The Burden of Respiratory Syncytial Virus Disease in Pre-Term Infants

Giovanni Corsello¹ and Paola Di Carlo¹*

¹Dipartimento di Scienze per la Promozione della Salute “G. D’Alessandro”, Università degli Studi di Palermo, Palermo, Italy.

Authors’ contributions

This work was carried out in collaboration of both authors. Author PDC have designed and wrote the first draft of the manuscript. Author GC have managed the literature searches. Both authors have collaborate to manuscript editing and manuscript review. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/22894

Editor(s):
(1) Nurhan Cucer, Erciyes University, Medical Biology Department, Turkey.

Reviewers:
(1) Denise Rossato Silva, Universidade Federal de Ciencias da Saude de Porto Alegre, Brazil.
(2) Adekunle Sanyaolu, Saint James School of Medicine, USA.
(3) Julius Oloke, Ladoke Akintola University of Technology, Ogbomoso, Nigeria.

Complete Peer review History: http://sciencedomain.org/review-history/12783

Received 3rd November 2015
Accepted 15th December 2015
Published 24th December 2015

ABSTRACT

This mini-review summarises the risk factors for acquiring Respiratory Syncitial Virus (RSV) infection, and describes the harmful effects of the infection in pre-term infants. Moreover, theoretical considerations are discussed for the prevention of RSV infection in high-risk infant categories, such as pre-term infants.

Background: Neonates positive for RSV are more prone to severe infection than neonates infected with other common respiratory viruses. Despite RSV infection being more common in late neonates than in early ones, pre-term infants ≤ 35 wk gestational age (GA) are at high risk for developing severe RSV disease. Efforts to prevent infection include case management, vaccination and the identification of risk factors. The morbidity and mortality risks of RSV disease are highest in pre-term newborns with other underlying disease, such as bronchopulmonary dysplasia (BPD) or hemodynamically significant congenital heart disease (hsCHD). Associations between RSV-positive neonates and climate factors are also discussed. Nosocomial-acquired respiratory syncytial virus infections in pre-term infants in Neonatal Intensive Care Units (NICUs) are reported. The development of an RSV vaccine has been challenging, and vaccine in pre-term
infants is currently unavailable. Palivizumab, a monoclonal antibody licensed for the prevention of RSV, lowers respiratory tract disease in pre-term infants. The home healthcare nurse can play an important role. By developing patient and caregiver trust, the nurse can implement an RSV prevention plan, leading to a decrease in the hospitalization of premature infants with RSV.

**Conclusions:** Commercially-insured late pre-term infants with RSV infection are at high risk of recurrent wheezing and infantile asthma for 1 year after the initial episode, and pose a significant economic burden on the healthcare system. Education is critical for the continuing development of clinical NICU nursing practice.

**Keywords:** Ovariectomy; estradiol; ibandronate; anti-oxidant enzymes; DEPPD free radical; rat’s liver.

1. INTRODUCTION

Respiratory syncytial virus (RSV) belongs to the Pneumovirus genus of the Paramixoviridae family. It was first isolated in 1956 from a monkey with respiratory tract illness. Later, the same agent was isolated from respiratory secretions obtained from children with laryngotracheitis and bronchopneumonia. The infectious agent was subsequently named respiratory syncytial virus due to its characteristic cytopathic effect in culture (large syncytial cell clusters). It is an enveloped, roughly spherical, pleomorphic virus. The capsid has helical symmetry around the genome, consisting of a single-stranded RNA of negative polarity [1-3].

Using monoclonal Antibodies, two major antigenic groups of RSV, type A and type B, have been identified. They differ in the characteristics of the surface glycoprotein G, head of the link between the virus and the host cell. Within these two groups of different genotypes, changes in genomic sequence can be found. While several studies [4-6] claim that there are differences in the clinical manifestations of the two main variants of the virus, others have shown that the group A and the GA2 genotype are associated with more severe symptoms than group B 4 [6-8].

Over the last year, there have been a number of studies determining predisposition to severe bronchiolitis and its consequences [5,6, 8-10]. They have indicated that various single nucleotide polymorphisms (SNPs) are significantly associated with respiratory syncytial virus (RSV) hospitalization, and a candidate gene approach demonstrated that innate immune gene SNPs had the strongest association with bronchiolitis [6]. The appearance in South Africa of new sub genotypes such as BA genotype with a 60-nucleotide duplication dominating the subtype B genotypes appears to have improved the fitness of this virus [7].

Moreover, several reports have suggested that genetic factors contribute to the severity of RSV infection and associated risk of both recurrent wheezing and childhood asthma [6,11-13].

Uteroglobin-related protein 1 (UGRP1) and other proteins that are thought to play a role in lung inflammation and allergic diseases have been investigated for their role in severe RSV infection [13].

2. RESPIRATORY SYNCYTIAL VIRUS IN PRE-TERM INFANTS

Pre-term infants are at increased risk of being re-hospitalized during the first few months of life with severe respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI), which usually manifests as apnea and hypoxemia [14-18]. Morbidity and mortality are significantly higher among pre-term infants than among their full-term counterparts [17-20].

Pre-term infants < 33 weeks gestational age (GA) require hospitalization more frequently, whereas recent studies have demonstrated discordant results for late pre-term infants (those born between 34 weeks and 0 days to 36 weeks and 6 days GA). The risk of hospitalization was 60% lower for breastfed babies, and four times higher during the RSV season [15,19-23].

Pre-term infants are particularly susceptible to the disease, due in part to their immature immune system, low birth weight and lung immaturity. The susceptibility of human pre-term neonates to severe RSV infection is partly due to the immaturity of the neonatal immune response. Factors associated with severe LRTI include immaturity of both the humoral and cell-mediated immune system and interrupted lung development prior to 36 weeks GA, which results in lower functional residual capacity, reduced compliance, diminished forced expiratory airflow and impaired gas exchange. Compared to full-term lambs, lung defense mechanisms of
pre-term lambs have a heightened pro-inflammatory response after infection, with significantly increased MCP-1, MIP-1alpha, IFN-gamma, TNF-alpha and PD-L1 mRNA [24].

Levels of maternally-derived RSV neutralizing antibody are inversely associated to the risk of lower respiratory tract infection and pneumonia in infants during the first 6 months of life [25]. Maternal IgG antibodies cross the placenta in the final weeks of gestation and protect a full-term newborn against RSV disease. However, in infants born prematurely, these antibodies do not achieve protective levels [25-27].

Nosocomial viral respiratory infections (NVRI) due to RSV in neonates and children hospitalized in paediatric and neonatal intensive care units (PNICU) were recently reported. Risk factors for severe RSV were duration of hospital stay, antibiotic treatment and long-term parenteral nutrition [28,29].

Finally, the development of RSV-LRI in infancy in pre-term infants was associated with an increased prevalence of serious early childhood wheezing (SECW) between the ages of 2 and 3 years. Patients with SECW incurred higher total health care costs than those who did not have SECW [30].

Studies on the economic impact of RSV- lower respiratory infection (LRI) have shown that early pre-term infants had the greatest mean number of inpatient, outpatient and emergency department visits after an RSV-LRI episode when compared with late pre-term infants. These findings suggest that pre-term infants could be exposed to a combination of more strongly interrelated risk factors for severe RSV than full-term infants.

Higher post-episode costs and rates of respiratory events, procedures and medications in RSV infants versus comparisons indicate that infection has a long-term economic impact, and the impact is greater among pre-term infants [31-33].

2.1 Epidemiology and Seasonality

In cold geographical areas, the RSV epidemic usually peaks between autumn and winter, while in countries with a temperate climate, outbreaks generally occur during the winter and last until spring. In tropical and subtropical regions, on the other hand, where climate variations are less pronounced, epidemics generally occur during the rainy season [34-37]. The seasonal distribution of RSV infections in Italian patients shows that infections peak in late spring in Southern Italy, and in winter and autumn in Northern Italy [37,38].

Knowledge regarding the seasonal distribution of infection could help to identify, from region to region, the most appropriate time to start prophylactic interventions. It is important for families and caregivers to learn how to protect their children at-risk.

