Irish Medical Journal
Established 1867

Issue: Ir Med J; Vol 113; No. 1; P9

Risk Factors for Respiratory Syncytial Virus Bronchiolitis Admissions

S. Meenaghan[1], C. Breatnach[1,2], H. Smith[1,2,3]

1. Children's Health Ireland at Crumlin (CHI@Crumlin), Dublin, Ireland
2. Paediatrics, Trinity College Dublin, Ireland
3. School of Nursing, Midwifery and Health Systems, University College Dublin, Ireland

Abstract

Aim
Determine the seasonal incidence of hospital Respiratory Syncytial Virus (RSV) bronchiolitis and explore the variables associated with admission to ward versus the Paediatric Intensive Care Unit (PICU).
Method
Retrospective case-control study. Children, aged ≤2 years, between November and March, over a 3 year period with a positive RSV nasopharyngeal aspirate test.
Results
A total of 557 children were included; 19% (n=106) required PICU admission. Children admitted to the PICU were younger in age, median (IQR) 6.93 (3.96, 11.89) weeks compared to children who remained on the wards 11.00 (5.86, 24.14) weeks. Being underweight at the point of admission (adjusted odds ratio 3.15, 95% 1.46, 6.70, p=0.003) was associated with a PICU admission.
Conclusion
Number of RSV bronchiolitis hospitalisations are increasing each year. Age, weight and the use of HFNC were independent predictors for PICU admission.

Introduction

Respiratory Syncytial Virus (RSV) bronchiolitis is one of the leading causes of respiratory tract infections in infants and young children with 90% being infected by age two worldwide[1,2]. It is estimated that in Europe 10% of children acquiring RSV bronchiolitis will need hospital care, with one in eight admissions requiring treatment in a Paediatric Intensive Care Unit (PICU)[1,3]. Since 2012 RSV bronchiolitis has been a notifiable disease in Ireland with annual epidemiological reports showing year on year increases that peak between November and February[4]. RSV bronchiolitis is now the second most common respiratory virus in Ireland after influenza[5].

Clinical risk factors such as prematurity, age, chronic lung disease, neurological and cardiac conditions have all been identified as contributing risk factors to patients requiring hospitalisation, including admission to a PICU[6,7,8,9]. Current research demonstrates a rise in the proportion of previously healthy infants with no known co-morbidities being admitted to PICU due to RSV bronchiolitis[6,7]. With trends showing a decrease in the number of infants with co-morbidities requiring PICU treatment[6,7]. The factors associated with admission to hospital with RSV bronchiolitis have not been described in an Irish context before, nor, whether the observed yearly increase in hospital admissions is associated with a change in patient characteristics. Therefore, the aim of this study is to determine the incidence and characteristics of RSV bronchiolitis admissions among children less than two years old, during three winter seasons and examine for risk factors associated with admission to the PICU.

Methods

Retrospective, unmatched case-control, single centre study, conducted at Ireland's primary tertiary paediatric hospital which houses a 23 bedded PICU with over a 1,000 admissions per year[10]. All children, aged two years or less, whose

primary reason for admission between November and February during the years 2014 to 2017 was bronchiolitis secondary to RSV confirmed by a positive Nasopharyngeal Aspirate (NPA) test were included in this study. Laboratory data and the patient administration system (PAS) were cross-referenced to ensure inclusion of eligible children.

Children who were not admitted to hospital, whose age on admission was greater than 2 years, whose admission occurred outside of the study period or whose primary reason for admission was not RSV bronchiolitis were excluded. Cases were defined as those requiring admission to the PICU at any point during their hospital stay. Controls were children cared for exclusively at ward level. Healthy children were defined as the proportion of children who were admitted to hospital with no pre-existing co-morbidities or no known medical condition at the time of admission. Any child who presented with a known cardiac, neurological, respiratory or genetic diagnoses was characterised as having a co-morbidity.

