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Respiratory syncytial virus outbreak defined by rapid screening in a neonatal intensive care unit

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SUMMARY

Palivizumab is currently licensed for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in infants and children with chronic lung disease, with a history of preterm birth, or with haemodynamically significant congenital heart disease, but its routine use during outbreaks in neonatal intensive care units (NICUs) is not currently recommended. Here we report an outbreak in a NICU detected during a screening trial for RSV infection using a rapid antigen test (Respi-Strip®). Eleven preterm infants in our NICU tested positive for RSV during January 2009. Subsequent testing of the remaining infants in the NICU revealed two additional asymptomatic cases. In addition to precautions against cross-infection, palivizumab prophylaxis was administered to the remaining 37 premature infants. Two days after treatment, RSV was detected in two additional infants who had become symptomatic. To our knowledge this is the largest RSV outbreak in a NICU to be identified at an early stage by rapid testing and effectively controlled by infection control measures and palivizumab prophylaxis.

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Introduction

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia in infants. RSV infection is more severe in premature infants and in those with pre-existing cardiac or pulmonary diseases such as chronic lung disease (CLD).^{1,2} Because of the limited antibody response and reduced concentration of passively acquired maternal antibodies in neonates, preterm neonates are highly susceptible to RSV.³ Given the high rates of mortality and morbidity in preterm infants, particularly among those with CLD, prophylactic treatment against RSV is recommended in certain situations following exposure.⁴

Palivizumab is a humanised monoclonal antibody directed against the F glycoprotein of RSV. Palivizumab is currently licensed for the prevention of RSV lower respiratory tract disease in infants and children with CLD, with a history of preterm birth or with haemodynamically significant congenital heart disease.⁴ It is given monthly by injection during the RSV season and is usually continued for five months in the Northern Hemisphere. However,

routine or outbreak use in neonatal intensive care units (NICUs) is not currently recommended.⁵

Here we report an outbreak of RSV which affected 15 hospitalised infants in our NICU, identified at an early stage by rapid testing and controlled by palivizumab prophylaxis and infection control measures.

Methods

Our NICU is a reference centre for central Turkey and serves about 4000 patients annually, including 500 extremely low birth weight neonates. The NICU spans two floors, one of which is exclusively for premature infants. This section has 50 incubators and open beds, although the total capacity of the unit is 120.

Our NICU provides family-centred care, and parents are permitted to visit and take part in the care of their babies, which renders infants susceptible to exposure to external pathogens such as RSV. The RSV season in Turkey is usually between October and April in northern and central regions and between November and April in southern regions of the country. In July 2008 we initiated a screening study to search for cases of RSV infection otherwise overlooked and to determine the real incidence of RSV infection.

Every two weeks infants hospitalised for more than seven days who had respiratory symptoms were screened using Respi-Strip® (Coris BioConcept, Gembloux, Belgium). The principle of this

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point-of-care immunochromatography test is that a nitrocellulose membrane is sensitised with a monoclonal antibody directed against RSV while a mobile anti-RSV monoclonal antibody is conjugated to colloidal gold particles. If the sample contains RSV, the conjugate–RSV complex will remain bound to the anti-RSV antibody adsorbed onto the nitrocellulose, revealed as a red line that develops on the strip.

Testing was performed in accordance with the manufacturer's instructions. A nasopharyngeal swab was obtained and placed in a tube containing saline solution and agitated. An aliquot was then mixed with extraction buffer and stirred thoroughly. The strips were then inserted into the tube and incubated for 15 min before reading. The presence of a positive control line with a positive test line was considered a positive result. All tests were performed by the primary investigator (E.A.D.) and testing was available out of working hours throughout the outbreak period. Each box of Respi-Strip was checked with a positive control included in the box before being used in patients.

No cases were found between July and December 2008. However, early in January 2009 screening detected RSV positivity in 11 preterm infants on the same day. Following this, all infants in the NICU were screened, revealing two more cases: these infants were initially asymptomatic (cases 6 and 10) but developed respiratory symptoms within 24–48 h. The 37 remaining premature infants in the NICU, all of whom were <34 weeks' gestational age at birth, were given palivizumab prophylaxis (administered i.m. at 15 mg/kg) within a few hours of detection of the index cases. The diagnosis of RSV was subsequently confirmed in all 13 cases by polymerase chain reaction (PCR). Surveillance testing for RSV was repeated using Respi-Strip every 48 h until all of the infected infants became negative. Infants who tested negative with Respi-Strip were tested again if they became symptomatic on follow-up. Two days after palivizumab administration, RSV was detected in one additional infant (case 4) who had become symptomatic. Another infant (case 7), whose clinical picture was suggestive of RSV infection but who tested negative by Respi-Strip, was subsequently found to be positive by PCR. Besides RSV, patients were tested by PCR for influenza A and B, parainfluenza 1, 2, 3 and 4, coronavirus 63/43, metapneumovirus and rhinovirus, and screened for bacterial sepsis by blood culture.

