Epidemiology of Bronchiolitis: Multicentric Study Policlinico-Garibaldi-Bronte-Caltagirone-Siracusa

Betta P[*1], **Giacchi V**[5], **Caracciolo MC**[1], **Mattia C**[1], **Giallongo AA**[1], **Tina G**[2], **Motta A**[2], **Palermo T**[2], **Pennisi D**[3], **Giugno R**[4], **Tirantello M**[5], **Scuderi MG**[1], **Leonardi S**[1] **and Sciacca P**[1]

[1]Neonatal Intensive Care Unit, University of Catania, Catania, Italy
[2]Hospital Garibaldi-Nesima (CT), Catania, Italy
[3]Bronte Hospital (CT), Catania, Italy
[4]Hospital of Caltagirone (CT), Catania, Italy
[5]Syracuse Hospital (SR), Catania, Italy

[*]**Corresponding author:** Betta P, Neonatal Intensive Care Unit, University of Catania, via Santa Sofia 78, Catania, Italy, 95123, Fax: +0390953781123, Tel: +0390953781125, E-mail: mlbetta@yahoo.it

Abstract

Bronchiolitis is the most common infection of the lower airways of the 1st year. Infants with severe respiratory distress (2-3%) require hospital care. The aim of the study is to evaluate the frequency of Respiratory Virus (VRS) infection, the usefulness of the diagnostic score, the ventilatory support and the protective effect of vaccinations. 173 patients <2years admitted to 5 hospitals divided into two groups on the basis of gestational age (EG) and weight (P) were enrolled: the first (1G) of 106 (EG 38.9≤1 w, P 3253≤385,7 g) and the second (2G) of 67 (EG 35.6≤2.44 w, P 2549.8≤467.7 g). A severity score (SG) was used based on the presence of risk factors, of SaO2 <92%, respiratory distress. Age of onset, respiratory support, vaccinations, and prophylaxis with Palivizumab was evaluated.

The average age of onset is in 1G 108.5≤99 days and 2G 157.29≤134 days, the SG is 1G 1.5≤0.54 and 2G 2.19≤0.53 (p<0.05). In 1G treated with non-invasive ventilation are 15%, in 2G 40%. 50% in 1G and 37% in 2G have benefited from the therapy. The etiology was sought in 103/173 (60%) and in 43% VRS was identified (41% in 1G versus 96% in 2G). 38.5% of 1G and 47.7% of 2G were vaccinated, 8.9% of 2G received the first dose of Palivizumab.The study shows the role of VRS in the etiology of bronchiolitis in preterm infants with a high SG and need for ventilation: can prophylaxis with Palivizumab reduce the hospitalization and improve respiratory outcome of the newborn?

Keywords: Bronchiolitis; RSV; Epidemiology; Palivizumab

Introduction

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract illness in infants and young children, causing annual epidemics. RSV is estimated to cause up to 75% of all infant bronchiolitis and 40% of all pediatric pneumonias [1]. The American Academy of Pediatrics Committee on Infectious Diseases (COID) in mid-2014 recommended against the use of RSV IP among preterm infants born at 29 to 35wGA except for those with another qualifying medical condition, such as chronic lung disease of prematurity (CLDP) or hemodynamically significant congenital heart disease (HS-CHD) [2]. Current Italian Guidelines recommend with a Level of Evidence II and Strength of recommendation A that: for infants of 29–35 weeks gestational age and age ≤6 months at the beginning of the epidemic season, prophylaxis with palivizumab might be taken into consideration in presence of risk conditions predisposing to severe infections and/or need for hospitalization [3,4].

The aim of our study is to assess the incidence of RSV infection in correlation with the mechanical ventilatory support and the utility of Bronchiolitis Respiratory Score. Also we point out the protect role of immunoprophylaxis to prevent the illness and to avoid hospitalization.

Material and Methods

We performed a prospective study on 173 infants <2 years old, hospitalized at the NICU Department and Pediatric Ward of 5 hospitals. The 173 infants were divided into two groups in according to gestational age (GA) and weight (W): Group 1 (106 patients) with GA 38.9 ± 1 week and weight 3.253 ± 385.7 gr and Group 2 (67 patients) with GA 34.9 ± 2.3 week and weight 2.218 ± 619.4 gr.

