Abstract

Aims: To describe the epidemiology and treatment of respiratory syncytial virus (RSV) infection in a tertiary paediatric intensive care unit, including the clinical presentations, comorbidities, respiratory support required, costs, and outcomes.

Methods: Analysis of a database for all children with RSV infections admitted to the paediatric intensive care unit in Melbourne between 2005 and 2015.

Results: Six hundred and four episodes of community-acquired RSV infections were analysed, median age of children was 4 months (IQR 2-14 months). 94% of cases had lower respiratory tract infection, principally bronchiolitis, 8.9% presented with extra-pulmonary features. Respiratory support included humidified high flow nasal cannula (HHFNC) oxygen therapy (76% of patients since its introduction in 2011), non-invasive ventilation (41%) and intubation and mechanical ventilation (32%). Almost half (n=270; 45%) had one or more pre-existing comorbid condition. Risk factors for intubation and mechanical ventilation were presence of comorbidities (odds ratio 1.97; CI 1.39-2.79, $p<0.001$) and transfer from an external hospital (OR 1.82; CI 1.58-2.57, $p<0.001$). 25% of children without pre-existing comorbidities required intubation and mechanical ventilation. Following the introduction of HHFNC oxygen therapy, the number of annual PICU admissions for RSV infection doubled, however the number of children requiring intubation remained unchanged. The median length of ICU stay was 3.7 days and further hospital stay was 3.6 days, and the average cost per case was approximately AU\$20,000.

Conclusion: RSV infection carries a high burden in PICU, in bed-days and cost. Chronic comorbidities and transfer from a peripheral hospital were associated with a higher rate of need for mechanical ventilation.

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What is already known on this topic

- RSV is the commonest cause of acute lower respiratory infection in high-income countries.
- Underlying comorbidities are common in patients admitted to PICU with severe RSV infection

What this study adds

- Although comorbidities increase the risk of requiring intubation, in this unit 25% of children with severe RSV infections without any pre-existing comorbidities required intubation and mechanical ventilation.
- The introduction of humidified high flow nasal cannula oxygen therapy led to a greater number of admissions to PICU, but did not seem to reduce the number of patients requiring intubation and mechanical ventilation.
- An episode of bronchiolitis requiring PICU admission cost approximately AU\$20,000 in hospital costs, and bronchiolitis admissions to PICU cost about \$1.2 million annually in a state with a population of 5 million. This is small proportion of the overall hospital and societal costs related to RSV infection.

Introduction

Respiratory syncytial virus (RSV) is the most common viral cause of acute lower respiratory tract infections (ALRI) in young children (1), resulting in the hospitalisation of approximately 3% of otherwise healthy infants (2, 3), and is the most common cause of respiratory failure in infants in high income countries (4, 5). The global burden of RSV is increasingly appreciated, with recent estimates of 3.2 million hospital admissions and 59,600 in-hospital deaths related to RSV-ALRI per year in children under the age of 5 years worldwide (6).

RSV belongs to the *Paramyxoviridae* family and has two antigenic subtypes - A and B (7). RSV leads to illness by invasion and necrosis of ciliated epithelium of the respiratory mucosa with impairment of muco-ciliary clearance and the inflammatory immune response leads to submucosal oedema and airway hyperactivity that can manifest as bronchiolitis or pneumonia (8).

Prevalence studies indicate that RSV infection rates are highest in the third and fourth months of life and that virtually all children are infected by two years of age (2, 9). Known risk factors for RSV infection include lack of breast feeding, passive smoking exposure, attendance at childcare, school-age siblings in the home, over-crowded housing and lack of care-giver health literacy (2, 10, 11).

The Global Burden of Disease Study estimated that RSV accounted for 1.6% of deaths in children aged 1-4 years worldwide in 2010, increasing to 2.3% in subgroup analyses for infants aged 0-27 days(12); most deaths occurring in low and middle income countries. The case fatality rate for RSV bronchiolitis is uncertain in such settings, as these patients are rarely distinguished from children with other acute lower respiratory infections, including bacterial pneumonia, which carry a higher risk of death. A case fatality rate less than 0.5% is reported in high-income countries, but chronic conditions place children at higher risk (5). Underlying conditions that are known to increase disease severity include chronic lung disease, cardiac anomalies, neurodevelopmental disorders, chromosomal abnormalities, and conditions associated with immune suppression (2, 13-16).

