Review Article

Management of acute viral bronchiolitis in children: Evidence beyond guidelines

Shaikh Mohammed Iqbal

Department of Pediatrics, College of Medicine,
King Saud University, Riyadh, Saudi Arabia

ABSTRACT

Acute viral bronchiolitis is one of the leading causes of worldwide admission of children under 2 years of age during winter months. There is a lack of consensus regarding the clinical definition of acute viral bronchiolitis in children and hence the management varies across the globe. The purpose of this article is to review the epidemiology, etiology, risk factors, pathophysiology, clinical presentation, assessment and management of children with respiratory syncytial virus (RSV) bronchiolitis. The available evidence in the worldwide literature suggests that supportive and symptomatic management is still the mainstay of management in this condition.

The key to reducing the morbidity and mortality in children with RSV bronchiolitis is through prevention of infection through immunoprophylaxis especially in high-risk children.

What is already known:

Despite bronchiolitis being a leading cause of childhood admissions under 2 years of age, there is a lack of consensus in its definition and management worldwide. According to the evidence based guidelines, supportive management is still the mainstay of management of this condition

What this review adds:

Newer viruses continue to be isolated and identified as causative agents.

In addition to supportive care, the following can be added to the guidelines in management of acute viral bronchiolitis:

1. Infant beds need to be separated in bays by at least 3 feet to prevent iatrogenic spread.
2. Racemic epinephrine appears to offer slight edge over salbutamol and can be offered as a bronchodilator trial in emergency room settings in infants with atopic predisposition.
3. Hypertonic saline or high volume normal saline seems to reduce clinical severity scores by possibly decreasing mucosal oedema and improving mucociliary clearance.

Key words: Respiratory syncytial virus, viral bronchiolitis, infants, children, evidence based management.

Correspondence to:
Dr Shaikh Mohammed Iqbal
Consultant Pediatric Pulmonary and Sleep Physician
Department of Pediatrics, College of Medicine,
King Saud University, PO Box 7805, Riyadh 11472, KSA.
Email: siqbal@ksu.edu.sa

How to cite this article:
Iqbal SM. Management of acute viral bronchiolitis in children: evidence beyond guidelines? Sudan J Paediatr 2012;12(1):40-48.

INTRODUCTION

Acute viral bronchiolitis is a clinically diagnosed spectrum of lower respiratory tract infection in children usually less than 2 years of age. It is the leading cause of admission worldwide during the winter periods especially in infancy. The differences in the diagnostic criteria in the guidelines published in UK [1] and USA [2] have led to differences in treatment practices and clinical outcomes. Respiratory syncytial virus (RSV) is thought to be the commonest aetiological agent. The development of newer molecular diagnostic methods has led to not only the discovery of newer viruses, but also their isolation in nasopharyngeal aspirates of these patients and implication as causative organisms for bronchiolitis and acute wheezy episodes [3,4]. In this article bronchiolitis caused by RSV will be discussed.

Pathophysiology

RSV is an enveloped RNA virus that belongs to the paramyxovirus family. Two major subtypes (A&B) have been identified. After an incubation period of 3-5 days, it causes the necrosis of the ciliated epithelium within a day of infection [5].

Goblet cell proliferation causes greatly increased mucus production and mononuclear cellular infiltration results in submucosal oedema. The muco-ciliary clearance is however impaired by replacement of epithelium by non-ciliated cells. The infected epithelial cells release chemokines and cytokines causing further cellular recruitment into the airways and amplifying the immune response [6,7]. Chemokine receptor may contribute to mucus production and airway hyperactivity [8].

The small airway diameter in the vulnerable pediatric population makes them susceptible to bronchiolar obstruction from the submucosal oedema, mucous overproduction and cellular debris causes, increases airway resistance, generalized hyperinflation with areas of patchy atelectasis and ventilation-perfusion mismatch.

Although the epithelium recovery starts after 72 hours, the cilia repair takes several weeks [9]. Clearance of the virus was reported to take about 1-3 weeks [10]. There is emerging data that some patients harbor the virus up to 100 days in their respiratory tract. Viral clearance and tissue recovery does not however provide prolonged resistance to RSV, as re-infection is common not only in infants but also in adults [11].

Clinical presentation and assessment

Most children under 2 years of age infected by the virus, develop a spectrum of disease, ranging from only coryza from mild upper respiratory tract infection to full house of bronchiolitis symptoms (Table 1). The disease is self-limiting in most of the healthy children and only 1-3% of these actually require admission to the hospital [12]. For infants born below 35 weeks of gestational age, the RSV-hospitalization rate ranges between 3.6% and 9.8% [13-15]. Hydration status should be assessed and pulse oximetry should be done in all children who are admitted to the hospital [2]. It is essential to look for signs of respiratory distress signs like tachypnea, nasal flaring, retractions and grunting. Children who are restless or lethargic may be hypoxemic or developing respiratory failure. