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Review

Prevention of bronchiolitis from the hospital to home: enviromental and pharmacological strategies

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From the womb to the adult
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Abstract

Bronchiolitis is one of the major cause of mortality and morbidity during infancy, with high hospitalization rate during epidemic season for high risk infants during the first year of life. There is no specific therapy with proven efficacy apart hydration and hypertonic saline. Mild forms can be treated in outpatient setting avoiding a useless hospitalization. Enviromental prevention is crucial in hospital setting, in outpatient ambulatory and at home: for this purpose hand hygiene, tobacco exposure, breastfeeding must be emphasized with families and caregivers. Pharmacological prophylaxis uses a humanized monoclonal antibody (palivizumab) shown effective in reducing hospitalization rate in preterm infants < 35 weeks gestational age, infants with bronchopulmonary dysplasia and infants with congenital heart disease. During the last 2 years different recommandations and guidelines confirmed the importance of prophylaxis with palivizumab with some differences between Groups and Societies based on different healthcare systems. In any case it is important a good contact between hospital and all caregivers of these patients to reduce the viral exposure and increase the defense capability of high risk patients.

Keywords

RSV, bronchiolitis, prematurity, palivizumab, late preterm, low respiratory tract infection.

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Introduction

Acute bronchiolitis is the most frequent cause of Lower Respiratory Tract Infection (LRTI) during infancy. The etiology is due to a viral infection with high hospitalization rate for infants younger than 1 year of age. Respiratory Syncytial Virus (RSV) is the most common infecting agent, but other viruses (Rhinovirus, Parainfluenza, Metapneumovirus) and bacteria (*Pneumococcus spp.*, *B. Pertussis*) can be present as infecting or co-infecting agents [1-3]. Furthermore RSV bronchiolitis is the first cause of hospitalization of infants, some of them requiring admission in intensive care units. Preterm infants, patients with Bronchopulmonary Dysplasia (BPD), Congenital Heart Disease (CHD), immunodeficiency, neuromuscular disorders, congenital pulmonary malformations, cystic fibrosis, trisomy 21 are at high risk for hospitalization for bronchiolitis. Patients with underlying medical disorders are also those with highest mortality rate [4]; considering viral surveillance data from 1990 to 1999, RSV infection was the leading viral cause of infant mortality, with almost nine times the mortality rate of influenza [5]. In developing countries the prevalence, the incidence and the mortality rate for bronchiolitis in infants is much higher estimating that nearly 33.8 million new cases of RSV-associated LRTI occur worldwide in children under 5 years of age and leading to approximately 3.4 million hospitalizations annually [6]. Pediatric primary health care assistance can adequately manage in the outpatient setting the milder form of bronchiolitis thus limiting hospital admissions and reduce direct and indirect costs of hospitalization [1]. Since during autumn and winter seasons the admission rate for bronchiolitis is very high the indications to hospitalization should be strict and assessed case-by-case. The Italian inter-society consensus of 2014 [1] defines very well the anamnestic, clinical and diagnostic pathways to identify the criteria for hospitalization. At Bambino Gesù Children's Hospital in 2013 there were 1,188 children at the emergency department with diagnosis of bronchiolitis, 489 (41%) of whom were hospitalized. During the same period 66 patients were admitted at the Department of Medical and Surgical Neonatology with a mean length of stay of 7.2 ± 4.1 days. Apart short term outcomes like hospitalization and mortality, late respiratory outcomes of bronchiolitis must be taken into account to understand in the wright way the clinical impact of bronchiolitis during the childhood and adult ages. It has been very well defined the relationship between early life bronchiolitis with an increased incidence of recurrent wheezing in preschool-aged infants and with asthma and decreased respiratory function in school-aged children [1]. In adult age a recent study conducted in North Europe [7] has demonstrated that 30-40% of adult subjects (18 and 30 years) who had been hospitalized because of bronchiolitis presents with asthma and uses anti-asthmatic drugs. It seems that this is mostly due to the intrinsic characteristics of RSV capable of modifying epithelial cells from low respiratory tract [8]. Pharmacological treatment for acute bronchiolitis has not been yet identified by any of the different extensive systematic reviews suggesting that there are no available therapies that clearly shorten the natural course of infection or provide clinical improvements [9].

Prevention

The aim of the infection prevention and control measures is to interrupt RSV transmission in the health care setting limiting the risk for more sensitive infant population. Considering the spread diffusion or bronchiolitis worldwide, the severity of the disease in more fragile patients and the long term impact on respiratory function the best intervention would an effective vaccination that unfortunately it is not yet identified. At the present state of art prevention must be based on both two different level: environmental strategies and seasonal administration of monoclonal antibodies (palivizumab) in selected populations. In this article I will summarize the indications for both environmental and pharmacological use based on the most recent reviews considering that beside some strong evidence there are some important differences, which can be explained with the different reality of each health service.