At the admission at least one parent or legal guardian of each patient gave their written informed consent to collecting and processing of personal data. The study protocol was performed according to Declaration of Helsinki.

We used a gravity score (GS), assessed the presence of perinatal risk factors (smoke, atopy, prematurity, chronic diseases), SaO_2 <92%, respiratory distress (expiratory grunting, chest wall retractions, fast breathing, more than 70 per minute) and assigned to any parameter a score from 1 to 3. We considered predictors of severity in bronchiolitis age (younger age predicts increased risk) dehydration, increased work of breathing (retractions), tachycardia (heart rate > 97% for age), whereas it indicated a mild disease an adequate oral intake, age ≥ two months, history of eczema, initial oxygen saturation of at least 94%, lower respiratory rate, no history of intubation, no or mild retractions [5].

We valued age at illness, ventilator support, etiology, seasonality, vaccinations, and immune prophylaxis with Palivizumab. At admission all babies were subjected to a nasopharyngeal cotton swabs. We tested respiratory samples by PCR-real time (Filmarray of Gamma Argene) to investigate virus (RSV, Influenza virus, parainfluenza virus, Adenovirus, and Rhinovirus) and bacteria.

Statistical Analysis

For nominal characteristics, the number of patients and percentages are given. Descriptive statistics were calculated for all demographic and clinical variables. Quantitative measures were compared using the t-test. Statistical significance was set at levels of $p<0.05$, $p<0.01$, and $p<0.001$.
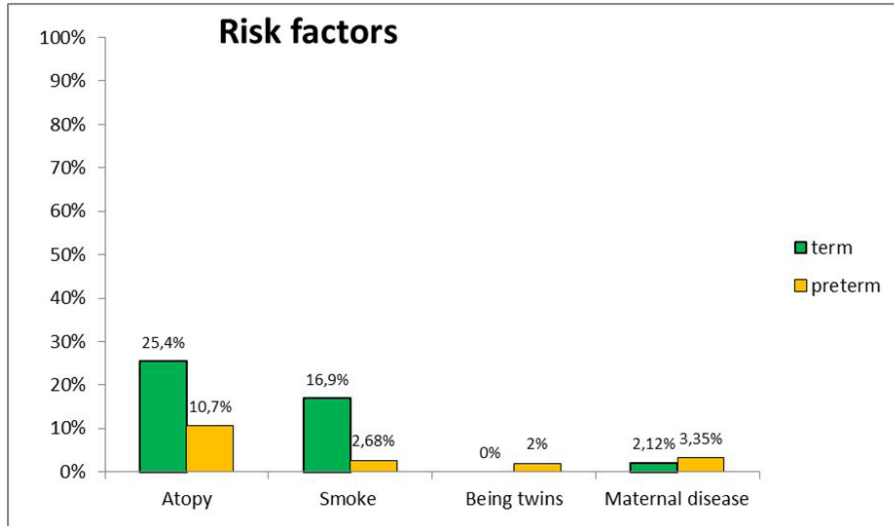
Results

