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Increase in use of non-invasive ventilation for infants with severe bronchiolitis is associated with decline in intubation rates over a decade

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Abstract *Purpose:* To redress the paucity of studies evaluating non-invasive respiratory support in bronchiolitis patients.
Methods: Following ethics committee approval, the clinical database of a tertiary 23-bed paediatric intensive care unit (PICU) was reviewed for bronchiolitis admissions from January 2000 to December 2009. Length of stay (LOS), ventilatory requirements and risk factors, including prematurity, respiratory syncytial virus (RSV) status, chronic lung, neuromuscular, immune and congenital heart disease, were analysed. *Results:* Of 8,288 admissions, 520 (6.27 %) had bronchiolitis with 343 (65.9 %) having RSV. Median (±SD) age and LOS were 2.78 months and 2.68 (±4.32) days. One (0.2 %) patient died. Assisted ventilation was required for 399 (76.7 %) patients. A total of 114 (28.6 %) patients were intubated directly and 285 (71.4 %) had a trial of non-invasive ventilation (NIV). Significant increase in the use of NIV was seen (2.8 %/year) with decline in intubation rates (1.9 %/ year) ($p = 0.002$). Of NIV patients, 237 (83.2 %) needed only NIV and 48 (16.8 %) failed and therefore needed intubation. The median LOS was shorter in those who succeeded NIV (2.38 ± 2.43 days) compared to those with invasive ventilation (5.19 ± 6.34 days) and those who failed NIV (8.41 ± 3.44 days). Presence of a risk factor increased the chances of failing NIV from 6 to 10 %. *Conclusion:* NIV was successful in the vast majority of patients, particularly in those without risk factors and halved the LOS in intensive care. Failure of NIV was associated with increased duration of invasive ventilation and PICU LOS. A prospective study comparing different techniques of NIV will be helpful in defining the risks of failure of NIV.

Keywords Non-invasive positive-pressure ventilation · Bronchiolitis · Intubation · Continuous positive airway pressure · Respiratory syncytial virus · Congenital heart defect · Length of stay

Introduction

Bronchiolitis is an important respiratory illness in infancy, particularly for those with co-morbid conditions, such as chronic lung disease and/or congenital cardiac disease [1]. It is the most common indication for non-

elective admissions to paediatric intensive care units (PICU) in Australia and New Zealand, comprising 11.5 % of such admissions in 2008 as per the Australia and New Zealand Intensive Care Registry [2]. Whilst outcomes are typically good, supporting the respiration of an infant entails a significant length of stay in intensive care,

typically 4–7 days [3, 4]. Increasingly, this respiratory support has been provided using various non-invasive ventilation (NIV) techniques; however, there is a paucity of studies describing its use and effectiveness in this setting.

NIV techniques have developed over the last 80 years and have been increasingly refined in the last 20 years since their use begun in obstructive sleep apnoea and related conditions [5]. The use of NIV in adult critical care patients has shown benefits when compared to intubation or venturi mask in terms of mortality, reduced length of stay, reduced ventilator-associated pneumonia and associated cost savings [6–8]. NIV has improved the outcome of neonatal respiratory distress syndrome and has a solid evidence base [9]. Despite the perceived benefits of NIV, there are a limited number of small studies and a shallow research base exists for its use in paediatric critical care.

NIV support of infants with bronchiolitis was first described by Beasley and Jones [10] and later developed by Soong et al. [11]. Twenty three children with bronchiolitis had improved respiratory rates and carbon dioxide clearance after NIV support; all avoided invasive ventilation. Thia et al. [12] compared NIV with no ventilation support over three winters in 29 infants and showed improved CO_2 clearance with NIV use. In a retrospective historical cohort trial, NIV was compared with invasive ventilation in 80 French infants with bronchiolitis. NIV was associated with an absence of ventilator-associated pneumonia and a reduced requirement for supplementary oxygen post ventilation; length of stay was unchanged [3]. These limited studies suggest that NIV in the setting of bronchiolitis may be associated with benefits compared with no ventilation or invasive ventilation. However, given the small number of patients involved it is difficult to draw definite conclusions. We have used NIV for over 10 years in the setting of bronchiolitis and so undertook a review of its use and the impact of its increasing use on the associated outcomes. The primary objective of this review was to delineate the trend in the use of NIV and its associated impact on the need for intubation and length of respiratory support and stay in the PICU. We also tried to find out whether there were any risk factors at admission that would predict failure of NIV.