2.2 Clinical Pattern

RSV should be considered as the most likely cause of a significant acute LRI in an infant or young child during the epidemic season. While the diagnosis of an RSV infection is relatively straightforward, the clinical diagnosis of RSV-associated illness is far less clear. Assessment criteria are based on clinical assessment of severity at examination and associated risk factors. Social factors may further influence the likelihood of admission to hospital. Guidelines are consistent in noting that there are no scoring systems or other tests that can reliably predict the need for supportive care or Neonatal Intensive Care Unit (NICU) admission. There are marked differences between the USA, UK and Scandinavia regarding the duration of hospitalization for RSV admissions [39]. In Italy, the incidence of hospitalization for bronchiolitis, and its associated risk factors, is similar to that found in other countries [40].

Although severe prematurity is the most important cause of NICU admission, other aspects such as low Apgar score at birth, low birth weight, congenital heart disease and other social aspects like low maternal educational level are considered to be relevant risk factors [26,37].

Criteria for the administration of oxygen vary. Current evidence suggests that the addition of heliox therapy may significantly reduce a clinical score evaluating respiratory distress in the first hour after starting treatment in infants with acute RSV bronchiolitis. Nevertheless, there was no reduction in the rate of intubation, in the need for mechanical ventilation and/or length of PICU stay [41].

In conclusion, there is no known effective therapy and no accepted antiviral treatment exists for preterm-infants.
Recently, new drugs have showed an interesting efficacy against RSV. Rapid RSV clearance and a greater reduction of viral load, with accompanying improvements in the severity of clinical disease, were observed in the groups treated with ALS-008176 than in the placebo group [42].

2.3 Diagnosis

Accurate diagnosis depends on detection of RSV in respiratory tract specimens, because differentiation of RSV infection from other viral respiratory infections based on clinical signs and symptoms alone is inaccurate. Antigen detection methods such as rapid membrane immunoassays or specimen immunofluorescent-antigen testing (DSFA) of respiratory epithelial cells, viral culture, and nucleic acid amplification tests are the most suitable methods [43].

Rapid antigen detection methods for the documentation of respiratory syncytial virus (RSV) infections are widely used in paediatric patients. Significantly greater viral quantities were present in paediatric nasal wash [NW] specimens for the rapid diagnosis of RSV disease from hospitalized paediatric patients with suspected RSV infection [44,45]. The tests’ specificity and sensitivity make them most reliable when the prevalence of influenza or RSV infection is high, which suggests that their routine use should be restricted to the peak periods of viral circulation [45].

Furthermore, respiratory samples, combined NW-throat swab [TS], endotracheal tube [ET] aspirate, or bronchoalveolar lavage [BAL] samples may be collected for simultaneous culture and rapid antigen detection with the Direct antigen test kit in immune-compromised and adult patients [43,46].

2.4 Prevention

A study in the mid-nineties evaluated the safety and efficacy of Palivizumab, a humanized murine monoclonal anti-F glycoprotein antibody preparation, in pre-term infants with and without chronic lung disease [47,48]. Palivizumab received marketing approval from the US Food and Drug Administration in July 1998, and from the European Commission for Proprietary Medicinal Products in August 1999. A subsequent study conducted between 1998-2002 in infants ≤ 24 months of age with documented hemodynamically significant congenital heart disease (CHD) showed a 45% reduction in RSV-associated hospitalization [49-51].

Numerous post-marketing/phase IV studies have been conducted to collect additional safety and efficacy data on Palivizumab. In the USA, the RSV Education and Compliance Helpline (REACH) program was implemented to improve parental knowledge of RSV and compliance with monthly prophylaxis [52].

Delivery of Palivizumab requires monthly injections for five months throughout the RSV season. This may prove difficult in low-income countries for several reasons. In tropical and sub-tropical regions, the seasonality of RSV is not as clear as in temperate regions, and the administration of Palivizumab would most likely depend on the availability of hospital services rather than on the actual needs of the population.