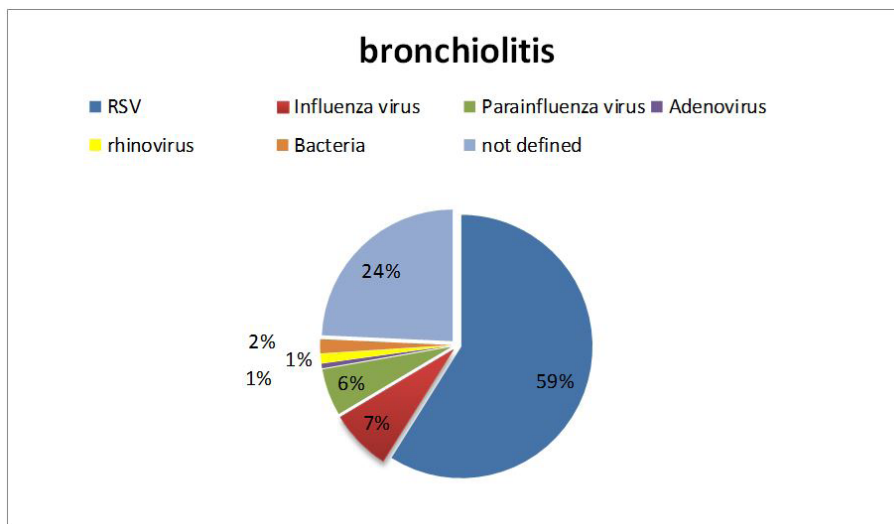| Results			
Newborns -173	Group 1 (106) term	Group 2 (67) preterm	p
GA(W)	38,9 +- 1	34,9 +-2, 3	< 0.01
BW (Kg)	3253+- 385, 7	2218+-619, 4	< 0.01
Perinatal factors (atopy, smoke, twins, maternal features)	40/106 37, 7%	28/67 41,7%	ns
Age at illness (<6 months)	80/106 75, 4%	43/67 64,1%	<0.01
Gravity Score	1.5 ≤ 0.54	2.19 ≤ 0.53	<0.05
RSV	42/106 39, 6%	60/67 89, 5%	<0.01
NIV	16/106 15%	27/67 40%	<0.01
oxygenotherapy	53/106 50%	25/67 37%	ns
Vaccination	43/106 40, 5%	32/67 47, 7%	ns
Immunoprophylaxis	-	8, 9	<0.01

Table 1: Results

The results show that the mean age at illness was 108.5 ± 99 days in Group 1 and 157.29 ± 134 days in Group 2, the GS was 1.5 ± 0.54 in Group 1 and 2.19 ± 0.53 in Group 2 (p< 0.05) (Table 1). We used noninvasive ventilation in 15% (16/106) of Group 1 and 40% (27/67) of Group 2, oxygen therapy in 50% of Group 1 and 37% of Group 2. The infants in 38.5% of group 1 and 47.7% of Group 2 were been vaccinated and in 8.9% of cases in Group 2 were been administered Immunoprophylaxis with Palivizumab. We found a significant difference in weight at birth, incidence of RSV, age at illness, noninvasive ventilation and in previous use of immunoprophylaxis, whereas we noted no difference in risk factors (atopy, smoke, being twins, maternal disease, Graph 1), use of oxigenotherapy and vaccination (Graph 1).

We looked for etiological agents in 132/173 (76%) patients and in 59% of cases we discovered RSV (Graph 2 and 3). In particular, we found in term and preterm infants, respectively, RSV in 39.6% and 89.5%, Influenza virus in 11.3% and 1.5%, Parainfluenza virus in 7.5% and 3%, Adenovirus in 0% and 1.5%, Rhinovirus in 0.9% and 1.5%, bacteria in 0.9% and 3%, whereas we did not found any agent in 39.6% and 0%. Moreover in 8 infants we found another infection (Mycoplasma or Chlamydia) associated to RSV.

