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Use of palivizumab to control an outbreak of syncytial respiratory virus in a neonatal intensive care unit

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Summary To evaluate the safety and effectiveness of a humanized respiratory syncytial virus (RSV) monoclonal antibody (palivizumab) to control an outbreak of RSV in a neonatal intensive care unit (NICU), we retrospectively analysed two RSV outbreaks. Between 11 November 1998 and 18 March 1999, two separate RSV outbreaks occurred in a large (26 beds) NICU. All procedures for preventing nosocomial spread of RSV (including the use of palivizumab in the second outbreak) were retrospectively analysed. The cumulative incidence (CI), secondary attack rate (SAR) and risk ratio of infection were determined before and after the use of palivizumab for all patients and for those with gestational age below and above 32 weeks in the NICU during the second outbreak. Standard infection control measures were effective in the first outbreak (three cases). In the second outbreak, after three index cases, five additional infants were newly RSV-infected within one month. Three infants had RSV pneumonia and required mechanical ventilation; one infant died. Standard infection control procedures were initiated from the beginning of this outbreak. Palivizumab was given to all infants in the NICU after the fifth case was identified. CI was 2.4% in the first 15 days and 10.5% in the second, and SAR was 2.9‰ in the first 15 days and 14.1‰ in the second, both dropping to zero after the administration of palivizumab. The risk ratio of infection was 4.65 times higher in infants under 32 weeks gestational age. After the use of palivizumab, there were no additional identified cases. In addition to careful infection control procedures, the use of palivizumab might have contributed to arresting the outbreak of RSV infection in the NICU, suggesting that it could be an additional resource in the control of severe nosocomial RSV outbreaks.

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Introduction

Respiratory syncytial virus (RSV) is the most common aetiologic agent identified in lower respiratory tract infections in infants. Risk factors for severe RSV infection include prematurity, chronic lung disease, immunodeficiency and congenital heart disease.[1,2] Premature infants are a particular risk group because of their small airways, immature immunological system, and low levels of maternally acquired RSV-specific antibodies.[3]

RSV outbreaks in neonatal units have been well described. Hospital staff are thought to be the main vector, transmitting the virus via contaminated hands. A number of studies have suggested that handwashing after patient contact, use of gowns and gloves, and cohort nursing are usually effective preventive strategies against nosocomial spread of RSV.[4,5]

Palivizumab (Synagis®—MedImmune Inc., Gaithersburg, MD, USA) is a humanized monoclonal antibody directed against the F glycoprotein of RSV, and was recently approved for the prophylaxis of RSV disease in high-risk infants.[6–8] If a RSV outbreak is documented in a high-risk unit, primary emphasis should be placed on proper infection control procedures. In uncontrolled outbreaks, however, the effectiveness of prophylaxis with palivizumab has not been evaluated.[6–11]

The aims of this study were to evaluate the procedures to control the infection and the safety and effectiveness of humanized RSV monoclonal antibodies (palivizumab) during an outbreak of RSV in a large neonatal intensive care unit (NICU).

Methods

The intensive care units of the Department of Paediatrics (Hospital Fernando Fonseca, Lisbon) are contiguous: the NICU contains 26 beds (six intensive and 20 special care units) and the paediatric intensive care unit (PICU) contains 11 beds. These rooms share some clinical staff. Altogether some 800 children are admitted per year. Between November 1998 and March 1999, two RSV outbreaks occurred in the NICU. All cases of RSV infection during this period and the procedures instituted to control the spread of the virus in both outbreaks were retrospectively analysed.

Infection was diagnosed by membrane-bound enzyme immunoassay for virus antigen from nasopharyngeal washings (Directigen™—RSV test, Becton Dickinson Microbiology Systems, USA). After the index cases (first cases identified), all infants were screened for RSV from nasopharyngeal washings. Those with upper respiratory symptoms were screened every two days until a negative result was reported.

In the setting of both RSV outbreaks, standard infection control procedures, including handwashing, use of gowns and gloves, and cohort nursing, were started immediately. In the setting of the second RSV outbreak, after failure of standard infection control procedures, palivizumab was also used. Palivizumab was administered to all the babies in the unit at a dose of 15 mg/kg intramuscular and repeated one month later.