Hospital management for severe RSV infections focuses on supportive care: correcting hypoxaemia, appropriate hydration and feeding, suctioning, and sometimes other respiratory support including continuous positive airway pressure (CPAP), and invasive mechanical ventilation(8, 17). Hypertonic saline, bronchodilators, adrenaline and steroids have been trialled in numerous studies. These therapies may benefit some children but are not conclusively widely applicable. RSV can be prevented with the monoclonal antibody palivizumab (RSV immunoglobulin). In Australia the use is restricted to a high risk population of children with chronic lung disease or cyanotic congenital heart disease (18).

The aim of this study was to describe the epidemiology of RSV infection in an Australian tertiary paediatric intensive care unit (PICU) with specific focus on the clinical manifestations, presence of comorbidities, respiratory support requirements, cost of care, and risk of mortality.

Methods

Study design and setting

This was a retrospective analysis of data collected prospectively in the PICU of the Royal Children's Hospital (RCH) in Melbourne, Australia, between March 2005 and August 2015. The year-to-year data trends were analysed from May 2005 to April 2015 at yearly intervals aiming to capture the RSV season, thus the numbers are fewer overall than if we had analysed March 2005 to August 2015. RCH is a tertiary teaching hospital serving a population of 5 million in Victoria and southern New South Wales. Children are referred if they are unstable or have severe disease, including requiring respiratory support beyond non-invasive therapies e.g. standard-flow oxygen therapy or humidified high flow nasal prong oxygen therapy.

Data collection

Data were retrieved from our ICU data-base STATIC (Statistics in Intensive Care), which contains information for all patients admitted to our PICU: patient demographics, diagnoses, interventions received and outcomes. We searched for all admissions where RSV was identified. RSV infection was confirmed via viral testing (immunofluorescence in the early years of the study and polymerase chain reaction in the later years) on naso-pharyngeal aspirates (NPA), nasal swabs or bronchoalveolar lavage. We recorded age, gender, comorbidities, additional inpatient diagnoses, length of stay in PICU, ventilation types and duration, and patient outcomes. Patients were excluded from final analyses if RSV was only isolated beyond the first week of admission, suggesting hospital-acquired infection or if details of management were unavailable.

Comorbidities were classified as congenital anomalies or syndromes, cardiac, endocrine, gastrointestinal, immunological/haematological/oncological, metabolic, neurological, prematurity, renal, respiratory, skeletal, and upper airway related disorders.

Based on personnel wages and drug budget only, the estimated average cost of an intensive care bed is AU\$4500 per day, and the cost of ward based care is AU\$1000 per day. This does not include building and service charges.

This study received ethical approval through the Royal Children's Hospital Human Research Ethics Committee. Specific consent was not required as this was a retrospective analysis of routinely collected data.

Data extraction and analysis

Data were analysed using Stata (StataCorp, College Station Texas). Descriptive analysis included frequency distributions, means (standard deviation), and medians (interquartile range). Risk factors for requiring intubation and mechanical ventilation were identified using multivariable regression analysis, and odds ratios and 95% confidence intervals are reported.

Results

Patient characteristics

Medical records were available on 678 patients with proven RSV infection. 26 episodes were excluded as their primary admission to PICU was for post-operative management (and acute burns in one case), the isolation of RSV was beyond a week and likely hospital-acquired. 48 episodes were excluded due to incomplete data, leaving 604 patient episodes included in the analysis.

Baseline patient demographics, clinical presentations and underlying comorbidities are presented in Table 1. Of the 604 children with RSV infection, 321 were male (53.1%). The median age was 123 days (IQR 59-390 days). Seventy-two percent of patients (n=440) were aged less than 12 months with 43% (n=258) younger than 3 months.

Since 2011 the number of RSV admissions per annum to the PICU increased: from a median of 38 patients (IQR 33-40) in the first 6 years of the study to 76 cases (IQR 65-88) by the last 4 years.