We observed that preterm infants sickened <6 months old in 43.2% of cases (n. 29) and >6 months old in 56.7% (n. 38), whereas term infants sickened <6 months old in 76.4% of cases (n. 81) and >6 months old in 23.5% (n. 25). Moreover we noticed that the most patients with gravity score ≥2 were preterm and become sick in the first six months of life, whereas the most term infants had a gravity score <2 (Graph 4). The most patients become sick in winter (118 cases), others in spring (36 cases) and autumn (19 cases) (Graph 5).
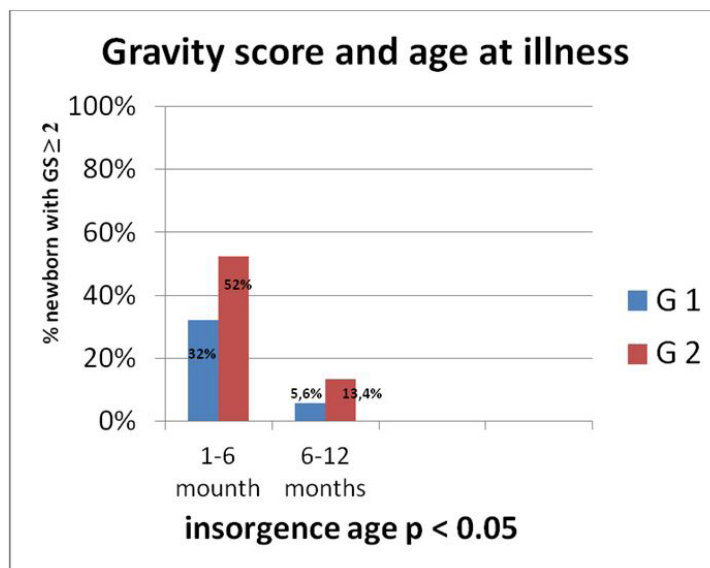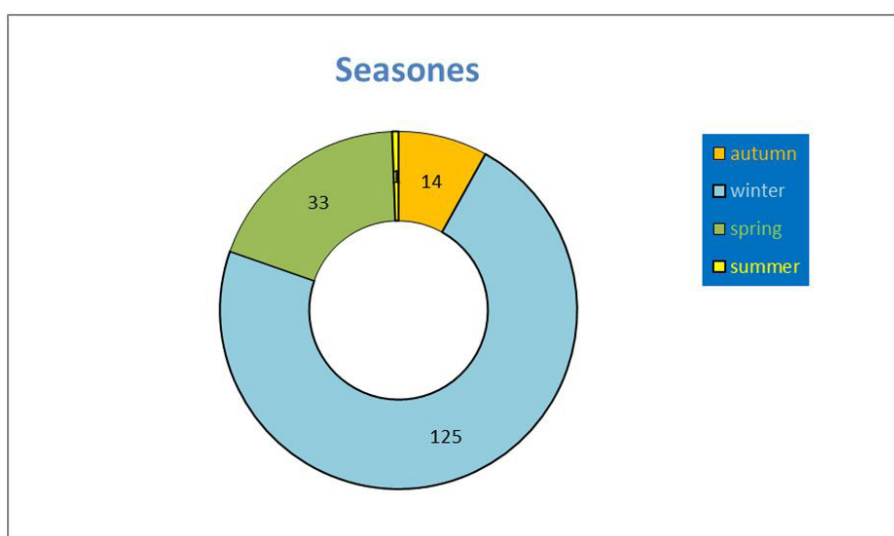
Graph 1: Risk factors

Graph 2: Etiology
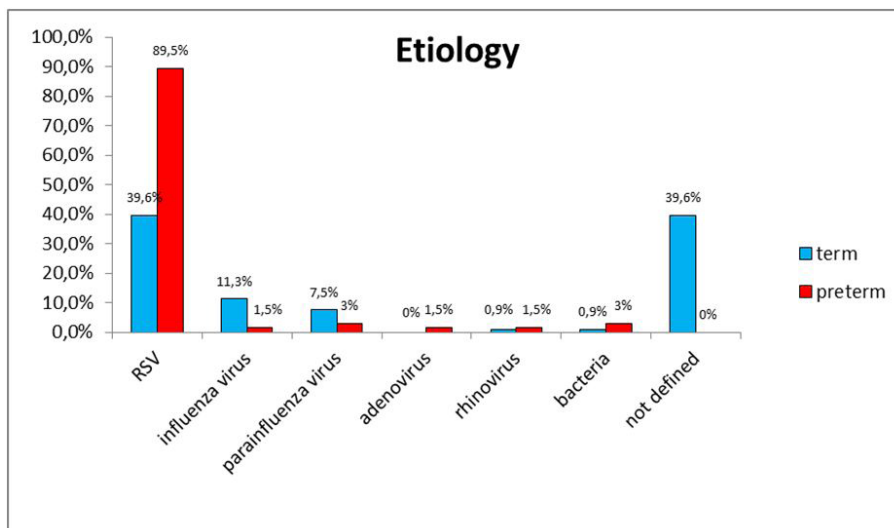
Graph 3: Etiology in term and preterm

Graph 4: Gravity score and age at illness

Graph 5: Seasonality

Discussion

Our results demonstrates the RSV play a role in etiology of bronchiolitis in case of preterm newborns with high values of GS and that need ventilation.