Methods

Following ethics committee approval, a retrospective cohort study of all the patients admitted with bronchiolitis from January 2000 till December 2009 was undertaken. The paediatric intensive care unit (PICU) is a 23-bed tertiary unit. Demographic and outcome data, such as length of stay and mortality, were retrieved from the PICU database. Co-morbidity risk factors, such as prematurity, chronic lung disease, airway disease, neuromuscular disease, immune deficiency and congenital heart disease, were obtained by reviewing individual medical records. Children with FiO_2 requirement more than 0.6, recurrent apnoea, clinical instability or poor perfusion after adequate fluid resuscitation were intubated as per the unit protocol. Children who showed the aforementioned signs while on NIV were considered as NIV failure and were intubated. Details of ventilation were obtained by reviewing the individual computerised medical records of those children who needed assisted ventilation. Respiratory syncytial virus (RSV) status was also noted from the records. NIV was administered using a nasal or full face mask continuous positive airway pressure (CPAP) device and invasive ventilation was administered via nasal or oral endotracheal intubation. NIV success was defined as discharge from PICU without the need for endotracheal ventilation after trial of NIV (NIV success). Those infants who commenced on NIV, but required endotracheal intubation were considered a failure of NIV (NIV failed) (Fig. 1).

Data were expressed as frequencies and percentages for categorical variables and as median or median ± standard deviation (SD) for continuous variables. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, Illinois, USA). For categorical variables, comparisons were performed using the χ^2 test reporting odds ratio and 95 % confidence interval (95 % CI). Continuous variables were analysed using the Mann–Whitney U test. Frequencies were calculated for each year to assess the trend in use of assisted ventilation techniques. Logistic regression analysis was used for analysing trends in different modes of ventilation. Predictors of NIV failure were assessed using logistic regression and χ^2. A p value of less than 0.05 was considered statistically significant.

Results

There were 8,288 admissions to PICU from January 2000 to December 2009, with 520 (6.27 %) admitted with a principal diagnosis of bronchiolitis. The average patient age was 4.81 (±0.25) months and 56.7 % were boys. One patient (0.2 %) died and the overall median (±SD) length of stay was 2.68 (±4.32) days. For the 121 (23.3 %) of children who did not need positive-pressure support the median (±SD) length of stay was 1.08 (±1.81) days. There were 399 (76.7 %) children with bronchiolitis who needed assisted ventilation (PPS). The majority of these patients, 285 (71.4 %), received a trial of NIV, whilst the remaining 114 (28.6 %) were intubated without a trial of NIV. This latter group had a median (±SD) length of stay of 5.19 (±6.34) days. Out of all the children having NIV,

