Outcomes of Nosocomial Viral Respiratory Infections in High-Risk Neonates

Shairbanu Zinna, MB BS, MRCPCH,[a] Arthi Lakshmanan, MB BS, MRCPCH,[a] Shin Tan, BM BS,[b] Rebecca McClaughry, BA,[b] Martin Clarkson, BSc,[b] Shiu Soo, PhD, FRCPath,[a] Lisa Szatkowski, PhD,[c] Don Sharkey, PhD, FRCPCH[a,b]

abstract

BACKGROUND AND OBJECTIVE: Neonatal respiratory disease, particularly bronchopulmonary dysplasia, remains one of the leading causes of morbidity and mortality in newborn infants. Recent evidence suggests nosocomially acquired viral respiratory tract infections (VRTIs) are not uncommon in the NICU. The goal of this study was to assess the association between nosocomial VRTIs, neonatal respiratory disease, and the health care related costs.

METHODS: A matched case–control study was conducted in 2 tertiary NICUs during a 6-year period in Nottingham, United Kingdom. Case subjects were symptomatic neonatal patients with a confirmed real-time polymerase chain reaction diagnosis of a VRTI. Matched controls had never tested positive for a VRTI. Multivariable logistic regression was used to test for associations with key respiratory outcomes.

RESULTS: There were 7995 admissions during the study period, with 92 case subjects matched to 183 control subjects. Baseline characteristics were similar, with a median gestation of 29 weeks. Rhinovirus was found in 74% of VRTIs. During VRTIs, 51% of infants needed escalation of respiratory support, and case subjects required significantly more respiratory pressure support overall (25 vs 7 days; $P < .001$). Case subjects spent longer in the hospital (76 vs 41 days; $P < .001$), twice as many required home oxygen (37%; odds ratio: 3.94 [95% confidence interval: 1.92–8.06]; $P < .001$), and in-hospital care costs were significantly higher (£49 664 [$71 861] vs £22 155 [$32 057]; $P < .001$).

CONCLUSIONS: Nosocomial VRTIs in neonatal patients are associated with significant greater respiratory morbidity and health care costs. Prevention efforts must be explored.

WHAT'S KNOWN ON THIS SUBJECT: Viral respiratory tract infections (VRTIs) cause severe respiratory morbidity in ex-preterm infants after NICU discharge. VRTIs are now recognized to be more prevalent in the NICU, but their impact, before discharge, during this early period of life is unclear.

WHAT THIS STUDY ADDS: This study identifies the adverse impact that VRTIs, particularly rhinovirus, have on newborn infants during their initial NICU admission. Identification of the associated significant respiratory morbidity and health care costs should focus efforts on reducing these nosocomially acquired infections.

Neonatal bronchopulmonary dysplasia (BDP) is associated with long-term respiratory morbidity, including asthma, chronic obstructive airways disease,[1–3] and poor neurodevelopmental outcomes.[4] Despite improvements in the respiratory management of preterm infants, and subsequent increased survival, many countries have not reported reductions in BPD. In the United Kingdom, 68% of extremely preterm survivors born in 2006 had BPD, unchanged from 1995 rates.[5] Current US estimates suggest there are between 5000 and 10 000 new cases of BPD annually,[2] with respiratory causes of death second only to immaturity in extremely preterm infants.[6]

The pathogenesis of BPD is multifactorial; the presence of inflammation and prematurity are key factors. The inflammatory changes observed are usually a result of infection, ventilatory trauma, and hyperoxia.[7] Few studies have explored the impact of viral respiratory tract infections (VRTIs) in this process, although animal studies have highlighted their potential adverse role.[7,8] After discharge from the NICU, surviving preterm infants with subsequent VRTIs are more likely to develop severe respiratory disease or experience recurrent wheeze and asthma.[9–11]

Nosocomial VRTIs are often unrecognized or clinically underdiagnosed in the NICU,[12,13] with up to 52% of admissions testing positive for viral DNA according to polymerase chain reaction (PCR).[14] It is therefore plausible that VRTIs acquired during the NICU period could worsen BPD in preterm infants, although previous studies have mostly been small observational cohorts.[12,13,15–19] The goal of the present study was to assess the association between nosocomial VRTIs acquired in the NICU and respiratory morbidity up to hospital discharge.