Respiratory syncytial virus (RSV) is the single most important cause of acute lower respiratory tract infection (ALRI) in infants, associated with significant morbidity and, sometimes, mortality in industrialized nations [6].

A systematic review estimated the global incidence among children <1 year of age at 19.19 per 1000 infants per year and a threefold higher rate for preterm infants with hospitalization costs of €2000–€4000 per patient [7,8]. In moderately preterm infants born at 32–35 weeks gestational age (WGA), it is reported that about 9% of infants require mechanical ventilation at a paediatric intensive care unit (PICU) [9].

Medical conditions in young children associated with an increased risk of severe RSV disease include chronic lung disease of prematurity (CLDP), hemodynamically significant congenital heart disease (HS-CHD), and preterm birth ≤ 35 weeks' gestational age (wGA) [10-12]. Our data show that RSV is the main agent that plays a role in bronchiolitis and its incidence is higher in preterm than term infants. Therefore a larger use of immunoprophylaxis could cut down the number of bronchiolitis events and/or decrease the gravity. In clinical trials, palivizumab reduced RSV hospitalization rates for premature infants [6]. RSV immunoprophylaxis (RSV IP) with palivizumab is the only safe and effective intervention approved for the prevention of severe RSV disease. RSV IP has been shown to reduce hospitalizations for severe RSV disease in preterm infants ≤ 35 wGA and children ≤ 24 months of age with CLDP or HSCHD compared with placebo in randomized, placebo-controlled clinical trials [13-15]. The current Italian Guidelines recommend palivizumab prophylaxis for infants of 29–35 weeks gestational age (wGA) and chronological age. ≤ 6

months at the beginning of the epidemic season, in presence of risk conditions predisposing the infant to severe infections and/ or need for hospitalization [4]. These include attendance of the child in a community setting and/or presence of one or more cohabitees younger than 5 years [16]. However, following the most recent modification by the American Academy of Pediatrics based on American studies on RSV epidemiology [2]. In September 2016, the Italian Drug Agency (AIFA) decided the total financial coverage of the palivizumab prescription to the healthy preterms by the National Health Service, should be limited to the <29 wGA group and age ≤12 months at the beginning of the RSV epidemic season (RES) [17].

We observed that preterm infants sickened when are older than term infants. This could be explained because the first usually are hospitalized in NICU for as long time and so would be protected and since they are administered immunoprophylaxis in first months after discharge, contrary to preterm infants.

Our study showed a higher GS and a bigger use of noninvasive ventilation in Group 2 than Group 1, therefore a largest use of immunoprophylaxis could decrease also the gravity of events and, subsequently, the use of noninvasive ventilation.

Although Blanken, *et al.* showed that targeted RSV prophylaxis results in an incremental cost-effectiveness ratio per quality-adjusted life year gained and therefore is not a cost-effective strategy to prevent severe RSV infection and wheeze in the first year of life, there are many studies that demonstrated the opposite [18].

Anderson, *et al.* demonstrated that the highest risk of severe RSV disease, as indicated by RSV-confirmed Hospitalization (RSVH), ICU admission, and the need for IMV, was associated with earlier GA and younger chronologic age. The cost of the index RSVH increased dramatically with increasing intensity of care, and in addition to hospital care, the majority of infants required outpatient care for the current RSV disease both before and within 1 month following the index RSVH discharge. Substantial morbidity and costs were identified among preterm infants 29 to 34wGA not receiving RSV IP based on the 2014 COID guidance but who would have previously been recommended for RSV IP according to the 2009 and 2012 COID guidances. Preventing severe RSV disease in this population would provide substantial health benefits, particularly during the first months of life when RSV disease incidence and severity are highest [1].

Capizzi, *et al.* demonstrated that the prescription limitation on RSV immunoprophylaxis in preterms was associated in the 2016–2017 RSV epidemic season with: a) a high proportion of admission for the <36 wGA infants, the great majority born at 33- <36 wGA and with chronological age of <6 months; b) a high proportion of preterms treated with HFNC ventilation, mostly in the at 33- <36 wGA subgroup [19].

