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Intensive care unit admissions and ventilation support in infants with bronchiolitis

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## Title Page

### ICU admissions and ventilation support in infants with bronchiolitis

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## **Abstract (word count 273)**

**Objectives:** To describe the rate of Intensive Care Unit (ICU) admission, type of ventilation support provided and risk factors for ICU admission in infants with bronchiolitis.

**Design:** Retrospective review of hospital records and Australia & New Zealand Paediatric Intensive Care (ANZPIC) registry data for infants 2 to 12 months old admitted with bronchiolitis

**Setting:** 7 Australian and New Zealand hospitals. These infants were prospectively identified through the comparative rehydration in bronchiolitis (CRIB) study between 2009 - 2011.

**Results:** Of 3884 infants identified, 3589 charts were available for analysis. Of 204 (5.7%) infants with bronchiolitis admitted to ICU, 162 (79.4%) received ventilation support. Of those 133 (82.1%) received non-invasive ventilation (High Flow Nasal Cannula [HFNC] or Continuous Positive Airway Pressure [CPAP]) seven (4.3%) received invasive ventilation alone and 21 (13.6%) received a combination of ventilation modes.

Infants with comorbidities such as chronic lung disease (OR 1.6 [95% CI 1.0-2.6]), congenital heart disease (OR 2.3 [1.5-3.5]), neurological disease (OR 2.2 [1.2-4.1]) or prematurity (OR 1.5 [1.0-2.1]), and infants 2-6 months of age (OR 1.5 [1.1-2.0]) were more likely to be admitted to ICU. Respiratory Syncytial Virus positivity did not increase the likelihood of being admitted to ICU (OR 1.1 [95% CI 0.8 - 1.4]).

HFNC use changed from 13/53 (24.5% [95% CI 13.7-38.3]) patient episodes in 2009 to 39/91 (42.9% [95% CI 32.5-53.7]) patient episodes in 2011.

**Conclusion:** Admission to ICU is an uncommon occurrence in infants admitted with bronchiolitis, but more common in infants with co-morbidities and prematurity. The majority are managed with non-invasive ventilation, with increasing use of HFNC.

## Introduction

Bronchiolitis is a common respiratory tract infection affecting infants under 1 year of age. Following an Emergency Department (ED) presentation, up to 40% of infants are admitted to hospital, and of these about 10% have intensive care unit (ICU) admission.<sup>1,2</sup> Bronchiolitis is one of the most common causes of non-elective intensive care admissions.<sup>3,4</sup>

There is no proven clinical benefit in administering medications to infants with bronchiolitis<sup>5</sup> and the mainstay of treatment is supportive care with oxygen therapy and supplemental fluids. There are also no clearly effective medicinal therapies available to improve the outcome of critically ill infants with bronchiolitis.<sup>6</sup>

The aims of this multicentre study were to determine the number of patients over 2 months of age with bronchiolitis receiving intensive care, the type of ventilation support and to determine factors associated with infants with bronchiolitis requiring ICU admission, over 3 bronchiolitis seasons.

## Methods

### *Study Design and Setting:*

This was a retrospective chart review of data collected from 3884 infants, admitted with bronchiolitis at 7 Australian and New Zealand Hospitals who were prospectively assessed for eligibility as part of the comparative rehydration in bronchiolitis (CRIB) study conducted between 2009-2011.<sup>3,4</sup> This was a National Health and Medical Research Council (NHMRC), Australia, funded randomised trial in Australia and New Zealand where infants between 2 and 12 months of age with bronchiolitis, requiring fluid therapy, were randomised to receive either nasogastric (NGT) or intravenous fluid (IVF) therapy<sup>3,4</sup>. The study

received ethical approval at all participating sites.

*Study Population, Inclusion and Exclusion:*

There were 7 recruitment sites in this multi centre study: Royal Children's Hospital (RCH) Melbourne, Sunshine Hospital Melbourne, Monash Medical Centre Melbourne, Princess Margaret Hospital Perth, Royal Children's Hospital Brisbane, and Kidz First Hospital Middlemore, New Zealand and Starship Hospital Auckland, New Zealand. Of note, Sunshine Hospital Melbourne does not have an ICU, therefore infants with bronchiolitis requiring respiratory support were transferred to one of two other hospital with ICU facilities, which are both participating sites of this multicenter study.