METHODS

Study Design

This study was a retrospective matched case–control trial conducted in 2 large tertiary NICUs in Nottingham, United Kingdom, between July 2007 and July 2013; this period included the worldwide influenza A (H1N1) pandemic in 2009/2010. This time frame was chosen because it represented the start of detailed electronic record collection for all NICU patients and the introduction of a PCR-based assay for viral detection rather than the immunofluorescence and culture methods used previously. The NICUs care for all newborn infants in the Nottingham area and those infants requiring intensive care from surrounding hospitals in the Trent Perinatal Network, covering ~26 000 births annually. Both NICUs are part of the same organization (Nottingham University Hospitals NHS Trust) with the same infection prevention and control measures. Infants with VRTIs are barrier nursed in an enclosed incubator until asymptomatic. No readmissions are allowed once discharged from the hospital after their birth. Parents could visit anytime, with siblings and other relatives permitted between 2:00 PM and 8:00 PM. A restricted visiting policy was in place during the months of November to April in 2009, 2010, and 2011, during which only parents could visit, as a precautionary measure in view of the H1N1 pandemic. Visitors with respiratory illnesses were advised not to visit until symptom free.

Case subjects were defined as any infant cared for in the NICU whom the clinical team deemed to have signs or symptoms consistent with a VRTI[17] and who had real-time PCR–positive viral DNA in airway secretions. After resolution of symptoms, infants who became symptomatic again with a new infection were included only if this occurrence was >14 days beyond the initial positive test result and with a different viral agent (to reduce the risk of genomic persistence in the airway).[20] Two control subjects were matched per case subject according to the following: (1) gestation (±1 week); (2) center in which they received the majority of their care; and (3) birth within 6 months of the case subject to minimize variations in care over time. All infants studied were admitted to the NICU after birth.

Data were collected on a standardized pro forma, from both the clinical notes and hospital electronic records. Gestational age was determined by ultrasound scanning or, if this option was not available, last menstrual period was used. Clinical data included birth weight, mode of delivery, number of siblings, number of courses of maternal steroids, maternal infections in pregnancy, maternal smoking, intrauterine growth retardation, and surfactant doses. Postnatal data included time in the hospital, days of respiratory support, and other comorbidities such as congenital heart disease, retinopathy of prematurity (requiring treatment), and a clinical diagnosis of necrotizing enterocolitis.

For case subjects, the escalation of respiratory care was defined according to set criteria by at least 1 step up the support pathway from their immediate preinfection status: no support → oxygen only → continuous positive airway pressure → bilevel positive airway pressure → invasive ventilation → high-frequency ventilation or extracorporeal membrane oxygenation. BPD was defined as the requirement in infants <32 weeks' gestation of oxygen for >28 days and at 36 weeks' corrected gestation.[21] Infants' requirements for home oxygen were based on the criteria defined by the British Thoracic

Society[22] using an agreed hospital-wide guideline.

Ethical approval was given by the University of Nottingham Medical School Ethics Committee (reference LTd10042014).

Sampling and Real-Time PCR Analysis

All respiratory samples, either nasopharyngeal and/or lung aspirates if ventilated, were collected at the time of the presumed infection and analyzed by using the multiplex PCR Respiratory Viral Panel assay according to a standard operating procedure in a certified National Health Service laboratory (Supplemental Table 3). Data were also collected on any other positive microbiologic samples found ±24 hours of the PCR diagnosis of a VRTI.

In-hospital Cost of Care

Costs of care were calculated based on the 2011–2012 published tariffs for neonatal care in the UK National Health Service.[23] Costs for each level of care (intensive, high dependency, and special care) were calculated to the point of discharge or death.