Homara, *et al.* affirmed that palivizumab can significantly reduce the burden of severe disease in high-risk children.27 28 As their previous analyses have shown that Indigenous children and high-risk children are likely to be hospitalized more frequently due to RSV, 12 those children who are aged <6 months during the RSV season or who have older siblings at home may be considered for prophylactic administration of palivizumab [20].

The analysis of Sanchez-Luna, *et al.* showed that palivizumab could be considered a cost-effective strategy to prevent the RSV infections and its sequelae independently of the perspective used and that it is efficient for preventing from RSV infections in preterm infants 32day 1-35day 0 wGA in Spain, including specific high risk subgroups [21]. Also Zuccotti, *et al.* affirmed that extending palivizumab prophylaxis to babies' 29–32 wGA, aged less than 6 months, appears to be a cost-effective strategy [22].

Picone, *et al.* founded a rising trend in rate of bronchiolitis and bronchiolitis requiring hospitalization from 2014-2015 to 2016-2017 epidemic season. Among hospitalized bronchiolitis, they showed an increased morbidity as suggested by the need of intubation procedures in a high proportion of hospitalizations during second season. Additionally, bronchiolitis and hospitalization occurred in subjects with younger chronological age in 2016-2017 compared with 2014-2015 [23]. Immunoprophylaxis with Palivizumab could decrease the number of hospitalization in NICU and improve respiratory outcome.

The high efficacy of palivizumab prophylaxis compared to no prophylaxis would result in a substantial number of prevented hospitalizations and generated a high number of Quality-adjusted life years gained. Although associated with uncertainty, there is clear evidence that palivizumab prophylaxis represents a cost-effective treatment option also in late preterm children [24].

Conclusion

Our study highlights the benefits of RSV passive immunization in infants for severe RSV infection. Palivizumab is efficient for preventing from RSV infections in preterm infants also still 35day 0 wGA, including specific high risk subgroups. In fact in our study we noticed an increase of incidence on RSV infection in 2017-2018 and we suppose that this event could be imputed to actual Italian guidelines according to American guidelines that suggest immunoprophylaxis to ≤29 W, not reducing risk of illness in infant's ≤35 W. Moreover immunoprophylaxis, reducing events of bronchiolitis in preterm, reduce the incidence of post viral wheeze in childhood [1].

It would be interesting to search RSV in cordon blood in newborns with RDS because we supposed also prenatal transmission as reported in the first case in the world described by Manti, *et al.* Because of the limitations of the study to few centers, these findings cannot be generalized, but strongly point to a need to reevaluate the role of palivizumab prophylaxis in the 29–35 wGA subpopulations. Debate on RSV prophylaxis is maybe not still definitely closed [25].

However, our results on RSV hospitalization clearly highlight the vulnerability of young preterms, especially in this last RSV season and point to a need to reevaluate the role of palivizumab prophylaxis in the >29 wGA subpopulation when specific risk factors are present.

Limitations of the current study include the relatively small sample size which was retrieved from a limited number of neonatal care centers, so further evaluation on wider simple size are warranted.

This is a common problem in these kinds of reports since preterms represent only a very small proportion in the general infant population, as shown also in studies that have been cited by the American Academy of Pediatrics in the guidance for palivizumab prophylaxis.

Not all cases of RSV are confirmed by laboratory testing, so our study may underestimate the number of patients admitted for RSV.

References

1. Anderson EJ, Krilov LR, DeVincenzo JP, Checchia PA, Halasa N (2017) SENTINEL1: An Observational Study of Respiratory Syncytial Virus Hospitalizations among U.S. Infants Born at 29 to 35 Weeks' Gestational Age Not Receiving Immunoprophylaxis. Am J Perinatol 34: 51-61.

2. American Academy of Pediatrics Committee on Infectious Diseases and Bronchiolitis Guidelines Committee (2014) Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatr 134: 415-20.

3. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee (2014) Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatr 134: e620-38.

4. Bollani L, Baraldi E, Chirico G, Dotta A, Lanari M, et al. (2015) Revised recommendations concerning palivizumab prophylaxis for respiratory syncytial virus (RSV). Ital J Pediatr 41: 97.