Infants were between the ages of 2 months and 12 months presenting to the ED with bronchiolitis showing symptoms and signs of respiratory distress (tachypnoea, recessions, nasal flaring, and cyanosis) associated with symptoms of viral respiratory tract infection (cough, runny nose, blocked nose)<sup>22,23</sup>.

Infants were excluded from final analysis if medical records or ICU data were unavailable.

*Data Collection:*

All infants were identified through the CRIB study<sup>3,4</sup> or the Australia and New Zealand Paediatric Intensive Care (ANZPIC) database. The CRIB study prospectively identified all infants presenting to the emergency departments of participating hospitals and recorded this in a log. At each participating site, investigators reviewed CRIB study records to identify all admitted infants presenting during the CRIB study. This included infants that were missed, or excluded from the study, or refused participation. Baseline demographic variables including age, gender, prematurity, previous bronchiolitis, comorbidities (chronic respiratory disease, chronic neurological disease and congenital heart

disease), length of stay in hospital, medications received and investigations done were collected.

Data were obtained directly from medical records or from electronically scanned medical records (ESMR). Results of chest radiographs (CXR) and viral panel testing with nasal pharyngeal aspirates (NPA) or nasal swabs were obtained from radiology and pathology databases of participating hospitals. NPA/nasal swab results were any positive results throughout the admission. Data on infants admitted to ICU were obtained from medical records, ESMR and the ANZPIC database from the participating hospitals. Abstracted data included information on modes of ventilation support, duration of ventilation and length of stay in ICU. Investigators from participating sites recorded information for all infants on standardized clinical report forms (CRFs).

Investigators from each site were trained based on an operations manual to ensure that all data were collected in a standardized and defined fashion. All study materials were piloted at two sites. Completed CRFs were entered into an Epidata database at a single site.

#### **Data Extraction and Analysis/ Synthesis:**

Data were extracted from the combined Epidata database (Epidata, Odense, Denmark) and analysed with Stata (Statacorp, College Station, Tx, USA) using logistic regression, reporting odds ratios (OR) with 95% confidence intervals (95% CI). A p-value less than 0.05 was considered to denote statistical significance.

## **Results**

From 3884 infants identified from the 7 sites, 295 infants were excluded, 293 due to unavailability of medical records and 2 due to unavailability of ICU data, leaving 3589 available records. There were 204 (5.7%) infants with bronchiolitis admitted to ICU with both

medical records and ICU data available. Eighty (39.2%) were direct admissions to ICU from ED or other sources while 124 (60.8%) were infants who were admitted to the wards from ED and subsequently to the ICU (**Figure 1**).

Of the 204 infants with bronchiolitis admitted to ICU, 162 (79.4%) received ventilation support. They comprised 133 (82.1%) receiving non-invasive ventilation only (NIV; HFNC or CPAP), 7 (4.3%) receiving invasive ventilation (endotracheal intubation) only, and 22 (13.6%) receiving a combination of both non-invasive and invasive ventilation modes (**Figure 1**). Of infants admitted initially to hospital inpatient wards with bronchiolitis 0.8% (95% CI 0.5%-1.2%) received invasive ventilation; of infants admitted directly to ICU 14.2% (95% CI 9.7%-19.8%) received invasive ventilation; and of infants admitted to ICU receiving any ventilatory support 17.9% (95% CI 12.3%-24.7%) received invasive ventilation. No infants received nitric oxide, high-frequency ventilation or extracorporeal membrane oxygenation and there were no deaths.

Baseline patient demographic and clinical characteristics, risk factors for ICU admission are presented in Table 1. Infants admitted with bronchiolitis requiring ICU care, compared to those not requiring ICU care, were younger (mean age ( $\pm$ SD) non-ICU care 195 ( $\pm$ 85) days, ICU care 177 ( $\pm$ 86) days, difference (95% CI) 18.8 (6.8-30.7) days,  $p=0.002$ ) and had a longer mean length of hospital stay (mean length of stay ( $\pm$ SD) ICU care 8.7 ( $\pm$ 7.2) days, non-ICU care 2.9 ( $\pm$ 4.0) days, difference (95% CI) 5.7 (4.7-6.7) days,  $p<0.001$ ). Overall, 62% of infants were male, with no difference between those requiring or not requiring ICU care. The median length of stay in ICU was 2.1 days (IQR 1.2- 3.3 days).