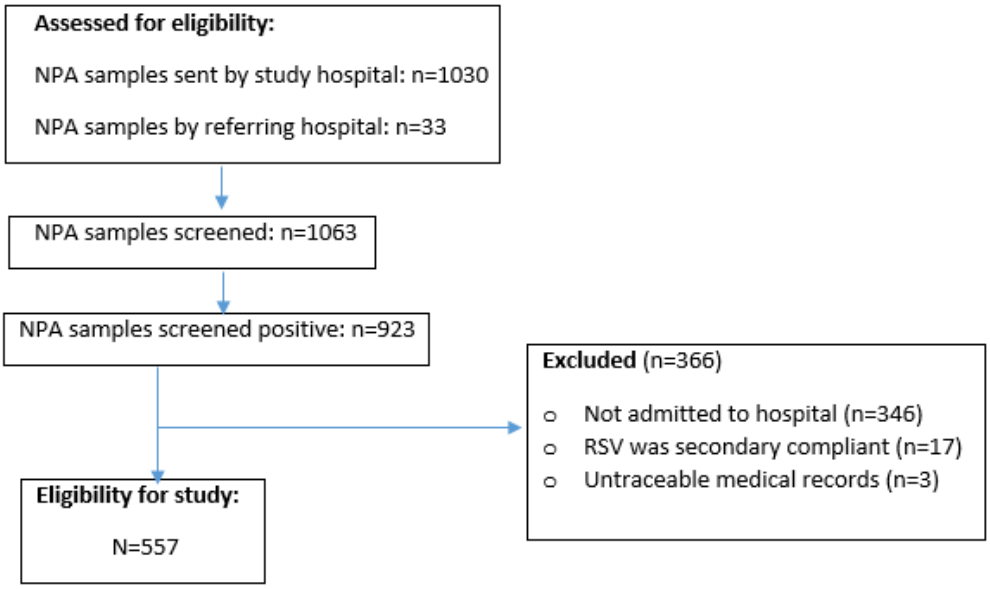
All demographic and clinical information was extracted from patients' medical charts. Criteria for transfer to the PICU comprises of escalation of respiratory support above High Flow Nasal Cannula (HFNC) due to deterioration in line with the National Model of Care in Ireland[11]. Children were classified as being born at term (gestational age at delivery ≥ 37 weeks) or preterm (gestational age at delivery ≤36 weeks). We further divided gestational age into three groups; Term (≥ 37 weeks), moderate to late preterm (32-36 weeks) and very preterm (≤ 31 weeks)[12]. The Paediatric Early Warning System (PEWS) is used across all hospitals in the Health Service Executive (HSE) and this data was collected[13]. PEWS is an observational tool used at the bedside to identify the deteriorating child based on physiology values. Weight-for-Age (WFA) z-score was calculated using the World Health Organization (WHO)'s Anthro software for child growth standards[14]. Children were grouped as underweight (WFA z-score <-1), normal weight (WFA z-score -1 to +1) and overweight (WFA z-score >-1). A child's Paediatric Index Mortality III (PIM III) Score was calculated throughout a child's length of stay on PICU[10,15]. All parameters that were analysed in this study were decided upon prior to data collect.

Categorical data is presented as numbers with their corresponding percentage and tested using Chi Square Test. Continuous parametric data and non-parametric data are shown as mean (SD) and examined using Student's T-Test or displayed as median (IQR) and examined using Mood's Test, respectively. In multivariate analyses we used logistic and linear regression for categorical and continuous outcomes, respectively. Non-parametric continuous variables were log transformed prior to being entered into any of the models. We employed directed acyclic graphs (DAGs) in combination with the descriptive analyses described above to identify co-variates that should be included in the models to reduce confounding and improve causal inferences[16,17]. The Institutional Research Ethics Board waived the need to seek parental consent for this study.

Results

A total of 1030 NPA samples for suspected RSV bronchiolitis were obtained from the microbiology laboratory during the study period, of which 923 children were positive for the virus. In total 366 children were excluded from the study giving a final sample size of 557 (Figure 1). (Next page)..