Fig. 1 Total admissions with bronchiolitis and their distribution according to ventilation requirements. *PPS* positive-pressure support (non invasive + invasive ventilation), *NIV Trial* trial of non-invasive ventilation before intubation if needed, *NIV Success* non-invasive ventilation successful, intubation not required, *ET only* endotracheal intubation only, no trial of non-invasive ventilation, *NIV Failure* non-invasive ventilation unsuccessful, intubation required
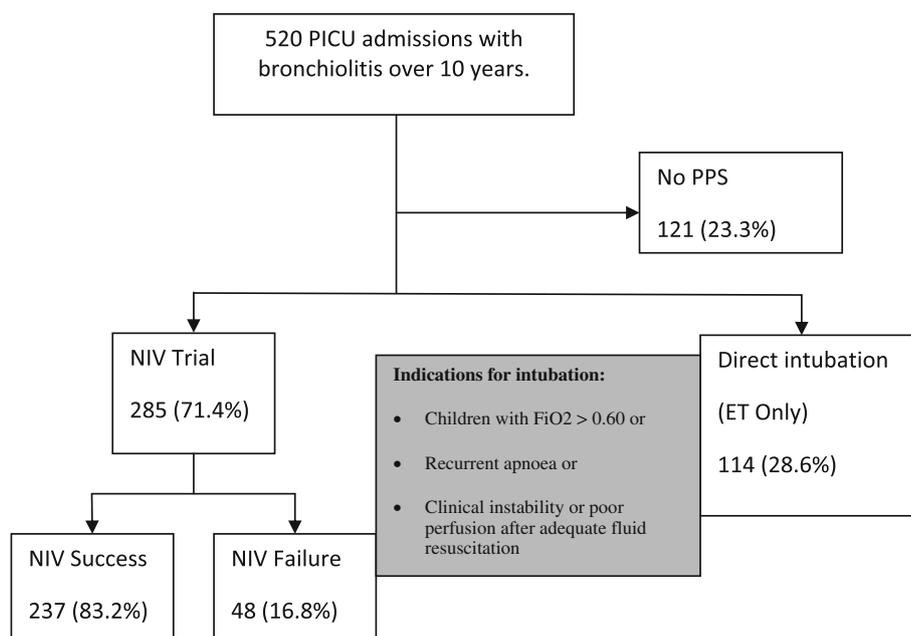
237 (83.2 %) only needed NIV and had a median (±SD) length of stay of 2.38 (±2.43) days. A minority of patients needing NIV, 48 (16.8 %), failed and had a median (±SD) length of stay of 8.41 (±3.44) days. Demographics and risk factors of the infants with bronchiolitis, according to the ventilation modalities they received, are shown in Table 1. Please refer to Fig. 1 for the branching decision tree regarding use of positive-pressure support (NIV vs. ET).

The proportion of children needing assisted ventilation (either NIV or invasive ventilation) per year remained similar ($p = 0.14$) over the 10-year study period. Linear regression analysis showed a 2.8 % rise in the use of NIV every year ($p = 0.002$), with decline in invasive ventilation by 1.4 % per year ($p = 0.04$) during the 10 years, see Fig. 2. Patient characteristics on admission to ICU and risk factor profile did not change significantly over the study period.

There were 48 (16.8 %) children who failed a trial of NIV and needed invasive ventilation. Over the study period, the percentage of children failing NIV declined significantly from 31.8 to 13.5 % as NIV was increasingly used over years. The median (±SD) length of stay in PICU was significantly shorter in those with a successful trial of NIV compared to those requiring invasive ventilation [2.38 vs. 5.19; ($p < 0.001$)]. Those who failed NIV had a siginificantly longer length of stay as compared to those who did not (NIV success). The difference between the length of stay in the NIV failed and ET only groups failed to reach significance, see Table 2. There was significant difference in the duration of invasive ventilator support between those who failed NIV and those directly invasively ventilated (ET only) ($p = 0.022$). Those failing NIV typically did so just over 12 h after commencement. Amongst those who failed NIV, there was a significant negative correlation between the duration of NIV and the

Table 1 Demographics and risk factors according to different ventilation requirements

	All	No PPS	NIV success	ET only	NIV failed
Total *n* (%)	520	121 (23.3 %)	237 (45.6 %)	114 (21.9 %)	48 (9.2 %)
Age in months median (±SD)	2.78 (±0.25)	3.53 (±7.14)	2.67 (±5.61)	2.4 (±4.52)	2.87 (±3.47)
Male (%)	56.7 %	59.5 %	54 %	56.3 %	59.6 %
RSV positive	343 (65.9 %)	77 (63.6 %)	145 (61.2 %)	80 (70.2 %)	41 (85.4 %)*
Any risk factor	214 (41.2 %)	37 (30.6 %)	98 (41.4 %)	50 (43.9 %)	29 (60.4 %)#
Median length of stay (SD) days	2.68 (±4.32)	1.08 (±1.81)	2.38 (±2.43)	5.19 (±6.34)	8.41 (±3.44)