In addition to palivizumab prophylaxis, positive cases were nursed together in a separate section of the unit and contact precautions were instituted. Infection control measures were implemented including the use of gloves, gowns, and masks. All healthcare personnel who had respiratory symptoms were also screened, visitor numbers were limited, and the unit was closed to admissions until the outbreak subsided.

The charts of the infected infants were reviewed and the gestational age, date of birth, birth weight, sex and pre-RSV oxygen need were recorded along with clinical outcomes.

Results

The median age and birth weight of the patients was 30 weeks (range: 25–35) and 1300 g (range: 720–1980) respectively. All of the RSV-positive infants were below gestational week 35 and the median age at diagnosis was 22 (range: 6–51) days. Patient characteristics are given in Table 1.

Among 50 preterm infants, 15 were diagnosed with RSV and five died (33%). Ten of the 15 infected patients were treated with ribavirin 15 mg/kg for 3–5 days. All except one received a combination of supportive treatments including salbutamol, caffeine, budesonide, inhaled nitric oxide, systemic corticosteroids and clarithromycin. One infant, who had mild upper respiratory symptoms, received oxygen without any other medication and recovered

Table 1

Characteristics of infants with positive respiratory syncytial virus (RSV) screen

Case no.	Sex	Gestation (weeks)	Birthweight (g)	Age (days)	O ₂ support (pre-RSV infection)	Outcome
1	F	33	1850	6	Free O ₂	Survived
2	M	31	930	25	Free O ₂	Survived
3	M	30	1850	11	Head-box	Survived
4	F	26	990	41	No	Survived
5	M	30	1580	6	Nasal CPAP	Died
6 ^a	F	35	1280	9	No	Survived
7	M	25	720	37	Nasal CPAP	Died
8	F	29	1290	23	No	Survived
9	M	29	1310	51	Free O ₂	Died
10 ^a	F	32	1440	16	No	Survived
11	M	31	1980	14	No	Survived
12	M	31	1530	33	No	Survived
13	M	28	1090	25	No	Died
14	M	30	1170	22	Nasal CPAP	Died
15	M	30	1370	12	No	Survived

CPAP, continuous positive airway pressure.

^a Developed RSV infection after palivizumab administration.

within a few days. Those patients who developed acute respiratory distress syndrome (ARDS) ($N=5$) received surfactant as rescue treatment. The five patients who died had a median treatment duration of 8 (4–12) days after the diagnosis of RSV infection. The gestational age of these infants was ≤ 30 weeks and one had bacterial sepsis in addition to RSV infection. Tests for other viruses were negative. The similar clinical course of all the infants who died, i.e. rapid deterioration with increased oxygen demand, development of pneumonia and ARDS, suggested that the deaths were associated with superseding RSV infection.

The protection rate of palivizumab from overt clinical RSV infection was 94.6% (35/37 cases). Two cases (4 and 7) developed RSV infection after the implementation of preventive measures and administration of palivizumab. Among the 14 patients who tested positive for RSV by Respi-Strip, all tested positive with PCR, yielding a positive predictive value for Respi-Strip of 100%. Sensitivity and specificity of Respi-Strip could not be determined since not all of the infants who tested negative were subsequently tested by PCR.

Discussion

To our knowledge, the RSV outbreak that we experienced in our unit is the first such epidemic to be detected in a NICU by rapid antigen screening. Once an epidemic is identified, screening all infants in the NICU, isolating the symptomatic and infected infants, and imposing strict infection control measures are critically important. Our series indicates that palivizumab prophylaxis along with routine infection control measures may prevent the spread of an RSV epidemic in a large unit.