Data Analysis

Data were analyzed by using Stata version 12 (Stata Corp, College Station, TX). Continuous data are presented as means and SDs or medians and interquartile ranges (IQRs) for parametric and nonparametric data, respectively. Conditional logistic regression was used to compare the baseline characteristics of case subjects and matched control subjects, and then to compare respiratory outcomes; these outcomes included number of days of ventilation required, need for continuous positive airway pressure, and number of days spent in intensive care and high dependency. Univariable and multivariable logistic regression, with a priori adjustment for gestation and center, was used to calculate odds ratios

(ORs) for the association between several potential risk factors and escalation in respiratory support, as well as discharge on home oxygen. Potential predictors of respiratory morbidity studied included the following: sex, birth weight, mode of delivery, antenatal steroids, maternal infection, chorioamnionitis, intrauterine growth restriction, maternal smoking, surfactant, Apgar score, cardiac anomalies (including patent ductus arteriosus), and necrotizing enterocolitis. Variables significant at the 10% significance level ($P < .1$) in a univariable logistic regression model were included in a multivariable model. Data were summarized by using ORs with 95% confidence intervals (CIs). Analyses were 2-sided and considered significant if $P < .05$.

RESULTS

Baseline Characteristics

During the study period, there were 7995 admissions to the NICUs where the study was conducted (1332 per year) with a total of 79 642 bed-days. A total of 275 infants (92 case

subjects and 183 control subjects) met the inclusion criteria. All case subjects were matched with 2 control subjects, with the exception of 1 infant who only had a single control subject meeting the inclusion criteria. Case and control subjects were evenly matched, with a median gestation of 29.4 weeks (IQR: 26.9–33.9 weeks) for the case subjects and 29.6 weeks (IQR: 26.9–34.0 weeks) for the control subjects. Both groups had similar baseline characteristics (Table 1).

Viral Infections

There were a total of 95 nosocomial VRTIs diagnosed by using PCR in 92 symptomatic infants (Table 2). Of these, 84 (91%) were preterm, with 56 (61%) at ≤30 weeks' gestation. These findings equate to a symptomatic nosocomial VRTI incidence of 3.8% in infants admitted at ≤30 weeks' gestation. The median day of life of infection was 43 days (IQR: 25–76 days). Rhinovirus was the dominant pathogen and was detected in 70 case subjects (74%). There were 5 cases of influenza A H1N1 pandemic strain with escalation of respiratory support

TABLE 1 Baseline Characteristics of Study Subjects

Characteristic	Case Subjects (n = 92)	Control Subjects (n = 183)	P
Male sex	49 (53)	113 (62)	.19
Birth weight, g			.72
>2500	14 (15)	24 (13)	
1501–2500	18 (20)	44 (24)	
1000–1500	28 (30)	55 (30)	
<1000	32 (35)	60 (33)	
Antenatal steroids (full course)	64 (70)	127 (69)	.94
Chorioamnionitis	19 (21)	48 (26)	.27
IUGR	14 (15)	30 (16)	.80
Maternal smoking	25 (27)	43 (23)	.26
Mode of delivery			.86
Vaginal	49 (53)	92 (50)	
Elective cesarean delivery	7 (8)	17 (9)	
Emergency cesarean delivery	36 (39)	73 (40)	
5-min Apgar score <7	12 (13)	26 (14)	.66
Cardiac anomaly	28 (30)	48 (26)	.42
PDA only	4 (4)	12 (15)	
Necrotizing enterocolitis	20 (22)	36 (20)	.69
Retinopathy of prematurity	15 (16)	20 (11)	.21
Death before discharge	3 (3)	13 (7)	.26

Data are presented as n (%). P values represent conditional logistic regression. IUGR, intrauterine growth retardation; PDA, patent ductus arteriosus.
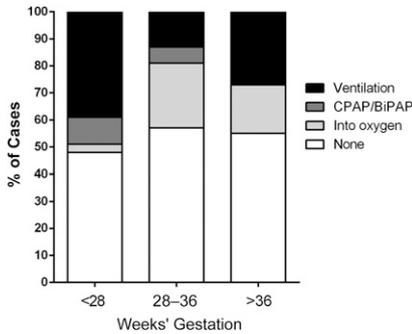
FIGURE 1
Percentage of case subjects requiring escalation of respiratory support at the time of VRTI diagnosis grouped according to birth gestation category; $n = 95$ episodes of infection. BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