Figure 1: Flowchart of Patient Recruitment



Majority of admissions received ward based care (n=451, 81%) with 19% (n=106) requiring PICU. Admission numbers increased from 149 in 2014-2015 to 236 in 2016-2017. The proportion of children with a co-morbidity decreased from 18.8% in 2014-2015 to 12.3% in 2016-2018. Overall, 83.7% (n=466) of children were born at term (≥ 37 weeks gestation). The median (IQR) age on admission and duration of total hospital stay for the whole population group was 10.0 (5.6, 21.9) weeks and 5.0 (3.0, 7.0) days, respectively. Over half of all children had a normal WFA z-score (n=329, 59.1%) and the majority of those with a normal WFA z-score were born at term (n=299, 90.9%), Table 1.

TABLE 1: Study Characteristics

Characteristics	Total Population	Controls (admission to ward only)	Cases (admission to PICU)
Study participants, n(%)	557 (100%)	451 (81.0%)	106 (19.0%)
Admissions during 2014-2015, n(%)	149 (26.8%)	119 (26.4%)	30 (28.3%)
Admissions during 2015-2016, n(%)	172 (30.9%)	145 (32.2%)	27 (25.5%)
Admissions during 2016-2017, n(%)	236 (42.4%)	187 (41.5%)	49 (46.2%)
Male, n(%)	317 (56.9%)	256 (56.8%)	61 (57.5%)
Gestational age at delivery (weeks), median (IQR)	39.00 (37.00, 40.00)	39.00 (37.25, 40.00)[a]	38.00 (35.75, 39.00)
Term (≥ 37 weeks' gestation) delivery, n(%)	466 (83.7%)	392 (86.9%)[a]	74 (69.8%)
Age (weeks) on admission, median (IQR)	10.00 (5.57, 21.86)	11.00 (5.86, 24.14)[a]	6.93 (3.96, 11.89)
Weight (kg) on admission, median (IQR)	5.31 (4.30, 7.30)	5.02 (4.13, 7.43)[a]	4.50 (3.89, 5.80)
Weight-For-Age z-score on admission, median (IQR)	-0.16 (-0.95, 0.61)	-0.05 (-0.76, 0.65)[b]	-0.53 (-2.12, 0.38)
Underweight on admission, n(%)	129 (23.2%)	82 (18.4%)[a]	47 (44.8%)
Co-infection, n(%)	79 (14.2%)	66 (14.6%)	13 (12.3%)
Co-morbidity, n(%)	96 (17.2%)	73 (16.2%)	23 (21.7%)
PEWS on admission to hospital, median (IQR)	2 (1, 3)	3 (2, 4)[a]	4 (2, 6)
PEWS response on admission: Nurse in charge n(%)	160 (28.7%)	321 (71.2%)[a]	18 (23.7%)
PEWS response on admission: Urgent PEWS call n(%)	18 (3.2%)	5 (1.1%)[a]	13 (17.1%)
Required HFNC on the ward, n(%)	123 (22.1%)	37 (34.9%)[a]	69 (65.1%)
Duration (days) of HFNC on the ward, median(IQR)	2.00 (1.00, 4.00)	4.00 (3.00, 5.25)[a]	1.00 (1.00, 1.00)
Chest x-ray, n(%)	339 (60.9%)	235 (52.1%)[a]	104 (98.1%)
Total duration (days) of hospital stay, median(IQR)	5.00 (3.00, 7.00)	7.00 (5.00, 10.00)[a]	9.00 (6.00, 11.00)

a: p=≤0.001; b: p=<0.05

Differences were noted between cases and controls. A higher proportion of cases had an urgent (≥7) PEWS score at the point of admission compared to controls, 17.1% versus 1.1%, p=<0.001. A greater proportion of cases required the use of HFNC on the wards compared to controls, 65.1% versus 34.9%, p=<0.001, respectively. All cases had lower WFA z-scores. No statistically significant difference was seen in the proportion of children with co-morbidities across the two groups.