The median length of ICU stay was 3.7 days, therefore costing about AU\$16,650 per episode in ICU, with additional hospital costs of approximately AU \$3,600 for the extra 3.6 days of median ward stay following ICU discharge (19, 20), therefore the total cost being about AU\$20,000.

Admission source

Sixty per cent (n=365) of patients were admitted from the RCH emergency department or inpatient wards, and 40% (n=239) were transferred from peripheral centres. The majority (94%) presented with a diagnosis of bronchiolitis or lower respiratory tract infection (LRTI). The presenting

manifestations were extra-pulmonary in 54 (8.9%) cases. These included apnoea (n=25), acute neurological events including seizures and encephalopathy (n=12), sepsis (n=9), cardiac arrest (n=6), hypovolaemic shock (n=1), and dysrhythmia (n=1).

Patient comorbidities

Three hundred and thirty three (55%) of RSV infections occurred in children with no preceding illness or condition; 270 (45%) had at least one underlying comorbidity (Table 1). These included prematurity (103; 17%), cardiac anomalies (58; 10%), chronic neurological conditions (52; 9%), upper airway abnormalities (45; 8%), chronic lower respiratory tract conditions (44; 7%), genetic disorders (32; 5%), cancer or immunodeficiency syndromes (11; 2%).

Respiratory support

Data on respiratory support provided in the PICU are presented in Table 2. Non-invasive respiratory support was required by the majority of patients, with 296 episodes involving treatment with humidified high flow nasal cannula oxygen therapy (76% of cases since its advent in 2011) and 245 (41%) episodes treated with non-invasive positive airway pressure (CPAP or BiPAP). Non-invasive positive airway pressure was predominantly delivered via nasopharyngeal CPAP administered through a cut-down endotracheal tube connected to a mechanical ventilator. We were unable to distinguish from the data source the numbers of children treated with this form of CPAP, CPAP using a mask, and bi-level positive airway pressure (BiPAP) therapy. In 2011, humidified high flow nasal cannula oxygen therapy (HHFNC) was introduced into the PICU. In that year, HHFNC was used in 48% of RSV admissions. By 2015, 90% of children with RSV received HHFNC therapy as part or all of their respiratory therapy in PICU. An increase in PICU admissions also resulted post 2011 where the

median number of admissions for the 6 years prior to 2011 was 36 cases per annum versus 76 cases per annum for the subsequent 4 years.

Endotracheal intubation and conventional mechanical ventilation was required by 190 children with RSV admitted to PICU (32%). 39.5% of 271 children with any comorbidity required mechanical ventilation (Table 3). Odds ratio of any comorbidity needing intubation 1.97 (1.39-2.79, $p<0.001$), with each comorbidity increasing the odds of being intubated by 1.4 times. Pertinent comorbidities included patients with pre-existing upper airway abnormalities (75% were intubated) and haematological/immunodeficiency/oncological problems (73% intubated with median mechanical ventilation time of 242 hours).

Eighty three of 333 (25%) children without any underlying comorbidity also required intubation and mechanical ventilation. Some of these patients were intubated due to signs of sepsis at presentation ($n=6$, 7% of the 83 episodes), or acute or impending cardio-respiratory arrest ($n=5$, 6% of the 83 episodes); overlap of one patient who presented in sepsis culminating in a cardio-respiratory arrest. One patient was intubated in the context of seizures. The remainder ($n=72$, 87% of 83 episodes) were intubated because of progressive respiratory insufficiency and failure of non-invasive respiratory support. Intubated patients with no comorbidities had a shorter duration of ventilation (93.9 hours median (IQR 54.5-149.8 hours), compared to 112.1 hours median (IQR 69.8-188.8 hours) in the presence of any comorbidity.

Two hundred and thirty-nine of these 604 cases (39.6%) were referred from other hospitals, of which 94 (39.3%) were intubated. This compared to 96 of 365 (26%) children who were not referred

but came to PICU through RCH emergency department or the general wards. The odds of being intubated if a child was referred from another hospital was 1.8 (95% confidence intervals 1.6-2.6).