Virus	N
Rhinovirus	65
Rhinovirus and adenovirus	1
Rhinovirus and H1N1	1
Rhinovirus and parainfluenza virus type 1	1
Rhinovirus and parainfluenza virus type 3	1
Rhinovirus and respiratory syncytial virus	1
Parainfluenza virus type 3	6
Respiratory syncytial virus	5
Influenza A H1N1 strain	4
Coronavirus	3
Parainfluenza virus type 2	2
Others (1 each of adenovirus, influenza A, influenza B, metapneumovirus, and parainfluenza virus type 4)	5

in 3 of those infants. Three deaths occurred before discharge in the case group (2 infants with H1N1 and 1 with rhinovirus). Of note, 9 (10%) of the case subjects had a diagnosis of gastroschisis. A total of 23 cases had blood culture specimens taken at the time of clinical deterioration, and 9 were positive (most for coagulase-negative *Staphylococcus* [$n = 6$]).

A total of 100 viral pathogens were identified in the 95 VRTIs. There were more than double the number of rhinovirus infections in the warmer months (April–September, $n = 47$) compared with colder months (October–March, $n = 23$). This pattern was reversed for other viruses, with 7 and 23 in the warmer and colder months, respectively.

Respiratory Support

Overall, 51% ($n = 47$) of infants required escalation of respiratory support during a VRTI episode (Fig 1). A greater proportion of infants <28 weeks' gestation required new respiratory pressure support during the VRTI (48%) compared with those ≥28 weeks' gestation (20%; $P < .01$). For case subjects, there were no associations identified with the need for escalation of respiratory support and key patient characteristics (Supplemental Table 4).

Outcomes: Case Subjects Versus Control Subjects

Case subjects required significantly more ventilation, with a median of 7 days (IQR: 2.5–27.5 days) compared with 2 days (IQR: 0–8 days) for control subjects ($P < .001$). Similarly, case subjects had a greater requirement for continuous positive airway pressure at a median of 18 days (IQR: 1–37 days) compared with 5 days (IQR: 0–33 days) for control subjects ($P = .026$). Case subjects spent significantly more care days at the level of intensive care and high dependency; they also remained in the hospital longer (76 vs 41 days; $P < .001$) (Fig 2).

Among case subjects <32 weeks' gestation, 65% ($n = 40$) had a diagnosis of BPD at 28 days compared with 52% ($n = 71$) of control subjects ($P = .09$), which remained not significant at 36 corrected weeks' gestation (case subjects, 52%; control subjects, 39% [$P = .81$]). Univariable conditional logistic regression did not identify any clinical variables associated with VRTI at the predefined statistical level ($P < .1$) to include in a multivariable model.

Requirement for Home Oxygen

At time of discharge, 37% ($n = 34$) of case subjects required home oxygen compared with 17.5% ($n = 32$) of control subjects ($P = .002$). Case subjects were also more mature,
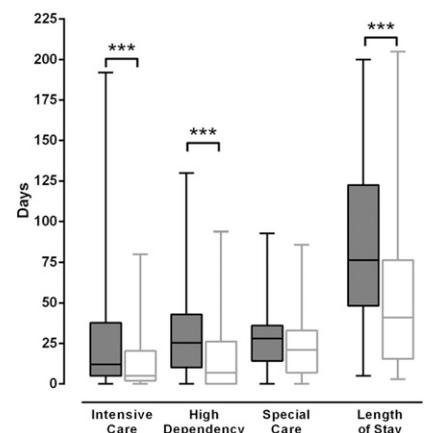

FIGURE 2
Median (95% CI error bars) days spent at each level of care and total hospital stay for case subjects (shaded boxes) compared with control subjects (clear boxes). ***$P < .001$.

with a mean gestational age of 28.7 ± 4.1 weeks compared with control subjects at 26.8 ± 1.8 weeks ($P = .014$). According to the univariable analysis (logistic regression adjusted a priori for gestation and center of care), clinical factors associated with the requirement for home oxygen ($P < .1$) were as follows: a confirmed VRTI, birth weight, maternal infection, 1-minute Apgar score <7, delivery room surfactant, and a cardiac anomaly. These factors were included in the multivariable model for home oxygen, and statistically significant associations were identified with VRTI (adjusted OR: 3.94 [95% CI: 1.92–8.06]; $P < .001$), maternal infection (adjusted OR: 2.4 [95% CI: 1.12–5.13]; $P = .024$),

1-minute Apgar score <7 (adjusted OR: 2.17 [95% CI: 1.02–4.61]; P = .047), and a cardiac anomaly (adjusted OR: 2.17 [95% CI: 1.06–4.45]; P = .035).