Age (months), WFA z-score, PEWS response on admission, requiring HFNC on the ward, co-infection and co-morbidity were all entered into the multivariate logistic model. Overall, PEWS response on admission showed the highest odds of admission to the PICU. An urgent PEWS call had the highest odds (aOR 38.41 (95% 9.94, 148.37), p=<0.001) of admission to the PICU when compared to nursing care only being indicated. Children who were underweight had triple the odds of admission to the PICU compared to children with a normal weight for their age (aOR 3.15 (95% 1.46, 6.79),

p=0.003). Children aged between two to twelve months had reduced odds of admission to the PICU (aOR 0.43 (95% 0.21, 0.87), p=0.02) compared to children younger than two months of age, Table 2.

TABLE 2: Adjusted odds ratio for admission to a PICU with RSV bronchiolitis

N= 551/557	Adjusted Odds Ratio (95% CI)
≤2 months old on admission	*Reference*
≤12 months old on admission	0.43 (0.21, 0.87)[b]
≤24 months old on admission	0.30 (0.07, 1.23)
Normal weight (Weight-For-Age z-score -1 to +1)	Reference
Underweight (Weight-For-Age z-score <-1)	3.15 (1.46, 6.79)[b]
Overweight (Weight-For-Age z-score >1)	0.53 (0.19, 1.47)
***PEWS response on admission:* Nurse in charge to respond**	*Reference*
PEWS response on admission: physician on call to respond	3.69 (1.79, 7.63)[a]
PEWS response on admission: senior physician / consultant to respond	20.03 (3.27, 122.54)[b]
PEWS response on admission: urgent call	38.41 (9.94, 148.37)[a]
Did not require HFNC while on the ward	*Reference*
Required HFNC while on the ward	17.30 (8.70, 34.41)[a]
No co-infection	*Reference*
Co-infection	1.67 (0.67, 4.17)
No co-morbidity	*Reference*
Co-morbidity	1.23 (0.51, 2.94)

a: p=≤0.001; b: p=<0.05

Results from the multiple linear regression model showed that increased age and WFA z-score on admission decreased length of stay in the PICU by -0.15 ((95% CI -0.27, -0.03), p=0.02) days and -0.03 ((95% CI -0.05, 0.00), p=0.05) days, respectively. Once admitted to the PICU having a co-morbidity increased length of stay by 0.12 (95% CI 0.004, 0.23) p=0.04) days, Table 3.

TABLE 3: Multiple linear regression for duration of stay (days) in the PICU

N= 105/106	ß/Beta (95% CI)
Age (weeks) on admission	-0.15 (-0.27, -0.03)[b]
Weight-For-Age z-score on admission	-0.03 (-0.05, 0.00)[b]
Has a co-infection	0.07 (-0.06, 0.20)
Has a co-morbidity	0.12 (0.004, 0.23)[b]
Had HFNC on the ward pre-admission to PICU	-0.04 (-0.133, 0.05)
Paediatric Index Mortality Score III on admission to PICU	0.17 (-0.13, 0.46)

a: p=≤0.001; b: p=<0.05

Discussion

This paper is the latest to confirm that RSV bronchiolitis hospitalisation numbers continue to increase with each winter season. However, we did not find a corresponding rise in admissions to the PICU. We have found that WFA on admission, for children born both at term and preterm, is a risk factor for both admission to and duration of stay in the PICU independent of co-morbidities. The literature reports low birthweight as a risk factor for hospitalisation, but we have demonstrated how a child's weight at the point of admission influences both their need for and duration of intensive care[7,8]. Our findings are consistent with previously published research showing that patient numbers reduce with increasing age[1,18].

Many studies have confirmed that children born preterm have higher rates of admission to PICU[12,18]. Our study had significantly higher rates of preterm cases compared to the controls. We found that having a co-morbidity did not increase a child's odds of admission to the PICU but did increase their length of stay once admitted to the PICU. This study demonstrates a decline in the number of children with co-morbidities requiring hospitalisation due to RSV bronchiolitis. However, the numbers of healthy children being admitted continues to rise. These findings correlate

with other new research studies that report children who require PICU are less likely to have underlying conditions, a change from previous research in this area[19,20]. Patients categorised as being high risk due to co-morbidities or gestational age are offered the palivizumab injection in Ireland. As a result, these patients may experience milder signs and symptoms that can be managed at home or ward level and may contribute to a seemly steady rise in admission numbers of healthy children to PICU[20]. The reason for increasing RSV bronchiolitis numbers yearly is unknown with limited epidemiology data. Preventative strategies such as palivizumab injection for young healthy population groups needs to be reviewed and assessed to decrease the burden on acute services.

