



## THE EXPERIENCE OF PALIVIZUMAB ADMINISTRATION IN ROMANIA

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**Abstract. Introduction.** Viral bronchiolitis is the most frequent pathology of the respiratory tract in infants and toddlers (under 2 years of age), the respiratory syncytial virus being one of the most commonly incriminated agents. The incidence of respiratory syncytial virus bronchiolitis reported by the Clinical Emergency Hospital for Children "Grigore Alexandrescu" during the past years is increasing. **Materials and methods.** retrospective study over 2 years (2007 – 2008). In 2007, 9 Romanian Maternities started out in the program for prevention of the respiratory infection with respiratory syncytial virus with Palivizumab provided through donations. **Results.** 140 newborns were passively immunized, none of them presented respiratory syncytial virus infection. **Conclusions.** There is need for the elaboration of an administering guide for Palivizumab and there is need for a national program which would include clear selection criteria, specific to the newborn population from our country, which could benefit from the prophylaxis of the respiratory syncytial virus.

**Keywords:** bronchopulmonary dysplasia, prematurity, congenital heart disease, bronchiolitis

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### Introduction

RSV is an RNA paramyxovirus, enveloped, made up of 11 proteins out of which 2 are of clinical significance: glycoprotein G (it confers both gene variability and infectivity through the tropism for respiratory epithelium) and glycoprotein F (responsible for the formation of *syncytia* through fusing the infected cells with the healthy cells, which is relatively constant, reason why it is the target of studies and research regarding the disease's prophylaxis) [1].

The transmission and infections with the respiratory *syncytial virus* are seasonal, from November until March/April [2].

Man is the only source of infection, the virus being found in high concentrations on the nasopharyngeal mucosa, its incubation duration is of 2 to 8 days, the transmission occurring both directly, through the respiratory pathway, by inhaling the particles emitted through cough or sneeze by an infected individual and indirectly through particles from surfaces, gloves, clothes, where it can survive for several hours (up to 6-7 hours) [3,4].

The respiratory *syncytial virus* (RSV) is an important cause for inferior respiratory tract infections in infants and toddlers, most frequently determining acute viral bronchiolitis, which can be complicated by viral pneumonia and, extremely rare, by meningitis, ataxia, myelitis, myocarditis, third-degree *atrioventricular block* [1]. Specialty literature men-

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tions that in the United States of America almost all children present at least one RSV infection before the age of 2 years of age, approximately 10% of the cases being infections of the inferior respiratory tract, 2-3 % requiring hospitalization [1,5]. Moreover, Hall et al, in a CDC (Centers for Disease Control and Prevention) supported study, enrolled children under 5 years of age for studying the impact of the RSV infection. The results were overwhelming, suggesting that the respiratory morbidity was higher than estimated – out of 5067 patients, 18% had presented inferior respiratory tract infection with RSV. Out of these, 20% required hospitalization, 18% presented frequently to the emergency room, 15% were seasonal episodes [6]. The median annual rate of hospitalizations was of 17/1000 for infants under 6 months of age and 3/1000 for children under 5 years of age, most of them being premature, without coexisting pathology, only with independent risk factors.

Pneumonia in the early neonatal period (the first 7 days of life) is extremely rare [3], but small-reach epidemics appear every now and then with potentially catastrophic effects, particularly in prematures with bronchopulmonary dysplasia [7].

Prematures, particularly those with extremely low body weight (1000g) and low body weight (<1500g) at birth, represent the category of newborns with the highest respiratory morbidity, 50% presenting recurrent wheezing and cough during the first year of life, 33% during preschool years. Those with chronic pulmonary disease or with bronchopulmonary dysplasia show a predisposition for more severe disease outlines, recent studies considering that the genes involved in the remodeling of the airways in this category of newborns are associated with risk of disease [8]. On the other hand, there is increasingly more data considering that the healthy prematures, without chronic pulmonary disease, which did not need mechanical ventilation or oxygen therapy, whose evolution within the neonate time span was without complications or dramatic events, present during the first months of life a lowered maximal expiratory flow and after a year, present obstructive pattern. The exact physiopathologic mechanism is not yet known [9].