The incubation period of RSV is 2–8 days but viral shedding may last for up to four weeks. The virus can survive on hard surfaces for up to 7 h and remains detectable after 30 min on cloth, paper, and stethoscopes.⁶

The use of palivizumab for the control of nosocomial RSV outbreaks has been previously reported by Kurz et al., who successfully prevented an outbreak of RSV in a NICU following the detection of a case.⁷ Halasa et al. described an RSV outbreak involving nine infected infants.⁸ Standard infection control measures plus administration of palivizumab to the 49 remaining infants in the NICU were implemented, and no new cases were detected thereafter. Abadesso et al. analysed two RSV outbreaks: although standard infection control measures were effective in the first, five additional infants were infected during a single month in the second.⁹ Immunoprophylaxis with palivizumab was administered to all of the infants in the

NICU and the authors concluded that this helped to prevent an uncontrolled RSV outbreak in their NICU. Cox et al. reported an outbreak of RSV involving seven premature infants.¹⁰ Palivizumab was given to eight high-risk preterm infants and no additional cases occurred.

Fifteen cases of RSV were diagnosed in our NICU, all of which involved patients aged <35 weeks' gestation. Premature infants are highly susceptible to RSV disease because they have smaller airways, their immune systems are immature, and they have low levels of maternally acquired RSV-specific antibodies.² Diagnosis of RSV is largely based on clinical findings, but can also be based on virus isolation, detection of viral antigens or viral RNA, demonstration of a rise in serum antibodies or a combination of these approaches.¹ We used the Respi-Strip RSV rapid antigen test kit, which requires only two reagents (extraction buffer and the immunostrips) and two incubations. It is technically easy to perform, fast (the results were available within 25 min) and accurate (sensitivity of 92% and specificity of 98%).¹¹ The cost of Respi-Strip is much lower than that of PCR (€4.6 vs €136 per patient). Since early detection and implementation of infection control measures are important for outbreak control, rapid antigen testing represents an accurate, fast, and practical method for the diagnosis of RSV infection. Only one infant with negative Respi-Strip test had positive RSV PCR. The remaining infants with negative Respi-Strip test did not develop clinically suspected RSV infection although they were not tested with PCR. Therefore we believe that the sensitivity and specificity of Respi-Strip test are acceptable. However, it should be remembered that the test performance might be affected by the high incidence of the disease during an outbreak and may be lower when used for routine screening.

We were unable to identify the index case in our unit because we had a large number of RSV-infected patients in an outsized NICU. Therefore we decided to give palivizumab to the remaining unaffected high-risk infants in our NICU, even though this is not routinely recommended by current guidelines. We also implemented additional measures including isolation of the positive cases, contact precautions, limitation of visitors and closure to elective admissions. It is difficult to distinguish which, if any, of these interventions altered the course of the outbreak. However, given the high control rate in this study, and previous experience with palivizumab, we believe that palivizumab contributed to the favourable outcome. We detected RSV in two additional patients within 48 h of the administration of palivizumab. This may be explained by false-negativity of the Respi-Strip test during the screening period before palivizumab administration, or ineffectiveness of palivizumab in these patients.

Objective assessment of disease severity was not performed, but we believe that these two cases who developed RSV after palivizumab had milder disease. Eleven of 15 infants with RSV infection developed pneumonia, whereas four infants, including those two who had received prophylaxis, did not.

Apnoea, bradycardia, and cough were the major clinical findings, while atelectasis, hyperinflation, and infiltration were the common radiological findings observed in the RSV-infected infants in this study, consistent with previous data.^{12,13} RSV infection should be suspected in the presence of such symptoms, particularly in high-risk patients during the RSV season. The prognosis is

somewhat unfavourable and fatal infections may be seen.^{13,14} Seven of our patients required mechanical ventilation, and five with clinical and radiological findings of ARDS died. Severe RSV infections resulting in ARDS with a mortality rate of 40–70% have been reported in the literature.¹⁵ All seven infants who were intubated were born at <31 weeks of gestation, showing that prematurity also negatively affects the course of the disease.

In conclusion, neonatologists should consider RSV infection as a potential cause of fatal outbreaks in the NICU. Respi-Strip represents a feasible, inexpensive, easy-to-perform and fast option for the rapid diagnosis of infection in symptomatic premature babies, particularly during the RSV season. We believe that palivizumab administration is safe and may have a role in controlling RSV outbreaks in the NICU. Further studies are needed to determine the exact role of palivizumab in the optimal control of nosocomial RSV outbreaks.

Conflict of interest statement

None declared.

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None.

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