A more potent second-generation anti RSV monoclonal antibody, Motavizumab, is currently available. Compared to Palivizumab, this antibody has an 80-fold greater binding affinity for the RSV F protein, and is 23 times more potent at neutralizing RSV in vitro in a cotton rat model. A multinational, randomized, double-blind, phase III clinical trial in premature infants has shown that Motavizumab is not inferior to Palivizumab [53]. Despite recent, remarkable progress in the development of RSV vaccines and five-candidate vaccine types in clinical trials, including subunit vaccines and live attenuated vaccines, to date none of them have been licensed to prevent RSV infection in pre-term infants [54].

Therefore, hand washing is the best way to prevent RSV infection from spreading. It is also important to know that RSV is very easily spread. RSV is passed from person-to-person via sneezing, coughing, or by hands touching the nose or eyes, and then coming into contact with another person or object. The RSV virus can survive for up to 6 hours on hands, and up to 12 hours on surfaces. Spreading the virus within a family is very common.

Often day-care or school-aged children bring the virus into the home. Parents should try to limit their baby’s exposure to settings where they are in contact with people who might be sick, such as at malls, places of worship or holiday gatherings. Several studies conducted in both community and healthcare settings have also demonstrated that promoting hand-washing and good hygiene...
practices when coughing can help reduce the transmission of acute respiratory infection [29,55].

Education is critical for the continuing development of clinical NICU nursing practice. Education is essential in NICU nursing, because new efforts are being promoted to educate parents and, as a result, the role of nurses is expanding. In order to provide qualitative care and ensure patients' effective response to this care, nurses need special qualifications. Continuing education is essential for nurses working in the neonatal setting of pre-term nursing. There are many factors that contribute to this need. All nurses must cooperate at state and international level in order to promote new education strategies, and meet the growing needs of their patients.

In our previously published study [55], we described the characteristics of cases of RSV infection occurring in 2006–2007 in the city of Palermo, in the Mediterranean area of Southern Italy. In interviews with parents, we evaluated their knowledge and behavior concerning prevention and control of acute respiratory infections (ARIs). Figs. 1 and 2 report some responses given by parents regarding transmission routes, control and prevention of respiratory infections conducted during the hospitalization of their infants.

![How are Acute Respiratory Infections transmitted?](image)

**Fig. 1.** Answers to the question of 198 parents of Sicilian infants hospitalized for RSV infection

![How do you wash your hands?](image)

**Fig. 2.** Answers to the question of 198 parents of Sicilian infants hospitalized for RSV infection
Overall, parents appeared to be aware that ARIs can be transmitted through sneezing and/or coughing, but less conscious of the risk of acquiring infection through contact with contaminated objects or hands. Responses to the questions on prevention and control of transmission of ARIs showed that most parents were correctly identifying safe behaviors, with special reference to hand washing methods and tools.

3. DISCUSSION

In pre-term infants, RSV is a major health concern. It is the number-one cause of sickness and re-hospitalization for newborns, and prematurity is the greatest risk factor for severe RSV infection [14,15,56]. Pre-term infants show an immature brainstem respiratory control system and periodic irregular breathing, with potentially detrimental apneas that increase the burden of RSV disease during infectious episodes. Increased susceptibility and vulnerability to infection is reflected in the increased risk for central apneas in pre-term infants exposed to respiratory syncytial virus (RSV) compared to children born at full-term [17-19]. Moreover, recent research suggests that the apoptotic machinery is activated as a result of lung immune response triggered by RSV infection [24].

Progress in understanding and preventing RSV infection in premature babies is an important part of bringing a preemie home. NICU discharge is a joyous occasion—no longer do parents have to follow the routines of the hospital's special care nursery or NICU, or be separated from their baby. Most importantly, going home means that the baby has made it through all of the immediate health problems caused by being born early.

The prevention of RSV disease continues to be a challenge to the medical and scientific community. Currently, there are no available vaccines to protect against RSV. Prophylaxis with either RSV immune globulin intravenous (RSV-IGIV) or Palivizumab has been shown to be effective in reducing RSV-related hospitalizations. Motavizumab, a new enhanced-potency humanized RSV monoclonal antibody, is being evaluated in clinical trials [53].

Cost effectiveness of RSV prophylaxis tends to be more favorable in populations with specific risk factors, including premature infants < or =32 weeks’ gestational age, and infants or children aged < 2 years with chronic lung disease or congenital heart disease [57].