The infection of the inferior respiratory tract determines necrosis of the bronchiolar epithelium, inflammation of the mucosa, microvascular proteic losses, edema, increase of the mucus production, peribronchiolar lymphatic and mononuclear infiltrate. The alveolar exudate contains gigantic

multinucleate cells circumscribed by syncytia. These pathologic alterations determine the obstruction of the small airways with prolonging of the expiration and characteristic wheezing [1,6].

Clinical manifestations include: functional respiratory syndrome, from tachypnea, wheezing, prolonged expiration, to apnea crises at young age. The predictive factors for the severe infection are oxygen saturation < 95% in atmospheric air, respiratory frequency > 70 breaths/minute, gestational age < 34 weeks, postnatal age ≤ 6 months.

In case of seasonal hospitalization, the measures for prophylaxis of the intrahospital infections need to focus on the training of medical personnel and of the patients' relatives (particularly mothers whose newborns are admitted to neonatal or premature intensive care units) regarding the general hygiene measures (covering of the mouth and nose when coughing or sneezing, proper washing of the hands), isolation of newborns which develop the diseases (alone in the hospital room), medical personnel only distributed to the respective hospital room [1,5].

The incidence is higher in children with postnatal age of under 6 months, with predilection in infants with preexistent pathology: chronic pulmonary diseases, congenital heart malformations, congenital or acquired immunodeficiencies, as well as high risk factors such as: prematurity (gestational age under 35 weeks), low weight at birth, birth during the season of RSV infection, male sex, precarious socioeconomic conditions, large number of siblings, passive exposure to smoking [3,4,7,10].

The development of an anti-RSV vaccine has encountered multiple issues over time. In 1960 Crowe administered a form of live attenuated vaccines in the form of 3-5 months-old infants and observed a lowered production of neutralizing antibodies. Later on, Food and Drug Administration (FDA) recommended that live attenuated vaccines not be administered to infants prior to a first natural contact with the virus [11].

In 1980, taking into account the high mortality and morbidity through RSV infection, passive immunization, immunological prophylaxis had become clinical priorities, and in 1996 FDA approved the specific intravenous immunoglobulin – polyclonal antibody [12].

20 years later, FDA approved Palivizumab – the first monoclonal antibody used for immunoprophylaxis in toddlers under 2 years of age and with high risk of RSV infection [13].

The American Academy of Pediatrics recom-

mends administration of Palivizumab in 5 doses of 15mg/kgbw/dose (one dose/ month, starting in November). None of these products have been approved for administration in case of infection.

The administration criteria are outlined in table I [14].

a high risk of RSV infection, with possibly fatal evolution.

During 2005 – 2006 the Clinical Hospital for Children “Grigore Alexandrescu” reported that 40% of bronchiolitis are determined by RSV, just as RSV is the etiologic agent in 40% of pneumonias and in 9% of the cases with laryngeal component.