Enviromental prevention

VRS diffusion can be due to airborne transmission, via saliva droplets and through direct contact

with contaminated objects and surfaces (hands, toys, utensils, medical devices etc). Enviromental prophylaxis is absolutely indispensable to decrease diffusion of the virus particularly during epidemic season in the hospital setting, outpatient clinic and at home [1]. Three major points have to be highlighted because they play a fundamental role in envrimental prevention:

a. Hand hygiene: American Academy of Pediatrics (AAP) guidelines identify as key actions that all people should disinfect hands before and after direct contact with patients, after contact with inanimate objects in the direct vicinity of the patient, and after removing gloves and again all people should use alcohol-based rubs for hand decontamination when caring for children with bronchiolitis; when alcohol-based rubs are not available, individuals should wash their hands with soap and water. Both key actions are considered strong recommendations with evidence quality B [2].
b. Tobacco smoke: AAP indicates as strong recommendation that clinicians should counsel caregivers about exposing the infant or child to environmental tobacco smoke and smoking cessation when assessing a child for bronchiolitis; AAP indicates as moderate recommendation, but still a key action, that clinicians should inquire about the exposure of the infant or child to tobacco smoke when assessing infants or children for bronchiolitis [2].
c. Breastfeeding: Lanari et al. in a prospective cohort study enrolled 1,814 newborns ≥ 33 wks gestation from 30 Italian Neonatology Units concluded that breastfeeding even in association with formula milk reduces the risk of hospitalization for bronchiolitis during the first year of life [10]. Breastfeeding is also considered by AAP guidelines a key point in the prevention of bronchiolitis [2].

Pharmacological prevention

Pharmacological prevention is based on the use of Vitamin D and the administration of a humanized monoclonal antibody (palivizumab; Synagis®, Medimmune, Inc., Gaithersburg, MD) that binds the F protein on the surface of RSV avoiding the fusion of the virus with the membrane of the target cell.

a. Vitamin D: Belderbos et al. showed that decreased levels of vitamin D in the cord blood were associated with higher risk of developing RSV infection during the first year of life [11]. Vitamin D supplementation allows to decrease risks for viral respiratory tract infections [1, 12].
b. Palivizumab: in 1998 the RSV-Impact trial [13] used palivizumab at 15 mg/kg with intramuscular administration once a month during the epidemic season for 5 doses, showing a significant reduction in hospitalization for RSV bronchiolitis in 1,502 preterm newborns with gestational age ≤ 35 weeks, postnatal age ≤ 6 months at the beginning of the epidemic season, or preterm newborns with BPD with a postnatal age ≤ 2 years. AAP [14] in the same year published the first guidelines concerning the use of palivizumab in preterm and BPD infants. In 2003 Feltes et al. [15] in a prospectic multicenter study enrolling 1,287 infants younger than 24 months with hemodinamically significant CHD showed a reduction of 4.4% of hospitalization rate for RSV bronchiolitis. In the following years different guidelines and recommendations have been published also in Italy. Other population of high risk infants have been considered for possible eligibility in prophylaxis with palivizumab during the first 1-2 years of age; for these special populations (cystic fibrosis, Down syndrome, congenital diaphragmatic hernia, neuromuscular disease, immunodeficiency, inborn metabolic defects, esophageal atresia, lung and other transplantation) [1, 2] insufficient data are available to recommend routine prophylaxis, nevertheless all these infants and children must be considered as subjects at higher risk of hospitalization for bronchiolitis and in each situation the use of palivizumab can be applicable. In 2014 AAP updated guidelines [2] and Italian inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants [1] were published. These two important documents, like other different guidelines from different countries differ in some important aspects, mostly concerning the gestational ages between 30-35 weeks. Both documents agree regarding the use of palivizumab prophylaxis in the lowest gestational ages < 29 weeks for infants younger than 1 year at the beginning of the epidemic season, and in CHD infants younger than 2 years of age; for BPD infants palivizumab use is indicated during the first year of life and during the second year if the patient needed in the last 6 months oxygen or steroid or diuretic or bronchodilator therapies. In 2015 the Italian Society of Neonatology is publishing (in press) the new recommendations for the use of palivizumab

in which for each population the level of evidence and the strength of recommendation are indicated. In particular, for infants with gestational age between 29-35 weeks, prophylaxis with palivizumab can be considered in presence of risk factors for bronchiolitis hospitalization. The identification of such risk factors become very important in deciding the use of palivizumab; Lanari et al. in 2015 identified for 33-34 wks gestational age infants the following risk factors associated with higher rate of hospitalization for bronchiolitis: male gender, prenatal exposure to maternal smoking, neonatal surfactant therapy, having siblings < 10 years, living in crowded conditions and being exposed to epidemic season during the first three months of life [16].

Conclusion

The impact of bronchiolitis in healthcare in terms of mortality, morbidity, short and long term outcomes, costs, social involvement is very high for newborn infants and young children. Because of a lack of an effective therapy the importance of prevention and prophylaxis is clinically very high. For risk population of infants the organization of a good plan at the time of discharge from the hospital and the following outpatient ambulatory controls can play a key role in educating family and caregivers and limiting hospitalization. Prevention must start with environmental and educational strategies, but in high risk population pharmacological prophylaxis with palivizumab must be used.

Declaration of interest

The Author had in 2015 a collaboration with fee with ABBVIE.

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