Infants with co-morbidities such as chronic lung disease (OR 1.6 [95% CI 1.0-2.6]), congenital heart disease (OR 2.3 [95% CI 1.5-3.5]), neurological disease (OR 2.2 [95% CI 1.2-4.1]), prematurity (OR 1.5 [95% CI 1.0-2.1]) or age between 2-6 months (OR

1.5 [95% CI 1.1-2.0]) were more likely to be admitted to ICU. Viral testing was performed on 2329 out of 3385 (68.8%) infants. RSV positivity did not increase the likelihood of being admitted to ICU (OR 1.1 [95% CI 0.8 - 1.4]).

There was some evidence of a difference between sites in rates of admission to ICU for the six sites which have an ICU ( $p=0.03$ ). ICU admission rates ranged from 4.1% to 9.1% with an average of 5.7%. There was evidence of a difference between sites in the rates of ventilatory support use ( $p<0.001$ ). Ventilatory support rates ranged from 2.8% to 5.9% across the sites with an average of 4.5%. There was no evidence of a difference between the sites in rates of ETI for all patients admitted with bronchiolitis (**Table 2**). For the 162 infants receiving ventilatory support admitted to ICU there was evidence of a difference between sites for the non-invasive ventilatory support use (HFNC and CPAP;  $p<0.001$ ), but no evidence of a difference between sites for the use of invasive ventilatory support (ETI) (**Table 3**).

Frequency of ventilatory support in ICU by year from 2009 to 2011, cumulative for all sites over the study period is shown in **Table 4**. There was no evidence of a change in the proportion of infants admitted to ICU over the study period, with percentages ranging from 5.1% in 2009 to 6.7% in 2011 ( $p=0.21$ ). Over the 3 years of the study period, there was no evidence that the proportion of infants admitted to ICU requiring ventilatory support changed ( $p=0.73$ ). .

**Figure 2** shows the number of episodes of use of each ventilation strategy in each study year. Ventilation assistance increased from 53 episodes in 39 patients admitted to ICU in 2009 to 91 episodes in 64 infants in 2011, with the proportion of infants requiring NIV varying slightly from 47/53 (88.7%) episodes to 84/91 (92%) episodes over the study period. Whilst there is no evidence of a change in the proportion of infants requiring NIV over the study period, there is evidence of a change in the type of non-

invasive support method, with HFNC use increasing from 13/53 (24.5%) patient episodes in 39 infants ventilated in 2009 to 39/91 (42.9%) patient episodes in 64 infants in 2011 an absolute increase of 18.3% (95% CI 2.9%, 33.7%).

## Discussion

The overall rate of ICU admission for infants 2-12 months was 5.7% which remained stable across the 3 study years, and is similar to that reported from Australia previously.<sup>3</sup>

The ICU admission rate across sites ranged from 4.3% to 9.1%. This likely reflects the differing resources available between hospitals with some hospitals having high-dependency units (HDU) capable of looking after infants with bronchiolitis requiring non-invasive ventilation in a ward based setting rather than an ICU. This variation is also likely due to other factors including bed availability, local guidelines, patient and clinician factors.

Compared with a study from New South Wales looking at a 10 year period from 2000-2009, our ventilation rate for infants admitted to ICU was 79.4% (compared with 76.7%) with 17.9% requiring invasive ventilation (compared with 28.6%).<sup>16</sup> These changes are consistent with recent data showing a high rate of ventilation support in ICU admissions for bronchiolitis (>70%) with an increasing number receiving non invasive ventilation (NIV).<sup>12,16</sup> NIV has been shown to be an effective ventilation strategy preventing clinical deterioration, avoiding endotracheal intubation (ETI), and shortening ICU length of stay.<sup>17 18 19 20 21</sup> NIV has become the preferred initial ventilation strategy with ETI reserved predominantly for failure of NIV.

We demonstrated there was no increase in the proportion of infants requiring NIV over the years of the study, however there was a noticeable and escalating increase in the use of HFNC (18.3% increase). In contrast to previous reports of a reduction in invasive ventilation with the institution of HFNC our rate of invasive ventilation did not decline with increasing use of NIV.<sup>24</sup> One postulated reason for this is that with increasing experience and comfort with use of HFNC, patients on this mode of ventilation assistance are more likely to be managed on the ward and an ICU admission avoided, however we did not analyze HFNC in non-ICU settings. What we have demonstrated is that the rate of HFNC usage is increasing over the years of the study. There is emerging evidence that HFNC can not only prevent ETI but shorten ICU and hospital length of stay with few complications (21, 23, 24). HFNC therapy has been shown to decrease respiratory rate more than other forms of respiratory support, and infants with the greatest decrease in respiratory rate were least likely to be intubated.<sup>25</sup> In addition, the introduction of HFNC has decreased median PICU length of stay for infants with bronchiolitis from 6 to 4 days.<sup>25</sup> Short and longer-term follow up data did not identify any adverse effects related to NIV.<sup>24,26</sup> Risk factors for NIV failure were apnea, prematurity, pneumonia, and bacterial co-infection.

This study showed infants with comorbidities (chronic lung disease, congenital heart disease, neurological disease) and that were younger (between 2 to 6 months of age), were more likely to have ICU admission supporting research by Richard *etal* showing that infants with a history of prematurity, chronic lung disease, congenital heart disease and other comorbidities are more at risk of requiring interventions such as supplemental fluids and oxygen or ICU treatment.<sup>8</sup> In a prospective multicentre study from the US comparing ward and ICU admissions in infants with bronchiolitis, predictors of ICU admission were age <2 months, an ED visit the past week, moderate or severe retractions

and inadequate oral intake. Unlike previous studies, no association with male gender, socioeconomic factors, insurance status, breast-feeding, or parental asthma was found to be associated with ICU admission.<sup>13</sup>

In our study 69% patients were tested for respiratory viruses. Our data indicate a lower rate of RSV positivity (50%) compared with earlier French (76%)<sup>12</sup> and New South Wales (66%)<sup>16</sup> studies in infants with bronchiolitis admitted to ICU. There is conflicting information about whether RSV positivity increased<sup>9-12</sup> or had no effect on<sup>27,28</sup> the likelihood of ICU admission and length of ICU stay. In this study RSV positivity was not associated with an increase likelihood of ICU admissions.

## **Limitations**

There were several limitations to this study. This is a multicentre retrospective study which relied on medical record reviews. Based on Gilbert et al<sup>29</sup> we defined inclusion criteria, determined the variables being analysed, trained the abstractors, used standardised and piloted abstraction forms and had periodic abstractor monitoring. However, the abstractors were not blinded to the study hypotheses. A strength was the prospective identification of patients with bronchiolitis (that is diagnosis on admission) rather than a discharge diagnosis, as we have picked up all patients initially treated as bronchiolitis, representing a real world view of the management of this clinically diagnosed disease.

Infants were pre-identified from the CRIB study which did not include all bronchiolitis admissions to hospital and intensive care during the annual study period. In particular it excluded infants seen between the end of one bronchiolitis season and the bron-

chiolitis season of the following year (November to March). The definition of bronchiolitis season was based on the perceived volume of maximum recruitment with a defined cutoff. There were a small proportion of medical charts and ICU data missing during the study period.

There was no standardised measure of disease severity used, and the need for admission to ICU and initiation of ventilation support was made by individual clinicians. Infants less than 2 months corrected gestational age were not included in this study. The CRIB trial studied hydration methods in non neonatal patients with bronchiolitis so no prospective log of these patients was available and we did not include a retrospective identification of these patients in this study. This age group has been previously shown to be have an increased risk of ICU admission.<sup>13</sup>

Some infants received more than one method of ventilation; therefore we captured ventilation events per patient episode. We were unable to describe the sequence of ventilation modes, escalation or step-down of ventilation modes and length of ventilation episodes as many infants had multiple episodes of ventilation within the same admission to ICU. A prospective study would obtain more accurate information on ventilation support usage.