Hospitalization due to RSV infection in the first 2 years after birth has been associated with increased healthcare utilization and associated costs up to 5 years of age, in children born prematurely at less than 32 weeks of gestation who developed bronchopulmonary dysplasia [58].

Few studies have examined long-term benefits such as Quality Adjusted Life Years (QALYs) or life-years gained. The endpoints examined varied and generally did not account for the potential impact of RSV prophylaxis on RSV-related complications such as asthma [36,59,60].

We have found that a variety of factors, such as gender, chronological age at the time of hospitalization, GA, birth weight, how premature the infant is, exposure to tobacco smoke and breast-feeding may affect the prevalence of RSV-related LRI and, possibly, the risk of developing asthma-like symptoms during the school years [55,59,61].

It should be stressed that a major aspect in the prevention of RSV infection in high-risk infants is parent and caregiver education, in order to reduce exposure to and transmission of the virus. Hand washing in all settings, as well as limiting exposure to high-risk settings (e.g. day-care centers) and environmental toxins such as cigarette smoke, are important preventive measures, particularly during the RSV season. Compliance has a positive association with decreasing RSV hospitalization rates; however, it is difficult for pediatricians to achieve optimal compliance on their own. In a previous study, we evaluated parents' knowledge and behavior concerning prevention and control of acute respiratory infections (ARIs). Nationality, age and education level of parents, as well as the age of the patients, proved to be associated with some self-reported knowledge and behaviors. Only 12% of parents and child-care workers had received advice from pediatricians about good hygiene practices [29,37,55]. It seems essential to implement public health interventions promoting behavioral changes aimed at the primary prevention of ARIs at community level.

4. CONCLUSIONS

In conclusion, infants born 35 weeks or less GA are at a particularly high risk of severe RSV
disease, which may result in frequent Neonatal Intensive Care Unit (NICU) admissions or long hospital stays, with a significant increase in subsequent health care resource utilization and mortality. A collaborative effort involving the hospital and NICU, pediatrician, parents, home healthcare provider and insurer is necessary to achieve optimal compliance. Developing a proactive RSV management strategy can help improve health outcomes and reduce unnecessary hospital resource use.

**COMPETING INTERESTS**

Authors have declared that no competing interests exist.

**CONSENT**

It is not applicable.

**ETHICAL APPROVAL**

It is not applicable.