Without chronic pulmonary disease (ex-premature)	With chronic pulmonary disease (regardless of gestational age - GA)
<ul style="list-style-type: none"> <li>• GA ≤ 28w, age ≤ 12 m from season’s beginning</li> <li>• GA = (28-32], age ≤ 6 m at season’s beginning</li> <li>• GA = (32-35], age ≤ 6 m season’s beginning and present ≥ risk factors:                             <ul style="list-style-type: none"> <li>• siblings of school-age</li> <li>• severe neuromuscular disease</li> <li>• exposure to passive smoking</li> <li>• congenital upper respiratory tract anomalies</li> <li>• placement</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• ≤ 12 months from first season’s beginning</li> <li>• ≤ 24 months with persistent signs of chronic pulmonary disease in the beginning of the second season</li> </ul>
<b>Infants and children with congenital heart disease</b> <b>At the season’s beginning, meeting the following criteria</b>	
<ul style="list-style-type: none"> <li>• ≤ 12 m postnatal age under treatment for congestive heart failure</li> <li>• ≤ 12 m postnatal age and uncorrected or partially corrected cyanogen heart disease, which stays cyanogen</li> <li>• ≤ 24 m postnatal age and cyanogen or non-cyanogen, hemodynamically significant heart disease</li> </ul>	
<b>Infants and children with pulmonary hypertension</b> <b>At season’s beginning, meeting the following criteria</b>	
<ul style="list-style-type: none"> <li>• ≤ 12 m postnatal age with moderate pulmonary hypertension</li> <li>• ≤ 24 m postnatal age with severe pulmonary hypertension</li> </ul>	

**Table I.** Recommendations American Association of Pediatrics for Palivizumab administration – 2003

Legend: GA = gestational age, w = week, m = month

### The experience of Palivizumab administration in Romania

In Romania, the development of neonatology over the past 15 years has made possible the survival of prematures with progressively lower gestational age (24-26 gestational weeks). This category of prematures records the highest pulmonary neonatal morbidity due to immaturity with incomplete development and alveolarization but also due to the employed therapy, respectively respiratory support and oxygen therapy.

On the other hand, the development of the neonatal cardiovascular surgery centers improved the survival rate of newborns with congenital heart diseases. These categories of newborns record

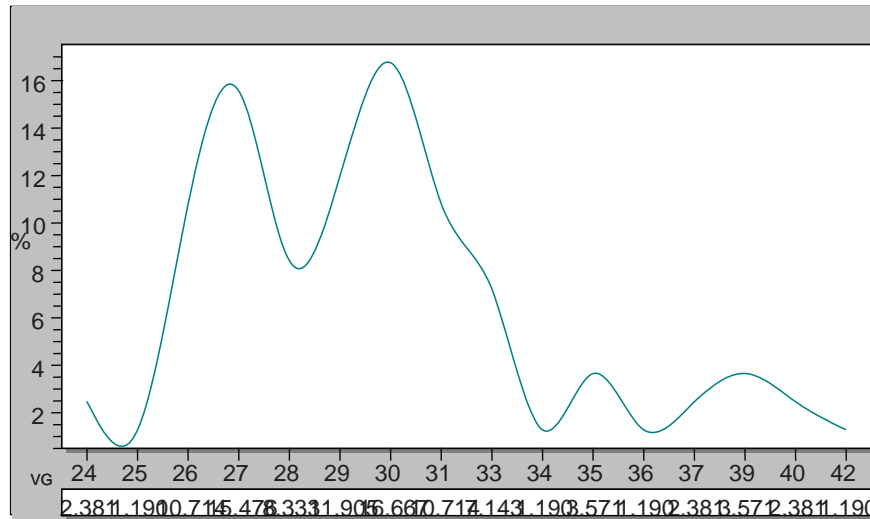
Moreover, the most affected age range is that of 2- 6 months old with mortality risk of up to 30%.

Two years ago (in 2007), through donations, 9 Romanian maternities started out in the program for RSV infection with Palivizumab.

### Materials and methods

Over two years (2007 – 2008), 140 newborns were immunized, the first dose being administered before maternity discharge. The patients were included in a monitoring program for 2 years. 84 cases were retrospectively analyzed, the difference consisting of cases which abandoned monitoring.

**Our objectives** have been: the identification of the gestation age group within the Romanian



Graphic 1. Distribution according to gestational age

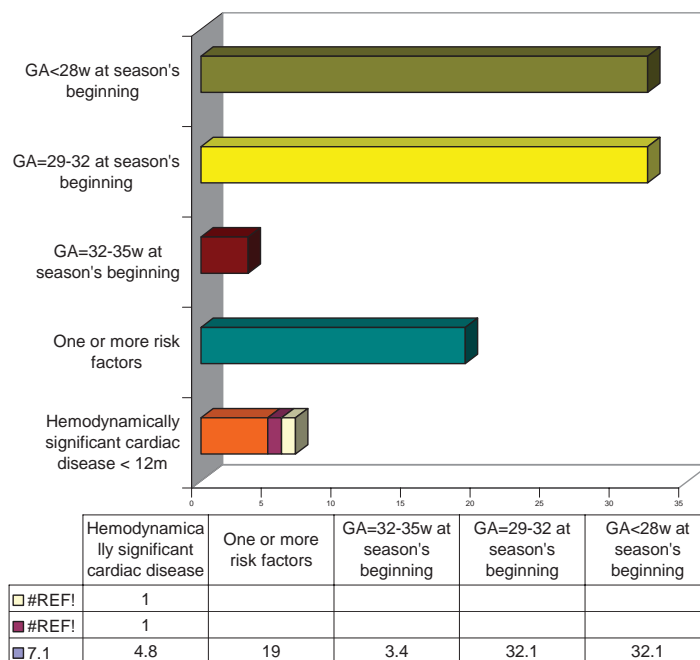
newborn population which should benefit from prophylaxis with Palivizumab and the elaboration of a national guide specific to our country.

**Results**

The distribution within the group was uniform, without significant differences regarding the repartition based on sex (51.8% female sex). The median gestational age (graphic 1) and birth weight were lower for the female sex compared to those of the

male sex (Median – 29 w/1200g; Pv=0.001 versus 30 w /1400g; Pv=0.05). 5 pairs of twins were included, out of which one had presented the disease prior to immunization, and another one had been immunized during the second season.

The main administration criteria for Palivizumab were: small gestational age (GA ≤ 32 w 64%), low body weight at birth (BW≤1500g 65%) and chronic pulmonary diseases (12%) (graphic 2). Other indications within the study group were: meconium aspiration syndrome (2 cases), severe perinatal asphyxia



Graphic 2. Main administration Guidelines Palivizumab

Risk factors	No	%
low body weight	73	86.9
low gestational age	74	88
RDS which required mechanical ventilation	26	31
precarious socioeconomic status	6	7.1
exposure to passive smoking	7	8.1
siblings of school-age	6	7.1
allergic predisposition	2	2.4

Table II. Risk factors

(4), recurrent wheezing (3), operated hydrocephaly (1), Down syndrome (1).

The associated risk factors were: idiopathic respiratory distress syndrome which required mechanical ventilation, low socioeconomic status, exposure to passive smoking, siblings of school age, allergic predisposition (table II). The patients were enrolled during their first 6 postnatal months. The immunization started in October. Doses of 15mg/kgbw/month were administered.

The total number of doses varied according to the compliance of the family practitioner and the availability of the drug (donations) – 60% 4 -5 doses, 40% 1-3 doses.

## Conclusions

Although 40% did not undergo the complete immunization pattern, none of the immunized patients developed the disease.

Upon medical charts' analysis, a logistic deficiency could be discerned, thus requiring a higher accuracy in filling out medical documents.

It is highly important to inform the relatives regarding the prevention manner and the benefits that immunoprophylaxis comports, as well as to employ training campaigns for family practitioners, campaigns which promote a good collaboration between the neonatologist, the family practitioner and the pediatrician. Therefore, infants of under 6 months of postnatal age could benefit from prophylaxis, infants which have been discharged from the maternity non-immunized (not only in the perinatal period) and which, later on, shall be monitored by family practitioners.

A more prejudicious list of recruiting criteria could lead to administering complete patterns (60% 4-5 doses).

The incidence of the precarious socioeconomic status, of the passive exposure to smoking and of the school-age siblings is similar in our group (~7%) which draws attention on the need for hygienic training of the families with newborns at risk.

The elaboration of a national guide which would contain the administration criteria specific to the Romanian population is necessary.

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