## **Conclusion**

Infants admitted to hospital with bronchiolitis requiring intensive care support represent a small but significant proportion of bronchiolitis admissions with the rate of ICU admission increasing over the study period. Comorbidities and younger age were risk factors for ICU admission. The use of NIV is increasing with HFNC ventilation becoming the strategy of choice, and reduces the need for invasive ventilation.

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## **Conflicts of Interest**

Franz Babl and Stuart Dalziel are Section Editors, Paediatrics Emergency Medicine, for Emergency medicine Australasia

## **Author Contribution:**

All authors contributed to the design and implementation of the study, or analysis and interpretation of the study results. EO, FB, MB, NP, JN, DK, MS, AD, AW contributed to all stages of the study. SDa contributed to the implementation of the study. EO was the principal investigator. SDo, and KJ performed the statistical analysis. KJ controlled the database. VC ensured appropriate data collection. EO, VC, FB, MB, SDa, DK, NP contributed to interpretation of the results. All authors contributed to the manuscript preparation and review, and approved the final version. The report was written by EO.

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## Figure Legends

**Figure. 1.** Flow chart of study process and mode of ventilation of infants admitted to ICU with bronchiolitis

ED, emergency department; CRIB, comparative rehydration in bronchiolitis; ICU, intensive care unit

**Figure. 2.** Graph of type of ventilation support by years (cumulative of all centres) from 2009 – 2011

ICU, intensive care unit; HFNC, high flow nasal cannula; CPAP, continuous positive airway pressure

n = number of patients

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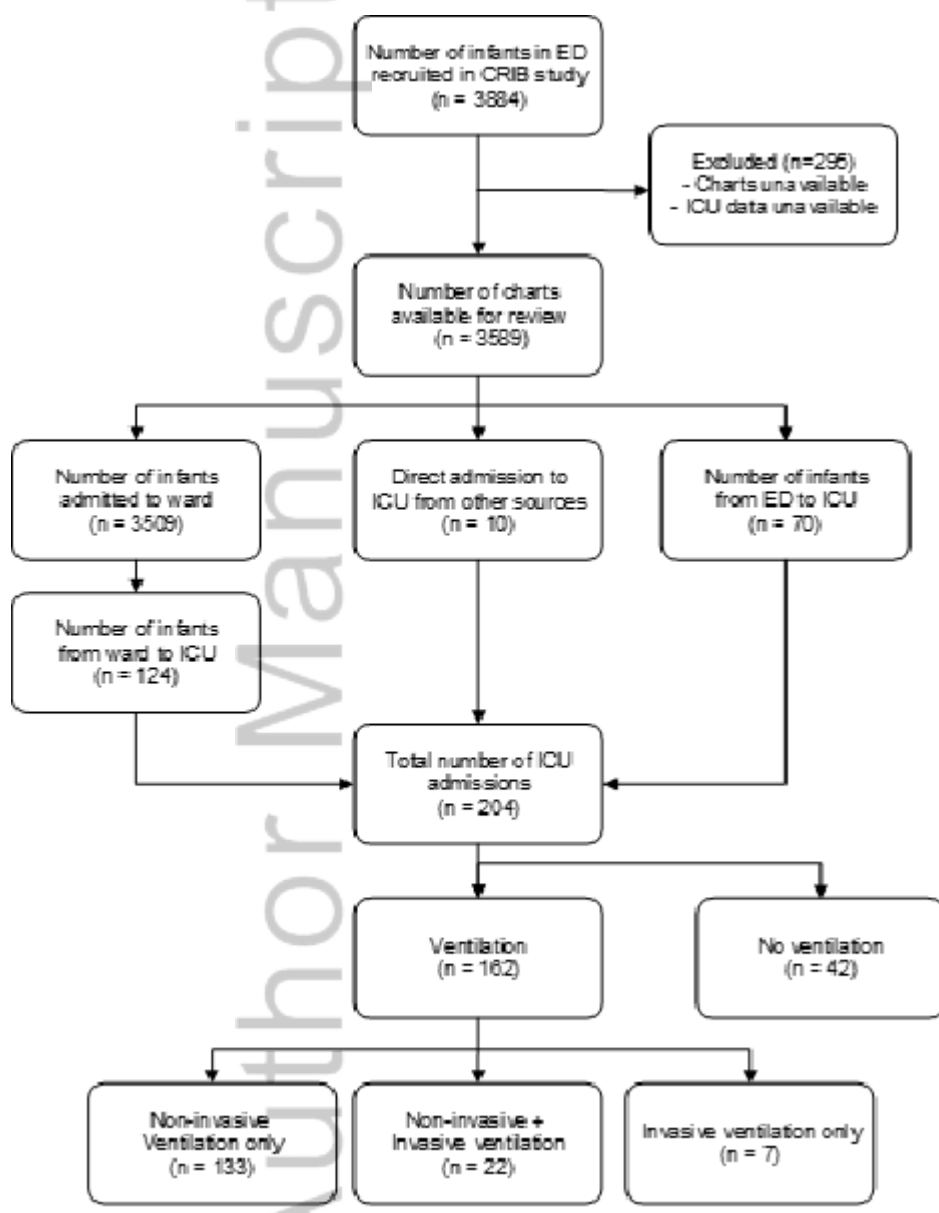