Intubation rates across the years showed a progressive annual decline from 49% in the first study year to 16% in the final study year. However, absolute intubation numbers per annum did not significantly change (18 out of 37 admissions in 2005-06 versus 14 out of 86 admissions in 2014-15) (Table 2). Overall median hours of intubation for those who required mechanical ventilation remained stable at 101.5 hours (IQR 97.4-117.6) across the 10 years.

Mixed modes of respiratory support were utilized in 234 episodes (39%). Besides conventional mechanical ventilation, other methods of ventilation and adjunctive respiratory support included high frequency oscillation (n= 25; 4%), inhaled nitric oxide adjunct (n=21; 3%) and extra-corporeal membrane oxygenation (n=3; 0.5%).

Mortality and resuscitation

Resuscitation was required at presentation in 53 cases (8.7%) because of cardio-respiratory arrest (n=6), respiratory failure, including apnoea (n=37), sepsis (n=9), or hypovolaemic shock (n=1) (Table 1). There were seven deaths from RSV during the time studied (case fatality rate 7/604, 1%) (Table 4). The only risk factor for death identified was the presence of comorbidities (odds ratio 2.59; 1.42 – 4.70).

Discussion

This study describes the epidemiology and treatment of 604 episodes of severe RSV infection in a tertiary hospital PICU over 10 years. The burden and costs were substantial. RSV in PICU at the Royal Children's Hospital costs at least \$1.2 million per year in hospital recurrent medical and nursing costs alone, and PICU patients represent a small fraction of all children with RSV bronchiolitis admitted to RCH and other hospitals throughout the State.

In this cohort 32% overall - and 25% of children without pre-existing illness - required intubation and mechanical ventilation. This was surprising as most infants with even severe bronchiolitis are adequately managed with non-invasive respiratory support. To a degree this is supported by our data which showed more than two-thirds of infants with RSV infection were managed with oxygen therapy alone or various forms of non-invasive positive pressure, principally HHFNC and nasopharyngeal CPAP. Children with proven RSV in PICU are a small fraction of children with bronchiolitis admitted to RCH each year. Viral testing patterns also introduce some bias causing a higher than expected proportion of children requiring intubation. Children who are ventilated are more likely to be tested thereby identifying RSV whereas children with moderate bronchiolitis, even if they are in PICU on HHFNC or CPAP, are less likely to have an NPA PCR test.

Referral from a peripheral hospital was associated with relatively high intubation rates. There are potential explanations for this, although it was difficult to control for severity of illness. In peripheral hospitals HHFNC oxygen therapy was the maximal respiratory support available. In the early years of HHFNC use, there was no facility for giving HFNC in an ambulance and if requiring transfer children

were often intubated. Had these children not had the risk of instability during transfer, it is possible that some could have been managed solely with NIV.

Extra-pulmonary manifestations

The majority of patients in this study presented with typical RSV lower respiratory tract infections. Extra-pulmonary manifestations were uncommon; 12 (2%) presented with acute neurological signs and less than 1% with seizures; 25 (4%) had central apnoea on presentation requiring CPAP, methylxanthines (aminophylline or caffeine) or mechanical ventilation. The incidence of RSV-related neurological events was lower compared to previous studies, including that by Kho et al which reported neurological signs in 39% of RSV positive patients in a PICU (2, 7, 21). Six patients (1%) suffered cardiovascular arrest requiring intubation and resuscitation and 11 (2%) had signs of sepsis, shock, or dysrhythmia on presentation requiring cardiovascular support, including fluid boluses and inotropes. Similar cardiovascular manifestations have been previously described in other reports (4).

Comorbidities and respiratory support required

Almost half (45%) of RSV infections in our ICU were associated with at least one underlying condition that likely influenced their treatment course. Comorbidities which were associated with high risk of being intubated included haematological malignancies, other causes of immunodeficiency, and upper airway anomalies.

Mechanical ventilation was more common in children with comorbidities (39%, n=107/272), however of the 332 children with no underlying medical condition, 83 (25%) required ventilation. In

this study, intubated patients with no comorbidities had a shorter duration of ventilation than those with comorbidities, suggesting a more rapid recovery unhindered by chronic illness.