A PEWS score on admission indicating a child requires more than nursing care alone had the highest odds of admission to the PICU. Although, it should be noted that the confidence interval was wide for most of the PEWS results suggesting uncertainty as to the true association of PEWS with admission to the PICU. Most admissions to the PICU were based on an urgent need for increased support and this could suggest that the PEWS was not identifying deteriorating children. Our findings reflect the EPOCH Randomized Clinical Trial that found implementing a validated bedside PEWS did not reduce the need for urgent PICU consultations or admissions compared to usual care[21].

The need for oxygen therapy has been reported in the literature as a predictor for disease severity with research reporting RSV bronchiolitis patients were more likely to require HFNC when compared to other respiratory illnesses[1,3,22]. In this study, children had increased odds of admission to PICU following the application of HFNC. Previous research has been unable to establish if HFNC is superior to oxygen alone in reducing length of hospital stay[22]. We hypothesize that in our study HFNC was applied as an escalation of care prior to the child being transferred to PICU and not given as a treatment to avoid transfer to the PICU. Further analysis is needed on HFNC as a treatment option for RSV bronchiolitis.

There are limitations to our study. This is a retrospective, unmatched case-control study which was impacted on the completeness of medical records for data collected.

This study does highlight that the clinical risk factors associated with PICU admissions are changing. Our cases mainly consisted of young previously healthy children with only a fifth reporting a co-morbidity. Being underweight, independent of other risk factors, was the strongest risk factor for admission and duration of stay to the PICU.

Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare.

Corresponding Author:
Samantha Meenaghan
Children's Health Ireland at Crumlin (CHI@Crumlin),
Dublin,
Ireland,
D12 N512
Email: sm386@live.ie

References:

1. Zorc JJ, Hall CB. Bronchiolitis; recent evidence on diagnosis and management. Pediatrics. 2010;125:342-349.
2. American Academy of Paediatrics (AAP). Clinical Practice Guideline - Diagnosis and Management of Bronchiolitis. Pediatrics. 2006;118:1774.
3. Schlapbach LJ, Straney L, Gelbart B, Alexander J, Franklin D, Beca J, Whitty JA, Ganu S, Wilkins B, Slater A, Croston E, Erickson S, Schibler A. Burden of disease and change in practice in critically ill infants with bronchiolitis. Eur Respir. 2017; 49:160-164.
4. Domegan L, O'Donnell, Cunney R, O'Kelly, Dooley S. Increased respiratory syncytial virus activity in Ireland. Euro Surveill. 2012;6(49).
5. Health Protection Surveillance Centre (HPSC). Annual Epidemiological Report. Dublin: Health Protection Surveillance Centre; 2014, 2015, 2016 & 2017. Available from: http://www.hpsc.ie/abouthpsc/annualreports/annualepidemiologicalreports1999-2016/HPSC%20Annual%20Report%202014%20%20.pdf [Accessed 28th March 2019].