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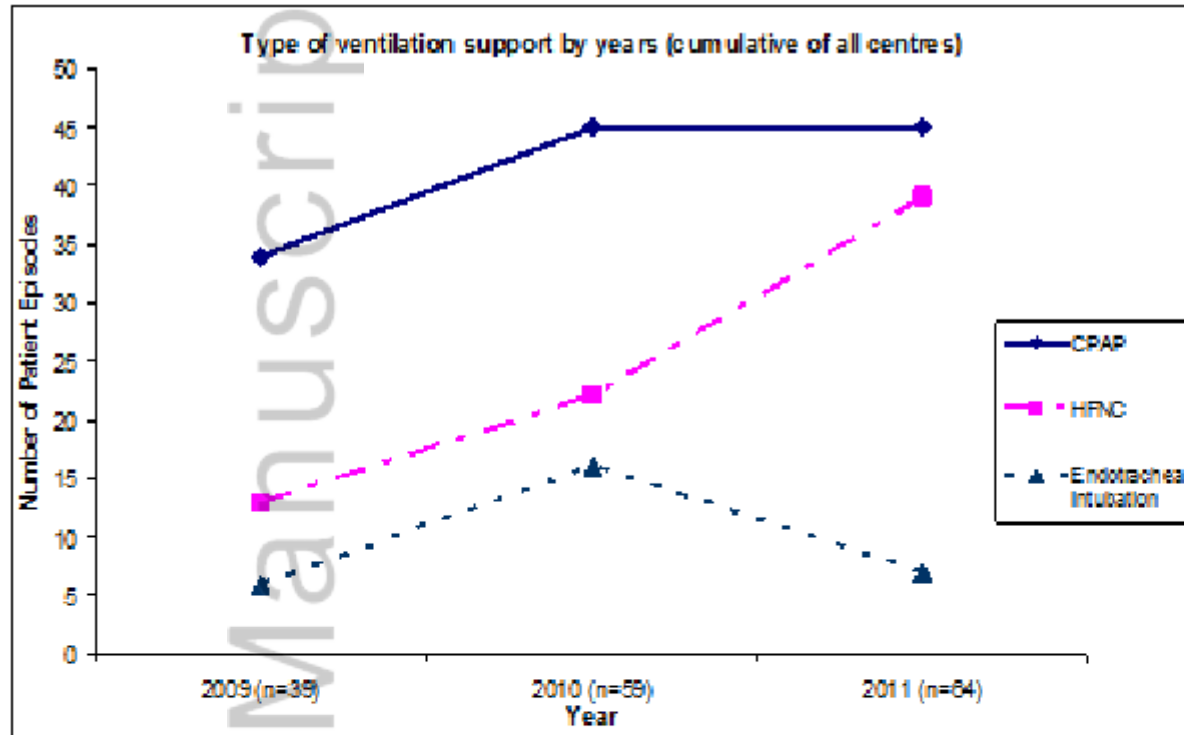


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