In Victoria palivizumab was used during the time of this study, and prophylactic indications were sometimes extended on a case-by-case basis. This study cannot determine the effectiveness of palivizumab, but may help to identify the other comorbidities that are associated with high risk of severe RSV disease.

Ventilation trends over time

During the course of this study there were changing patterns in respiratory support. Humidified high flow nasal cannula (HHFNC) oxygen therapy was first introduced in 2011, and was initially only available in the PICU, hence a perceived need for HHFNC warranted an ICU admission by default. Progressively, other regional and metropolitan hospitals, as well as the RCH general wards have utilised this form of respiratory support, allowing for patients to be managed external to the PICU.

In the four years since its introduction, HHFNC use increased from 48% to 90% of RSV episodes. This was associated with a substantial rise in RSV admissions to the PICU. Across the 10 years, there was also an increasing trend for in-house referrals to PICU: from 49% of total admissions in the first year to 69% in the last. From 2011-2015, though the proportion of RSV admissions episodes requiring intubation was reduced, the overall number of children requiring intubation remained unchanged. This suggests that the increase in admissions was due to referral practices both within the hospital and from peripheral hospitals driven by the service model. This was also found in other studies of HHFNC therapy (22).

Given the major increase in patient transfers from regional areas in the years immediately after HFNC was introduced - nearly 40% of children were referred from peripheral hospitals, and that mortality rates for bronchiolitis have remained extremely low in Victoria before and after HFNC introduction, there was likely considerable over-referral. This has been negated somewhat in recent years by increased capacity and comfort in administering HFNC and monitoring of moderately unwell children in regional hospitals in Victoria. There is need for further enhancing regional models of care for children with bronchiolitis that would enable more of these children to be safely managed in their community hospitals.

Limitations

There were some limitations to this study. Firstly, the data related only to confirmed RSV infections and not to all children with clinical bronchiolitis and, as not all children in PICU had viral testing, we may have missed some cases. We did not explore the presence of bacterial co-infection. In our ICU, antibiotics are neither given routinely to all children with bronchiolitis, nor even to all mechanically ventilated children with bronchiolitis, unless signs of bacterial infection were present, such as toxicity, high procalcitonin, high immature-total granulocyte ratio, or radiographic signs of consolidation or effusion.

Conclusions

Comorbidities and transfer from a referring hospital were associated with a higher risk of intubation and ventilation. With the initial introduction of HHFNC oxygen therapy throughout Victoria, PICU admissions for RSV infections increased but numbers of children requiring intubation did not change.

Enhancing regional models of care for children with bronchiolitis may enable more of these children to be safely managed in their locality. With the high economic and morbidity burden of RSV, efforts need to be focused on infection prevention. Many RSV infections cannot be prevented at present, but protection can be gained from public health measures to encourage breast milk feeding, reduce passive smoke exposure and ensure immune prophylaxis of high-risk children.

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Table 1: Patient characteristics on admission

Number of patient episodes	604
Age, median (IQR range), days	123 (59 - 390)
Age distribution, n (%)	
<30 days	39 (6%)
<3 months (90 days)	258 (43%)
<12 months (365 days)	440 (72%)
12-59 months	141 (23%)
5 years and above	26 (4%)
Sex, n (%)	
Male	321 (53%)
Female	283 (47%)
Admission source, n (%)	
In hospital admission to PICU	365 (60%)
Transferred from another hospital	239 (40%)
Presentation type, n (%)	
Lower respiratory tract infection (LRTI)	570 (94%)
Respiratory failure	37 (6%)
Apnoea	25 (4%)
Upper airway pathology (acute)	18 (3%)
Neurological event (acute)	12 (2%)
Sepsis	9 (1%)
Arrest: in hospital	3
Arrest: out of hospital	3
Dysrhythmia	1
Hypovolaemic shock	1
Number of comorbidities, n (%)	
0	333 (55%)
1	195 (32%)
2	52 (9%)
3	19 (3%)
4	5 (<1%)
Comorbidity type, n (%)	
Prematurity	103 (17%)
Cardiac	58 (10%)
Neurological	52 (9%)
Upper airway anomaly	45 (8%)
Respiratory	44 (7%)
Congenital/syndromic	32 (5%)
Immunological/haematological/oncological	11 (2%)
Renal	10 (2%)
Skeletal	9 (1%)
Metabolic	6 (<1%)
Endocrine	4 (<1%)
Gastrointestinal	2 (<1%)

Table 2: Respiratory support

Year	Episodes (n)	High flow (n)	High flow % of total episodes	High flow duration Median hours (IQR)	NIV (n)	NIV % of total episodes	NIV Median hours (IQR)	Intubated (n)	Intubation and mechanical ventilation % of total episodes	Intubation duration median hours (IQR)
2005-06	37				32	86%	53.8 (35.5-78.8)	18	49%	100.7 (71.4-163.1)
2006-07	57				53	93%	47.1 (25-76)	21	37%	129.3 (59.8-164.5)
2007-08	40				34	85%	40.8 (17.2-67)	23	58%	97 (62.4-158.6)
2008-09	33				29	88%	48.6 (39.5-78.2)	15	45%	113.9 (95.1-182)
2009-10	34				27	79%	51.8 (25.5-89.7)	13	38%	118.8 (80.6-126)
2010-11	26				24	92%	54.5 (9.2-109.2)	6	23%	98.5 (54.2-128.6)
2011-12	65	31	48%	29 (13.2-57.3)	39	60%	55.3 (36-94)	22	34%	82.6 (56.6-119.9)
2012-13	63	51	81%	33.1 (18.3-56.8)	25	40%	42.8 (14.6-58.3)	22	35%	70.5 (36.4-148.2)
2013-14	89	72	81%	19.3 (11.3-32.9)	43	48%	46.8 (34.1-60.6)	19	21%	102.3 (67.5-145.5)
2014-15	86	77	90%	25.5 (14.1-50.3)	30	35%	48.5 (24-68.9)	14	16%	128.5 (71.2-189)
Total	530 *	231			336			173		

* Annual trend patterns were analysed from May-April intervals and as such 74 patient episodes not included on either end

Table 3: Ventilation requirements as per comorbidity

Comorbidity	Number of cases (from 604 patient episodes)	Number intubated	Percentage of total intubated	Median intubation times in hours (IQR)
Ex-prematurity	101	28	28	108.2 (75-145.3)
Cardiac – congenital heart disease	57	32	56	108.3 (76.4-148.9)
Chronic neurological or neuromuscular disease	51	21	41	173.9 (109-314.4)
Upper airway abnormality	44	33	75	78.3 (37.7-144.9)
Chronic respiratory disease	43	17	40	122.3 (104.5-192)
Congenital syndrome	31	11	35	148.6 (65.9-241.4)
Immunodeficiency/Oncology/hematological	11	8	73	241.6 (120.1-373.1)
Chronic renal disease	10	2	20	52.8 (41.7-63.9)
Skeletal anomalies	9	2	22	279.6 (184.3-297)
Inborn error of metabolism	6	2	33	115.7 (100.2-131.3)
Endocrine	4	1	25	86.5
Chronic gastrointestinal disease	2	1	50	83.8
Any comorbidity	271	107	39	112.1 (69.8-181.1)
No comorbidity	333	83	25	85.3 (54.1-139.1)

Table 4: Characteristics of children with RSV who died

Case	Age	Gender	Number of comorbidities	Comorbidity types	Clinical presentation
1	1 year	M	3	Cardiac – congenital heart disease Chronic respiratory disease Chronic gastrointestinal disease	Hypovolaemic shock
2	4 months	M	1	Immunodeficiency/Oncology/haematological	Apnoea
3	2 years 8 months	M	2	Chronic neurological disease Congenital syndrome	LRTI
4	4 years 10 months	F	3	Chromosomal anomaly Chronic – congenital heart disease Chronic renal disease	LRTI
5	9 months	F	1	Immunodeficiency/oncology/haematological	Respiratory failure
6	5 years 6 months	M	1	Chronic neurological disease	LRTI
7	16 years	M	1	Immunodeficiency/oncology/haematological	LRTI

10 years of severe respiratory syncytial virus infections in a tertiary paediatric intensive care unit

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