PPS positive-pressure support, *No PPS* no positive-pressure support, *NIV success* non-invasive ventilation successful, intubation not required, *ET only* endotracheal intubation only, no trial of non-invasive ventilation, *NIV failed* non-invasive ventilation unsuccessful, intubation required, *Any risk factor* presence of any of the following: prematurity, chronic lung disease, airway disease, congenital heart disease, immune deficiency, neuromuscular disease

* p value = 0.002 (2-sided) for comparison between NIV success and NIV failed OR (95 % CI) = 3.3 (1.4–7.5)

p value = 0.009 (2-sided) for comparison between NIV success and failed OR (95 % CI) = 2.3 (1.2–4.2)
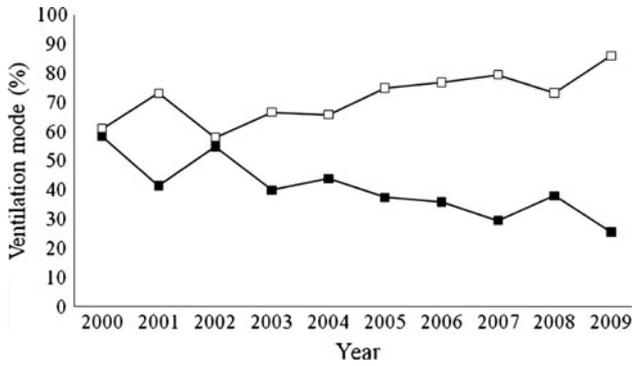
Fig. 2 Trends in modes of ventilation over 10 years. The percentage of ventilation modes over 10 years in bronchiolitis patients: *open box* non-invasive ventilation, *closed box* invasive ventilation. There is a statistically significant increase in NIV support of 2.8 % per year and a significant decline of 1.4 % per year in invasive support, $p < 0.05$ over the study period

duration of ET ventilation with a coefficient of -0.321 ($p = 0.028$) indicating that those who failed NIV early needed longer invasive ventilation. Over the period of 10 years, there was no significant change in the length of stay in any of the groups.

The presence of any co-morbidity risk factor, odds ratio (95 % CI) = 1.79 (1.16–2.78) ($p = 0.009$), neuromuscular disease odds ratio (95 % CI) 3.0 (1.1–8.56) ($p = 0.03$) and prematurity odds ratio (95 % CI) 2.1 (1.25–3.52) ($p = 0.004$) were associated with needing positive-pressure ventilation (Table 3). In patients who received NIV, there was no single risk factor significantly predicting failure of NIV support. Although the presence of any risk factor ($p = 0.03$) was associated with failure of NIV, none of the individual risk factors were

associated significantly with failure except for the presence of cardiac disease which failed to achieve significance ($p = 0.055$). Commencement on NIV without any risk factor had a 94 % chance of success, which was significantly reduced, but still reasonable with the presence of any risk factor, with 90 % of such patients successfully managed on NIV.

Discussion

Non-invasive support has been well studied in neonatal and adult respiratory failure, but a definitive randomized trial has not been performed in children. We have increasingly used NIV in various respiratory conditions, but particularly in infants with bronchiolitis. Despite these patients typically having a good outcome, they can spend a number of days in intensive care. NIV has been shown to reduce the length of stay in adult studies compared with invasive ventilation and patients with immune deficiency have better outcomes when managed with NIV [6, 8]. We have now used NIV support in over 500 infants and so reviewed associations with its use. Increasing NIV use in our unit was associated with a decline in invasive ventilation despite a similar patient risk profile over a period of 10 years.