**REFERENCES**

1. Ruuskanen O, Ogra PL. Respiratory syncytial virus. Current Problems in Pediatrics. 1993;23(2):50-79.
2. Heilman CA. Respiratory syncytial and parainfluenza viruses. Journal Infectious Disease. 1990;161(3):402-406.
3. Filippel MB, Rearick T. Respiratory syncytial virus. The Nursing Clinics of North America. 1993;28(3):651-671.
4. Zheng H, Storch GA, Zang C, Peret TC, Park CS, Anderson LJ. Genetic variability in envelope-associated protein genes of closely related group a strains of respiratory syncytial virus. Virus Res. 1999;59(1):89-99.
5. Jones LP, Zheng HQ, Karron RA, Peret TC, Tsou C, Anderson LJ. Multiplex assay for detection of strain-specific antibodies against the two variable regions of the G protein of respiratory syncytial virus. Clin Diagn Lab Immunol. 2002;9(3):633-8.
6. Becker Y. Respiratory syncytial virus (RSV) evades the human adaptive immune system by skewing the Th1/Th2 cytokine balance toward increased levels of Th2 cytokines and IgE, markers of allergy-a review. Virus Genes. 2006;33(2):235-52.
7. van Niekerk S, Venter M. Replacement of previously circulating respiratory syncytial virus subtype B strains with the BA genotype in South Africa. Journal of Virology. 2011;85(17):8789-97.
8. Vicencio AG. Susceptibility to bronchiolitis in infants. Current Opinion in Pediatrics. 2010;22(3):302-306.
9. Dixon DL, Griggs KM, Forsyth KD, Bersten AD. Lower interleukin-8 levels in airway aspirates from breastfed infants with acute bronchiolitis. Pediatric Allergy and Immunology. 2010;21(4):691-696.
10. Papoff P, Moretti C, Cangganio G, Bonci E, Roggini M, Pierangeli A, Scagnolari C, Antonelli G, Midulla F. Incidence and predisposing factors for severe disease in previously healthy term infants experiencing their first episode of bronchiolitis. Acta Paediatrica. 2011;100(7):17-23.
11. Löfgren J, Marttila R, Renko M, Rämet M, Hallman M. Toll-like receptor 4 Asp299Gly polymorphism in respiratory syncytial virus epidemics. Pediatric Pulmonology. 2010;45(7):687-692.
12. Rämet M, Korppi M, Hallman M. Pattern recognition receptors and genetic risk for RSV infection: Value for clinical decision-making? Pediatric Pulmonology. 2011;46(2):101-110.
13. Hashimoto K, Katayose M, Sakuma H, et al. Uteroglobulin-related protein 1 and severity of respiratory syncytial virus infection in children admitted to hospital. Journal of Medical Virology. 2011;83(6):1086-1092.
14. Meert K, Heidemann S, Abella B, Sarnaik A. Does prematurity alter the course of respiratory syncytial virus infection? Critical Care Medicine. 1990;18(12):1357-9.
15. Coffman S. Late preterm infants and risk for RSV. The American Journal of Maternal Child Nursing. 2009;34(6):378-84.
16. Schiller O, Levy I, Pollak U, Kadmon G, Nahum E, Schonfeld T. Central apnoeas in infants with bronchiolitis admitted to the paediatric intensive care unit. Acta Paediatrica. 2011;100(2):216-219.
17. Carbonell-Estrany X, Quero J, Bustos G, Cotero A, et al. Rehospitalization because of respiratory syncytial virus infection in premature infants younger than 33 weeks of gestation: A prospective study. IRIS Study Group. Pediatric Infectious Disease Journal. 2000;19(7):592-597.
18. McCormick J, Tubman R. Readmission with respiratory syncytial virus (RSV) infection among graduates from a neonatal...
intensive care unit. Pediatric Pulmonology. 2002;34(4):262-266.
19. Pedersen O, Herskind AM, Kamper J, Nielsen JP, Kristensen K. Rehospitalization for respiratory syncytial virus infection in infants with extremely low gestational age or birthweight in Denmark. Acta Paediatrica. 2003;92(2):240-242.
20. Law BJ, Langley JM, Allen U, Paes B, Lee DS, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. Pediatric Infectious Disease Journal. 2004;18(9):806-814.
21. Resch B, Paes B. Are late preterm infants as susceptible to RSV infection as full term infants? Early Human Development. 2011;87(suppl.1):S47-9.
22. Lanari M, Adorni F, Silvestri M, Coscia A, Musico M. Italian study group on risk factors for RSV-related hospitalization. The multicenter Italian birth cohort study on incidence and determinants of lower respiratory tract infection hospitalization in infants at 33 weeks GA or more: Preliminary results. Early Human Development. 2011;87(suppl.1):S43-6.
23. Doering G, Gusenleitner W, Belohradsky BH, Burdach S, Resch B, Liese JG. The risk of respiratory syncytial virus-related hospitalizations in preterm infants of 28 to 35 weeks' gestational age. Pediatric Infectious Disease Journal. 2006;25(12):1188-1190.
24. Sow FB, Gallup JM, Krishnan S, Patera AC, Suzich J, Ackermann MR. Respiratory syncytial virus infection is associated with an altered innate immunity and a heightened pro-inflammatory response in the lungs of preterm lambs. Respiratory Research. 2011;12(1):106-142.
25. Lamprecht CL, Krause HE, Mufson MA. Role of maternal antibody in pneumonia and bronchiolitis due to respiratory syncytial virus. Journal of Infectious Disease. 1976;134(3):211-217.
26. Glezen WP, Paredes A, Allison JE, Taber LH, Frank AL. Risk of respiratory syncytial virus for infants from low-income families in relationship to age, sex ethnic group, and maternal antibody level. Journal of Pediatrics. 1981;90(5):708-715.
27. De Sierra TM, Kumar ML, Wasser TE, Murphy BR, Subbarao EK. Respiratory syncytial virus-specific immunoglobulins in preterm infants. Journal of Pediatrics. 1993;122(5):787-791.
28. Simon A, Müller A, Khurana K, Engelhart S, et al. DSM RSV paed study group. Nosocomial infection: A risk factor for a complicated course in children with respiratory syncytial virus infection--results from a prospective multicenter human respiratory syncytial virus infection german surveillance study. International Journal of Hygiene and Environmental Health. 2008;211(3):241-250.
29. McCartney KK, Gorelick MH, Manning ML. Nosocomial respiratory syncytial virus infections: The cost effectiveness and cost benefit of infection control. Pediatrics. 2000;106(3):520-526.
30. Romero JR, Stewart DL, Buysman EK, Fernandes AW, Jafri HS, Mahadevia PJ. Serious early childhood wheezing after respiratory syncytial virus lowers respiratory tract illness in preterm infants. Clinical Therapeutics. 2010;32(14):2422-2432.
31. Shi N, Palmer L, Chu BC, Katkin JP, Hall CB, Masaquel AS, Mahadevia PJ. Association of RSV lower respiratory tract infection and subsequent healthcare use and costs: a Medicaid claims analysis in early-preterm, late-preterm, and full-term infants. Journal of Medical Economics. 2011;14(3):335-340.
32. Palmer L, Hall CB, Katkin JP, Shi N, Masaquel AS, McLaurin KK, Mahadevia PJ. Healthcare costs within a year of respiratory syncytial virus among medicaid infants. Pediatric Pulmonology. 2010;45(8):772-781.
33. Greenough A, Cox S, Alexander J, Lenney W, et al. Health care utilization of infants with chronic lung disease, related to hospitalisation for RSV infection. Archive Disease Child. 2001;85(6):463-468.
34. Sung RY, Murray HG, Chan RC, Davies DP, French GL. Seasonal patterns in respiratory syncytial virus infection in Hong Kong: A preliminary report. The Journal of Infectious Disease. 1987;156(3):527-528.
35. Tantivanich S, Chityothin O, Tharavanij S. Infection rates of respiratory syncytial virus in pediatric patients attending PhraMongkukkla Hospital, Bangkok. The Southeast Asian Journal of Tropical Medicine and Public Health. 1984;15(1):63-67.
36. Corsello G, Di Carlo P, Salsa L, Gabriele B, Meli L, Bruno S, Titone L. Respiratory syncytial virus infection in a Sicilian pediatric population: Risk factors, epidemiology, and severity. Allergy Asthma Proceeding. 2008;29(2):205-210.