6. Garcia-Garcia ML, Gabin OM, Calvo RC, Alvarez G, Ruiz JA, Sierra A. Viral infection of the lower respiratory tract in hospitalised infants; etiologic, clinical features and risk factors. An Esp Pediatr. 2001;55:101-7
7. Papoff P, Moretti C, Cangiano C, Bonci E, Roggini M, Pierangeli A, Scagnolari C, Antonelli G, Midulla F. Incidence and predisposing factors for severe disease in previously healthy term infants experiencing their first episode of bronchiolitis. Acta Paediatrics. 2011;100:17-23
8. Bont, L, Checchia PA, Fauroux B, Figueras-Aloy J, Manzoni P, Paes B, Simoes EAF, Carbonell-Estrany X. Defining the Epidemiology and Burden of Severe Respiratory Syncytial Virus Infection Among Infants and Children in Western Countries. Infectious Diseases and Therapy. 2016;5(3):271–298.
9. Department of Children and Young Affairs. State of the Nation's Children: Ireland 2016. Dublin: Government Publications; 2016. Available from: http://www.dcya.ie [Accessed 9th April 2019].
10. Provincial Infection Control Network of British Columbia (PICNet). Paediatric Intensive Care Audit Network Annual Report 2017. Paediatric Intensive Care Audit Network and Healthcare Quality Improvement Partnership; 2017 Available from: https://www.picnet.ca/publications/picnet-annual-reports/. [Accessed 3rd December 2018].
11. Health Service Executive. Paediatrics – A National Model of care for Paediatrics Healthcare Services in Ireland. Clinical Strategy and Programme Division; 2016. Available from: https://www.hse.ie/eng/services/publications/clinical-strategy-and-programmes/model-of-care-for-paediatric-healthcare-executive-summary.pdf [Accessed on 28th March 2019].
12. Hasegawa K, Pate BM, Mansbach JM, Macias CG, Fisher ES, Piedra PA, Espinola JA, Sullivan AF, Camargo CA. Risk Factors for requiring intensive care among children admitted to ward with bronchiolitis. Academic Pediatrics. 2015;15(1):77-81.
13. Health Service Executive. Paediatric Early Warning System (PEWS), User Manual, 2nd Edition. Clinical Strategy and Programme Division; 2017. Available from:https://www.hse.ie/eng/services/publications/clinical-strategy-and-programmes/pews-user-manual.pdf [Accessed the 28th March 2019].
14. World Health Organization (WHO) Anthro. Child growth standards. Switzerland; 2011. Available from: http://www.who.int/childgrowth/software/en/. [Accessed 9th April 2019].
15. Straney L, Clements A, Parslow RC, Pearson G, Shann F, Alexander J, Slater A. Paediatric index of mortality 3: An updated model for predicting mortality in pediatric intensive care. Pediatr Crit Care Med. 2013;14:673–81.
16. Greenland S, Pearl J, Robins J. Causal diagrams for epidemiologic research. Epidemiology.1999;10(1):37-48.
17. Fleischer NL, Roux AVD. Using directed acyclic graphs to guide analyses of neighbourhood health effects: an introduction. Journal of Epidemiology and Community Health. 2008;62(9):842-6.
18. Mecklin M, Heikkila P, Korppi M. Low age, low birth weight and congenital heart disease are risk factors for intensive care in infants with bronchiolitis. Acta Padiatr. 2017;106(12):2004-10.
19. Buckingham SC, Quasney MW, Bush AJ, DeVincenzo JP. Respiratory syncytial virus infections in the paediatric intensive care unit: Clinical characteristics and risk factors for adverse outcomes. Pediatr Crit Care Med. 2001; 2(4):318-323.
20. Sala KA, Moore A, Desai S, Welch K, Bhandari S, Carroll CL. Factors associated with disease severity in children with bronchiolitis. Asthma. 2015;52(3):268-272
21. Parshuram CS, Dryden-Palmer K, Farrell C, Gottesman R, Gray M, Hutchison JS, Helfaer M, Hunt EA, Joffe AR, Lacroix J, Moga MA, Nadkarni V, Ninis N, PARKIN pc, Wensley D, Willan AR, Tomlinson GA. Effect of a Pediatric Early Warning System on All-Cause Mortality in Hospitalized Pediatric Patients: The EPOCH Randomized Clinical Trial. JAMA. 2018;319(10):1002–12.
22. Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, Furyk J, Faser JF, Jones M, Whitty JA, Dalziel SR, Schibler A. A Randomized Trial of High-Flow Oxygen Therapy in Infants with Bronchiolitis. The New England Journal of Medicine. 2018;378:1121-31.