NIV was associated with a significant shortening of the PICU length of stay—half compared to invasively ventilated patients. Failure of NIV was associated with a 20 % longer length of stay compared to invasively ventilated patients and early failure was associated with a longer invasive ventilation and PICU length of stay. The vast majority, 94 % of patients, that were commenced on

Table 2 Ventilation and PICU stay characteristics according to different modes of ventilation

	Total	No PPS	NIV success	ET only	NIV failed	Comparing NIV success with ET only[a] and NIV failed[b] p value	Comparing NIV failed with ET only p value
PICU length of stay (days)	2.68 (±4.32)	1.08 (±1.81)	2.38 (±2.43)	5.19 (±6.34)	8.41 (±3.44)	<0.001[a] <0.001[b]	0.000[c]
PPS (days)	2.00 (±4.36)	–	1.08 (±2.38)	4.41 (±5.57)	6.23 (±3.51)	<0.001[a] <0.001[b]	0.414[c]
NIV (days)	0.96 (±2.21)	–	1.08 (±2.38)	–	0.39 (±0.60)	–	
Invasive ventilation (days)	4.54 (±5.25)	–	–	4.41 (±5.57)	5.55 (±3.63)	–	0.022[c]

Data are median ± SD

PPS positive-pressure support (non-invasive + invasive ventilation), *NIV success* non-invasive ventilation successful, intubation not required, *ET only* endotracheal intubation only, no trial of non-invasive ventilation, *NIV failed* non-invasive ventilation unsuccessful, intubation required

[a] p value for comparison between NIV success and ET only using Mann–Whitney U est

[b] p value for comparison between NIV success and NIV failed using Mann–Whitney U test

[c] p value for comparison between NIV failed and ET only using Mann–Whitney U test

Table 3 Co-morbidity risk factors associated with assisted ventilation and failure of NIV

Risk factor	Likelihood for needing PPS		Likelihood of NIV failure	
	Odds ratio (95 % CI)	*p* value	Odds ratio (95 % CI)	*p* value (2-sided)
Any risk factor present	1.79 (1.16–2.78)	0.006*	2.3 (1.2–4.2)	0.009*
At least 2 risk factors or more present	1.84 (0.84–4.02)	0.120	1.89 (0.85–4.19)	0.09
Prematurity	2.1 (1.25–3.52)	0.004*	1.49 (0.8–2.9)	0.225
Uncorrected congenital heart disease	1.07 (0.54–2.1)	0.847	2.26 (1.0–5.3)	0.055
Neuromuscular disease	3.0 (1.1–8.56)	0.03*	1.96 (0.8–4.7)	0.128

* Statistically significant

NIV were successful, if they were without risk factors. Patients with any co-morbidity or risk factor were more likely to fail NIV if any risk factors were present, but still succeeded with NIV in 90 % of cases. Overall 17 % of patients that started on NIV failed, which was comparable to a smaller French cohort, with a 20 % NIV failure rate [3].

NIV has been studied in the setting of bronchiolitis-associated respiratory failure in a small number of studies. Cambonie et al. [13] showed in a prospective study in 12 infants with bronchiolitis that nasal continuous positive airway pressure (nCPAP) deceased respiratory effort. Soong et al. and Thia et al. [11, 12] have both shown in pilot studies that there are improvements in indices of respiratory acidosis with NIV compared to no positive-pressure support. This is not surprising and it would be hoped that such improvements in respiratory status led to a reduced need for invasive ventilation and shorter lengths of stay in PICU and hospital. Javouhey et al. [3] studied two distinct eras of respiratory support and compared outcomes in these periods. Eighty children with bronchiolitis were studied over consecutive winters; the initial group was preferentially invasively ventilated, whilst the latter were non-invasively supported. Non-invasively supported patients had no ventilator-associated pneumonia and also a reduced oxygen requirement prior to discharge. In terms of length of stay, both groups had average hospital stays of longer than 10 days—supporting the notion that bronchiolitis has important impacts on child health and family function. Of those who stayed longer than 10 days in hospital this was non-significantly greater in the invasively ventilated cohort—8 % as opposed to 48 % in the NIV group [3]. It is difficult to determine if the rate of intubation varied in this study given the design. There was a tendency towards shorter lengths of stay associated with NIV, but certainly its size makes it inadequate to determine any associated benefits with NIV.