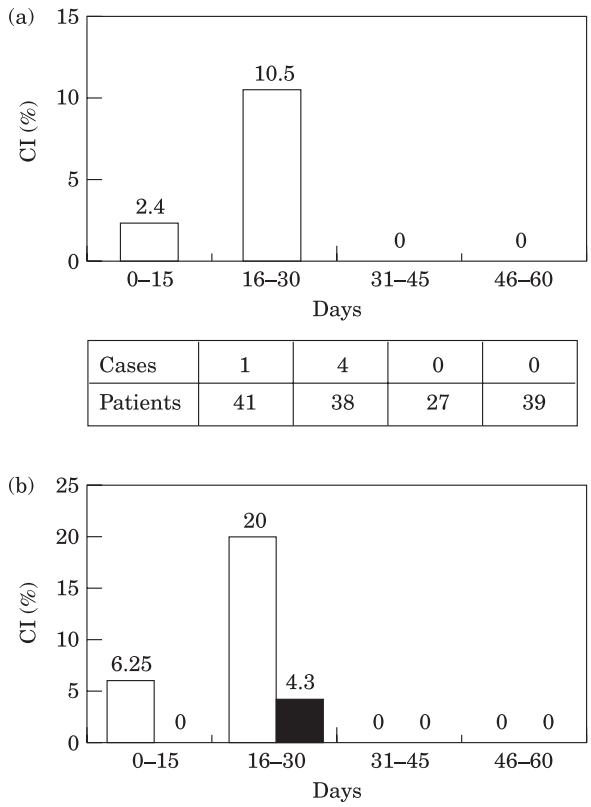
The cumulative incidence (CI; proportion of children at risk that became ill), secondary attack rate (SAR; relationship between the number of newly infected patients in each period and the total sum of days at risk) and risk ratio of infection were determined before and after the initiation of palivizumab for all the patients; these were also calculated separately for infants with gestational age below and above 32 weeks (WGA).

Results

In the first outbreak (November/December 1998), three cases of RSV infection (two in the NICU and one in the PICU) were identified simultaneously. Standard infection control procedures were rigorously employed and included handwashing, use of gowns and gloves, and cohort nursing; these measures were effective in halting the further spread of infection. After these, there were no more identified cases in the NICU.

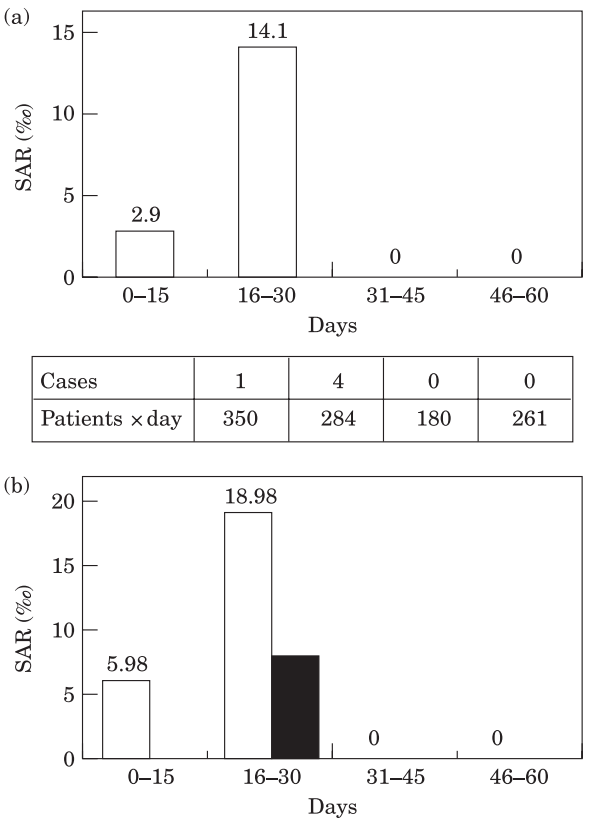
In February 1999, a second RSV outbreak occurred in the NICU. There were three index cases (two infants in the PICU admitted from the outside and one in the NICU identified at the same time as the other two). The index cases were epidemiologically responsible for starting the outbreak, which occurred only in the NICU. Standard infection control procedures were once again rigorously instituted; despite this, however, five additional infants were infected in one month in the NICU. Four of these five RSV cases were preterm under 32 WGA. Three developed pneumonia and required mechanical ventilation; one infant died. The overall fatality rate was 12.5%.

On 3 March 1999, it was decided to begin immunoprophylaxis with palivizumab; this was administered to all infants in the NICU (a total of 19). CI and SAR were determined for four periods of 15 days (the sum of average expected days of virus shedding and of incubation period), starting from



Cases	1	4	0	0
Patients	41	38	27	39

Figure 1 The CI (%) during the outbreak picked through the third and fourth weeks (a); children with gestational age less than 32 weeks had a much higher CI (RR = 4.65) (b). (□) < 32 weeks; (■) > 32 weeks.