In-hospital Cost of Care

The 2011 National Health Service tariff costs[23] for intensive care, high dependency, and special care were £997 ($1443), £726 ($1051), and £429 ($621) per patient per day, respectively. Individual patient costs for case subjects were £49 664 ($71 861); for control subjects, it was £22 155 ($32 057) ($P$ < .001) (Fig 3). The total median cost difference between case and control subjects was £27 509 ($39 804) (range: £1994–£58 269 [$2886–$84 312]) extra per patient. With less intensive and high dependency care, 45% (n = 83) of control subjects had care costs less than £20 000 ($28 939) compared with only 12% (n = 11) of case subjects.

DISCUSSION

Until recently, nosocomially acquired VRTIs in the NICU were believed to be uncommon. The present study is the largest to date and demonstrates that VRTIs in the NICU are associated with significant respiratory morbidity and increased requirement for home oxygen, and they result in more than double the in-hospital care costs before first discharge. Using a rigorous matched case–control method, the baseline characteristics of the infants were well balanced, supporting our belief of the validity of the results.

Neonatal patients often develop respiratory symptoms during septic episodes and are usually screened for bacterial infection before initiation of antibiotics. Recent studies have highlighted that either parallel screening at the time of sepsis concerns, or routine surveillance monitoring, identify VRTI in 8% to 52% of infants in the NICU.[12–14]
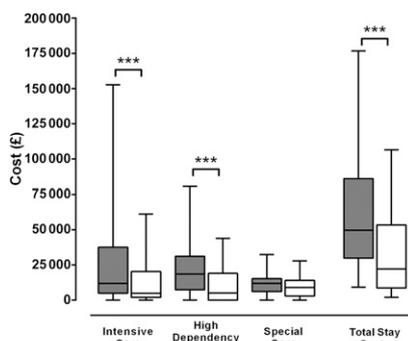

FIGURE 3
Median (95% CI error bars) health care cost according to level of care and total hospital stay for case subjects (shaded boxes) and control subjects (clear boxes). ***P < .001.

Our study focused on symptomatic infants with a suspected VRTI and identified that the most dominant pathogen was rhinovirus. Although other studies[13,14,19] have not found this pathogen to be the dominant finding, many of these studies were conducted before the widespread use of PCR, and their methods may not reliably identify rhinovirus. After respiratory syncytial virus infection, rhinovirus is a common pathogen and responsible for many community respiratory infections,[24–26] and it can cause severe respiratory disease in older children requiring hospitalization.[11,27] As the dominant pathogen in our cases, rhinovirus was associated with a need for increased respiratory support in one-half of the infants, with many of the premature infants requiring additional pressure support ventilation, similar to other smaller studies.[12,14,17] This scenario results in an increase in the level of care and barrier nursing, and it requires additional nursing and medical input to manage.

Rhinovirus infection was seen throughout the year, with many of the other viruses only observed during the colder months in keeping with seasonal trends in the United Kingdom.[25,28] Because asymptomatic children and older individuals can have viral DNA present in their airway secretions,[20,29] parents, siblings, staff, and visitors may be unaware

of the infection risk they could pose to vulnerable infants. VRTIs are known to cause more severe disease in younger individuals,[30,31] which may be further exacerbated in the preterm NICU population with a reduced transplacental maternal immunoglobulin G transfer[32] and an immature immune system. Traditionally during periods of deterioration in preterm infants in the NICU, clinical teams evaluate the infant for bacterial infection and initiate antibiotics until bacterial culture results are negative or the infant improves clinically. It is possible that preterm infants who deteriorate on respiratory support may actually have a VRTI, but this possibility is not considered by the attending team because the management is mainly supportive with limited treatment options, unlike bacterial infection. Bennett et al[14] also observed that VRTIs in preterm infants in the NICU were associated with worse respiratory outcomes, although, as in our study, causal effect could not be ascertained.

