,14

*Odds Ratio, **Respiratory Syncytial Virus, *Patients with Chronic Respiratory Diseases were Excluded

Discussion

Pediatric intensive care units are still not available homogeneously all over the world. Both the adequacy of tertiary care PICU and the number of pediatric critical care specialists in developing countries are still at low levels (7). Management of IMV is an important part of pediatric critical care and requires different strategies in different diseases. Serious complications may occur due to air trapping in severe AB when IMV technics are not used properly (8). The frequency of pneumothorax is reported to be around 10% in patients with AB under IMV even followed in PICU (9, 10) Therefore; early referral of risky patients to experienced pediatric intensive care units may reduce possible complications and associated mortality and morbidity.

Our study shows that the need for IMV is significantly higher in patients with low birth weight, RSV infection, low admission weight, young age, history of prematurity, and chronic lung or heart disease. The risk factors for continuous positive airway pressure (CPAP) or mechanical ventilation requirement in patients with acute bronchiolitis has been investigated in a study conducted in the United States and, younger age, small for gestational age at birth, maternal smoking history, the onset of breathing difficulties <1 day before emergency department visit, presence of apnea, presence of severe retractions, oxygen saturation <85% (in room air), and inadequate oral intake has been reported to be significant (11). Apnea, mWCAS ≥ 7 , and $SpO_2 \leq 75$ has been reported as important risk factors for intubation in another study which investigated risk factors for IMV in patients with AB (12). We think that intubation indications and intubation risk factors should be different terms. Therefore, in our study, we included the general characteristics of the patient and causative viral pathogens as risk factors, which were not associated with the course of the disease. mWCAS ≥ 4 (moderate disease) is an indication for PICU follow-up in our clinical practice and we think mWCAS ≥ 7 (severe disease) is an indication of intubation or NIPPV rather than a risk factor. In our study, mWCAS were not different between intubated and non-intubated patients because mWCAS were collected in admission, not just before intubation.

It is known that passive smoking exposure in the infantile period significantly increases lower respiratory tract infections (13). It has been reported that the risk of severe AB is 2.8 times higher in infants whose family members smoke (14). It has also been reported that in utero exposure to maternal smoking increases the risk of PICU admission and the need for CPAP / IMV in cases of AB (11, 15). Forty-seven (44.8%) of our patients had a history of passive smoking exposure. However, we could not show a relationship between passive smoking exposure and the need for intubation. This suggests that smoking exposure does not affect the IMV requirement among severe AB cases. However, this needs to be confirmed by larger studies.

We prefer HFNC rather than CPAP in our cases because of its ease of use and better patient compliance. There are many studies in the literature comparing rates of treatment failure of nasal CPAP and HFNC in AB patients. However, this is still controversial, because some of the studies claim the superiority of nasal CPAP (16, 17) while others affirm that HFNC is equivalent to nasal CPAP (18-20). In our study, HFNC failure was observed at a rate of 24.7% and S/T mode NIPPV failure was observed at a rate of 20.8%. However, these data were not statistically or clinically comparable because the decision of respiratory support type was made by different clinical criteria.

Bronchopulmonary dysplasia (BPD) has been reported as the most common cause of chronic lung disease in the infantile period. Incidence is reported as 40% in premature babies born at 28 weeks or less (21). Although RSV infection is a serious problem in BPD cases, it has been reduced significantly with the widespread use of palivizumab (22). In a study evaluating the effect of palivizumab on RSV-related hospitalizations, it was shown that palivizumab significantly reduced the RSV-related hospitalization rate in preterm babies with BPD from 12.8% to 7.9%. The presence of chronic lung disease is resulted as a more significant risk factor than prematurity in our study. The most likely reason for this is that almost all patients with chronic lung disease have a history of prematurity and when cases with chronic lung disease are excluded,

prematurity itself does not appear to be a significant risk factor for intubation. In our study, birth weight appears to be a significant factor in terms of intubation risk. Every 100 g decrease in birth weight increases the risk of intubation by 7%. Unlike prematurity, the relationship between birth weight and intubation risk continues even when the patients with chronic lung disease was excluded.

This study has some limitations. Retrospective study design and the small sample size are the major limitations of the study. Palivizumab data of the patients could not be reviewed because of the insufficient data in the patient files. This study includes severe AB cases that followed up in the intensive care unit so the

results of this study can not be generalized for AB cases followed-up outside of PICU.

In conclusion; IMV in severe acute bronchiolitis cases is a challenging process that requires experience. Early referral of patients to experienced centers may reduce mortality and morbidity. History of prematurity without chronic lung disease appears not to be a significant risk factor for intubation in our study. However, this needs to be confirmed by larger studies. We think that cases with chronic lung or heart disease, low birth weight, history of prematurity, especially when these are complicated with RSV infection should be transferred to experienced centers in the early period.

AUTHOR CONTRIBUTIONS:

Concept: HSK, EAO; **Design:** HSK, EAO; **Supervision:** HSK, EAO; **Materials:** HSK, EAO; **Data Collection and/or Processing:** HSK, EAO; **Analysis and/or Interpretation:** HSK, EAO; **Literature Search:** HSK, EAO; **Writing Manuscript:** HSK, EAO; **Critical Review:** HSK, EAO.

Ethics Committee Approval: This study was reviewed and approved by the University of Health Sciences Antalya training and research hospital ethical committee. Decision number:2019-25/9

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors have no conflicts of interest to declare.

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