Cases	1	4	0	0
Patients × day	350	284	180	261

Figure 2 The SAR during the outbreak picked through the third and fourth weeks (a); children with gestational age less than 32 weeks had a much higher SAR (RR = 2.37%) (b) (■) < 32 weeks; (□) > 32 weeks.

the index case's identification'. The number of patients at risk (in the NICU) were 41, 38, 27 and 39 in each 15-day period [Figure 1(a)]. CI was 2.4% in the first 15 days and 10.5% in the second, dropping to zero after the administration of palivizumab [Figure 1(a)]. RSV infection rates rose significantly in infants less than 32 WGA. These babies had a 4.65 times higher risk of becoming infected than infants above 32 WGA (CL_{95} 0.53 < relative risk < 40.2) [Figure 1(b)].

SAR was 2.9‰ in the first 15-day and 14.1‰ in the second 15-day [Figure 2(a)]. Rates of infection increased with increasing levels of exposure to RSV, as measured by the days that susceptible patients were exposed to patients shedding the virus.

After the day of identification of the index cases and over two additional months, a total of 126 infants were admitted to the NICU. After instituting palivizumab, there were no additional RSV-positive cases identified. Palivizumab was well tolerated and no adverse events were reported. The global cost of palivizumab administration was 7619 euros (401 euros per patient).

Discussion

RSV is highly contagious, spreading rapidly among infants, families and those on paediatric wards. The virus survives for up to 7 h on countertops, gloves, paper tissues and clothes, and for 30 min on skin.[12] The initiation of rigorous infection control procedures (handwashing, gowns and gloves, and cohort nursing) was effective in the first RSV nosocomial outbreak identified in the unit (November/December 1999). With the second nosocomial outbreak, however, these infection control policies were not effective in preventing further cases of RSV illness with significant morbidity. Palivizumab was therefore initiated for all infants in our NICU. There were no additional RSV cases and palivizumab was safe and well tolerated.

It is known that infected children will continue to shed the virus for up to two to three weeks.[12] This increases the risk of infection in a busy NICU. In this study, SAR was 2.9‰ in the first 15 days and 14.1‰ in the second. These observations were a clear sign that standard infection control measures were not

successful and that additional intervention was necessary. The cost for not initiating a new approach would be prolonged closure of the NICU to new admissions and potentially additional severe RSV cases and fatalities. Closing the NICU for two months would further overload the other four NICUs in Lisbon close to collapse.

It was observed in the NICU that babies below 32 WGA had a 4.65 times higher risk of becoming seriously ill than those above 32 WGA, which is consistent with what was expected.[1,3,8,13] Three babies had severe RSV illness (one death) and all were under 32 WGA.

Palivizumab is a humanized monoclonal antibody that specifically inhibits an epitope at the A antigenic site of the F protein of both RSV subtypes A and B. Antibody binding to the F protein has two effects. First, it prevents cellular infection by preventing the viral membrane from fusing with the respiratory epithelial cell membrane. Second, it prevents cell-to-cell spread of the virus, which in turn prevents the formation of syncytia and release of inflammatory mediators in the lung.[10] These properties provide the rationale for its clinical use.

The Food and Drug Administration approved palivizumab use for RSV disease prophylaxis among high-risk infants. The American Academy of Pediatrics and the European Commission for Proprietary Medicinal Products recently published recommendations for its use.[6,10] Palivizumab prophylaxis is considered for infants and children with chronic lung disease (CLD) younger than two years; infants born between 29 and 32 WGA, without CLD, up to six months of age; infants born less than 29 WGA, without CLD, up to 12 months of age, at the start of the RSV season; and infants born between 32 and 35 WGA, without CLD, who have additional risk factors. These recommendations also stress that use of palivizumab in nosocomial NICU outbreaks needs to be studied before specific recommendations in this area can be made.[6–11,14]

Cox *et al*.[15] reported a similar experience where palivizumab was also used to control an RSV outbreak in a special care baby unit. The need for, and efficacy of, prophylaxis in the setting of an RSV outbreak in an NICU needs further investigation.

In addition to meticulous infection control procedures, the use of palivizumab might have contributed to stop an uncontrolled RSV nosocomial outbreak in a large NICU. This experience suggests that palivizumab may be an additional resource for the containment of severe RSV outbreaks. Nevertheless, this is a costly intervention (400 euros per patient). It must be remembered that for high-risk and low-risk patients alike, this prophylaxis does not replace the simple and inexpensive preventive measure of handwashing. Further studies should be undertaken to assess the role of palivizumab in nosocomial RSV settings.

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