5. Smith DK, Seales S, Budzik C (2017) Respiratory Syncytial Virus Bronchiolitis in Children. Am Fam Physician 95: 94-9.

6. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, et al. (2009) The burden of respiratory syncytial virus infection in young children. N Engl J Med 360: 588-98.

7. Stein RT, Bont LJ, Zar H, Polack FP, Park C, et al. (2017) Respiratory syncytial virus hospitalization and mortality: systematic review and meta-analysis. Pediatr Pulmonol 52: 556-69.

8. Rietveld E, De Jonge HCC, Polder JJ, Vergouwe Y, Veeze HJ, et al. (2004) Anticipated costs of hospitalization for respiratory syncytial virus infection in young children at risk. Pediatr Infect Dis J 23: 523-9.

9. Korsten K, Blanken MO, Nibbelke EE, Moons KGM, Bont L, et al. (2016) Prediction model of RSV-hospitalization in late preterm infants: an update and validation study. Early Hum Dev 95:35-40.

10. Boyce TG, Mellen BG, Mitchel EF Jr,Wright PF, Griffin MR (2000) Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. J Pediatr 137: 865-70.

11. Langley GF, Anderson LJ (2011) Epidemiology and prevention of respiratory syncytial virus infections among infants and young children. Pediatr Infect Dis J 30: 510-7.

12. Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM (2000) Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: hospitalization and economic implications of prophylaxis. Arch Pediatr Adolesc Med 154: 55-61.

13. Simões EA, DeVincenzo JP, Boeckh M, Bont L, Crowe JE Jr, et al. (2015) Challenges and opportunities in developing respiratory syncytial virus therapeutics. J Infect Dis 211: S1-S20.

14. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijeret A, et al. (2013) Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med 368: 1791-9.

15. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, et al. (2003) Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 143: 532-40.

16. Baraldi E, Lanari M, Manzoni P, Rossi GA, Vandini S, et al. (2014) Intersociety consensus document on treatment and prevention of bronchiolitis in newborns and infants. Ital J Pediatr 40: 65.

17. Gazzetta Ufficiale della Repubblica Italiana (2016) GU Serie Generale 221: 21-9.

18. Blanken MO, Frederix GW, Nibbelke EE, Koffijberg H, Sanders EAM, et al. (2018) Cost-effectiveness of rule-based immunoprophylaxis against respiratory syncytial virus infections in preterm infants. Eur J Pediatr 177: 133-44.

19. Capizzi A, Silvestri M, Orsi A, Cutrera R, Rossi GA, et al. (2017) The impact of the recent AAP changes in palivizumab authorization on RSV-induced bronchiolitis severity and incidence. Ital J Pediatr 43: 71.

20. Homaira N, Mallitt KA, Oei JL, Hilder L, Bajuk B, et al. (2016) Risk factors associated with RSV hospitalisation in the first 2 years of life, among different subgroups of children in NSW: a whole-of population-based cohort study. BMJ Open 6: e011398.

21. Sanchez-Luna M, Burgos-Pol R, Oyagüez I, Figueras-Aloy J, Sánchez-Solís M, et al. (2017) Cost-utility analysis of Palivizumab for Respiratory Syncytial Virus infection prophylaxis in preterm infants: update based on the clinical evidence in Spain. BMC Infect Dis 17: 687.

22. Zuccotti G, Fabiano V (2017) Indications to respiratory syncytial virus immunoprophylaxis in the 29-32 wGA group: is there still room for debating? Ital J Pediatr 43: 17.

23. Picone S, Fabiano A, Roma D, Paolillo P (2018) Comparing of two different epidemic seasons of bronchiolitis. Ital J Pediatr 44: 11.

24. Schmidt R, Majer I, García Román N, Rivas Basterra A, Grubb E, et al. (2017) Palivizumab in the prevention of severe respiratory syncytial virus infection in children with congenital heart disease; a novel cost-utility modeling study reflecting evidence-based clinical pathways in Spain. Health Econ Rev 7: 47.

25. Manti S, Cuppari C, Lanzafame A, Salpietro C, Betta P, et al. (2017) Detection of respiratory syncytial virus (RSV)at birth in a newborn with respiratory distress. Pediatr Pulmonol 52: E81-4.