37. Di Carlo P, Romano A, Salsa L, et al. Epidemiological assessment of Respiratory Syncytial Virus infection in hospitalized infants, during the season 2005-2006 in Palermo, Italy. Italian Journal of Pediatrics. 2009;35(1):11-17.

38. Carbonell-Estrany X, Quero J - IRIS Study Group. Hospitalization rates for respiratory syncytial virus infection in premature infants born during two consecutive seasons. Pediatric Infectious Disease Journal. 2001;20(9):874-879.

39. Everard M. Diagnosis, admission, discharge. Paediatric Respiratory Review. 2009;10(suppl.1):18-20.

40. Pezzotti P, Mantovani J, Benincori N, Mucchino E, Di Lallo D. Incidence and risk factors of hospitalization for bronchiolitis in preterm children: A retrospective longitudinal study in Italy. BMC Pediatrics. 2009;10(9):56-66.

41. Liet JM, Ducruet T, Gupta V, Cambonie G. Heliox inhalation therapy for bronchiolitis in infants. Cochrane Database Systematic Review. 2010;14(4):1-27.

42. DeVincentz JP, McClure MW, Symons JA, Fathi H, Westland C, Chanda S, Lambkin-Williams R, Smith P, Zhang Q, Beigelman L, Blatt LM, Fry J. Activity of oral alsi-008176 in a respiratory syncytial virus challenge study. N Engl J Med. 2015;373(21):2048-58.