Yanez et al. [14] conducted a randomized trial comparing NIV and no invasive ventilatory support in 50 children with respiratory insufficiency and showed that intubation rates were higher in children without NIV, the most significant factor for failure of NIV being younger age. However, in this study, the patient group was slightly heterogeneous with approximately 80 % having bronchiolitis and the remainder a mix of bacterial pneumonitis or asthma. It is possible that the majority of smaller children who failed had bronchiolitis as asthma and pneumonia are commoner in older age groups. Similar to our study, children who were offered NIV required intubation less often and had more rapid improvement in indices of oxygenation and ventilation when compared with those who did not receive any non-invasive positive-pressure support. The NIV group overall had a trend towards staying longer in PICU, 6.7 days versus 5.5 days, whilst the hospital length of stay remained the same at ca. 10 days, which is significantly longer than the average length of stay for the NIV success group in our study. Moderate dose sedation with chloral hydrate and/or midazolam was administered to the NIV group in this study as well as in another report of a mixed group of children on NIV where over 50 % of patients received an infusion of midazolam [15]. Both these studies included slightly older children and administered sedation might have influenced the length of stay. Regardless of the age of patients it is not our practice to pharmacologically sedate non-invasively supported patients; typically if an infant is not tolerating NIV and their medical condition warrants it they will progress to invasive ventilation. In a similar retrospective study from Australia, comparing intubation rates before and after introduction of high flow nasal oxygen, Schibler et al. [16] reported a marked reduction in intubation rates from 37 to 7 %. High flow nasal oxygen is, however, not universally practised and the extent of positive-pressure support achieved with the high flow device is quite variable. The high flow device was not available during the study period in our institute despite achieving reduction in intubation rates using CPAP.

This study is weakened by the inherent limitations of being retrospective. Variations in viral virulence and patient-specific factors are hopefully reduced by analysing a decade of admissions. Increase in experience using NIV may have improved case selection for the NIV improving the failure rate. Individual clinical patient characteristics that may be relevant pertaining to the severity of bronchiolitis like recurrent apnea, initial blood gas, and indications for intubation were not available in

the electronic database for analysis. Our unit is a mixed paediatric and cardiac ICU and so our practice may not translate to dedicated medical PICUs. Hence the findings need to be cautiously accepted, despite the large effect size associated with the use of NIV in bronchiolitis.

What is clear from our study and the conclusions of studies showing that NIV is successful in the majority of children with bronchiolitis, despite not being proven using randomized trial, is that a randomized trial of invasive versus non-invasive support is difficult to justify [17]. A further study needing comparison amongst different modalities of NIV like nasal continuous positive airway pressure (CPAP), high flow nasal oxygen and nasopharyngeal CPAP will be beneficial in defining the impact of these modalities in the current scenario. Since failure of NIV signified longer invasive ventilation a prospective study comparing different modalities of administering NIV will help in further defining the risk factors of failure of NIV. An intervention that may shorten length/proportion of intubated children by even 25 % would be worth utilizing and an adequately powered trial should be able to demonstrate such an effect size, given our retrospective findings. It is important to undertake such a trial because, although successful NIV was associated in our study with a 50 % shorter length of stay in PICU, its failure was associated with a 20 % longer stay in PICU.

Conclusion

NIV was an adequate form of respiratory support in the vast majority of patients and its increasing use over last 10 years was associated with a decline in the need for intubation. NIV was successful in the majority (90 %) of patients including those with co-morbidity risk factors present. NIV success was also associated with a significant shortening of PICU stay. Apart from the presence of a co-morbidity, failure of NIV could not be predicted. Since NIV failure was associated with significant increase in the duration of invasive ventilation and PICU length of stay, a large randomized trial comparing different NIV techniques may be needed to determine if NIV is indeed beneficial and to define risk factors of failure of NIV.

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