Strong evidence is available regarding the adverse effects that VRTIs have on preterm infants during the first few years of life, but few studies have focused on the preterm infant at risk for BPD. The interruption of normal lung alveolarization caused by prematurity could be further compounded by VRTI inflammation and worsening of the long-term lung injury,[7] potentially supporting a causal relationship with VRTIs and respiratory morbidity in our study. This hypothesis is supported by other studies that have reported increased respiratory morbidity in preterm infants associated with early lung infection.[33] In addition, animal models offer evidence that viral infection, in combination with oxygen supplementation, has an adverse impact on the immune response and potential subsequent lung recovery.[34] It is interesting that, in the present

study, case subjects requiring home oxygen were significantly more mature (by ∼2 weeks) compared with control subjects requiring home oxygen. The reasons for this outcome are unclear but could reflect a more mature immune system mounting a greater inflammatory response to the viral pathogen, resulting in more lung injury.

There are few published reports on neonatal nosocomial-acquired H1N1, and our study adds to the data available highlighting the significant respiratory disease this strain causes, also evident in other outbreaks.[35,36] Three of the 5 case subjects with H1N1 required additional respiratory support, with 2 of the infants dying as a direct result of the infection. Our cases occurred over 2 separate winters despite restricted visiting practices. Future studies could address how best to minimize the risks to this population during global pandemics.

In the present study, 15 to 16 VRTIs occurred, on average, per year, mostly in preterm infants. In 2013, there were 6236 infants born alive between 23 and 30 weeks' gestation in England and Wales.[37] Extrapolating 3.8% of these infants developing a symptomatic VRTI would equate to 237 infants requiring an average of 35 extra days in the hospital or 8295 total days. This scenario equates to the annual bed capacity for a 23-cot NICU. Additional NICU costs for this group would be in the region of £6.5 million (range: £4.7 million–£13.8 million [$9.4 million ($6.8 million–$20 million)]) per year. Because a greater proportion of infants go home on oxygen, the ongoing postdischarge

health care costs are also likely to be significant.

Strategies aimed at reducing nosocomial VRTIs include isolation cohorts for infected patients, personal protective equipment use by staff, hand hygiene policies, and restriction of visitors during periods of high community VRTI prevalence.[17,38,39] Few of these methods have been studied in a systematic way in the NICU, and further high-quality studies are required. Furthermore, although many of these studies have focused on respiratory syncytial virus, our study highlights the importance of rhinovirus and the lack of seasonality, which should be considered with any prevention measures.

The main limitations of the present study include its retrospective nature, although the data were collected prospectively. In addition, only those infants the team believed were symptomatic were screened for VRTI, and thus the overall incidence may have been greater if asymptomatic infants were also screened. Because symptom data were not collected, the clinical diagnosis used a pragmatic approach rather than a clearly defined definition. This study is based on infants in only 2 tertiary NICUs, and the generalizability to other centers therefore must be established. However, the Nottingham NICUs during the period of study had a relatively low rate of BPD in ventilated infants 24 to 32 weeks' gestation according to the Trent Neonatal Survey,[40] with rates significantly lower than similar units during the 2010–2012 period, perhaps suggesting our study may underestimate the impact of VRTI

in other centers. More detailed lung function data in infancy and childhood would also provide valuable long-term information on the effects of VRTIs during early lung development.

CONCLUSIONS

This large, well-matched, case–control study reported the significant respiratory morbidity and resource implications associated with nosocomial VRTIs in the NICU. Rhinovirus was the dominant pathogen, and more than one-third of the infants required home oxygen. One could hypothesize that nosocomially acquired VRTIs not only contribute to BPD in symptomatic infants but also play a role in those infants with unrecognized infection. With little change in the incidence of BPD, despite advances in respiratory management, and increasing evidence that many infants have unrecognized VRTI, this hypothesis is plausible. Large, prospective studies could incorporate surveillance programs to test our theory. Strategies such as restricting visiting could reduce the burden of nosocomially acquired VRTIs,[17] especially when the viral community load is high during pandemics.

ABBREVIATIONS

BPD: bronchopulmonary dysplasia
CI: confidence interval
IQR: interquartile range
OR: odds ratio
PCR: polymerase chain reaction
VRTI: viral respiratory tract infection

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Pediatrics 2016;138;

DOI: 10.1542/peds.2016-1675 originally published online October 4, 2016;

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