43. Henrickson KJ, Hall CB. Diagnostic assays for respiratory syncytial virus disease. Pediatric Infectious Disease Journal. 2007;26(suppl.11):S36-40.

44. Munjal I, Gialanella P, Goss C, McKitrick JC, et al. Evaluation of the 3M rapid detection test for respiratory syncytial virus (RSV) in children during the early stages of the 2009 RSV season. Journal of Clinical Microbiology. 2011;49(3):1151-1153.

45. Principi N, Esposito S. Antigen-based assays for the identification of influenza virus and respiratory syncytial virus: Why and how to use them in pediatric practice. Clinical Laboratory Medicine. 2009;29(4):649-660.

46. Falsey AR. Respiratory syncytial virus infection in adults. Seminary Respiratory Critical Care Medicine. 2007;28(2):171-181.

47. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. The PREVENT Study Group. Pediatrics. 1997;99(1):93-99.

48. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces 20 hospitalization from respiratory syncytial virus infection in high-risk infants. The IMPACT-RSV Study Group. Pediatrics. 1998;102(3):531-537.

49. Meissner HC, Welliver RC, Chartrand SA, et al. Immunoprophylaxis with palivizumab, a humanized respiratory syncytial virus monoclonal antibody, for prevention of respiratory syncytial virus infection in high risk infants: A consensus opinion. Pediatric Infectious Disease Journal. 1999;18(3):223-231.

50. Pedraz C, Carbonell-Estrany X, Figueras-Aloy J, Quero J-IRIS Study Group. Effect of palivizumab prophylaxis in decreasing respiratory syncytial virus hospitalizations in premature infants. Pediatric Infectious Disease Journal. 2003;22(9):823-827.

51. Singleton R, Dooley L, Bruden D, Raelson S, Butler JC. Impact of palivizumab prophylaxis on respiratory syncytial virus hospitalizations in high risk Alaska Native infants. Pediatric Infectious Disease Journal. 2003;22(6):540-5.

52. Mitchell I, Paes BA, Li A, Lanctôt KL - the CARESS Investigators. CARESS: The canadian registry of palivizumab. Pediatric Infectious Disease Journal. 2011;30(8):651-655.

53. Carbonell-Estrany X, Simões EA, Dagan R, et al. Motavizumab for prophylaxis of respiratory syncytial virus infection in high-risk children: A non inferiority trial. Pediatrics. 2010;125(1):35-51.

54. Tongna Zhu, Chuanlong Zhang, Li Yu, Jingxian Chen, Huan Qiu, Weiwei Lyu, Shenghai Huang. The preventive effect of vaccine prophylaxis on severe respiratory syncytial virus infection: A meta-analysis. Virologica Sinica. 2015;30(5):371-378.

55. Di Carlo P, Romano A, Plano MR, Gueli A, Scarlata A, Mamma C. Children, parents and respiratory syncytial virus in Palermo, Italy: Prevention is primary. J Child Health Care. 2010;14(4):396-407.
56. Re B, Pasnocht A, Gusenleitner W, Müller W. Re hospitalizations for respiratory disease and respiratory syncytial virus infection in preterm infants of 29-36 weeks gestational age. Journal of Infection. 2005;50(5):397-403.

57. Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. Pediatrics. 1988;82(2):199-203.

58. Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnachie KM. Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: Hospitalization and economic implications of prophylaxis. Archives of Pediatrics & Adolescent Medicine 2000; 154(1):55-61.

59. Singleton RJ, Redding GJ, Lewis TC, Martinez P, et al. Sequelae of severe respiratory syncytial virus infection in infancy and early childhood among Alaska Native children. Pediatrics. 2003; 112(2):285-292.

60. Greenough A, Alexander J, Boit P, et al. School age outcome of hospitalization with respiratory syncytial virus infection of prematurely born infants. Thorax. 2009; 64(6):490-495.

61. Figueras F, Meler E, Eixarch E, Francis A, Coll O, Gratacos E, Gardosi J. Association of smoking during pregnancy and fetal growth restriction: Subgroups of higher susceptibility. European Journal of Obstetrics Gynecology and Reproductive Biology. 2008;138(2):171-175.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciedomain.org/review-history/12783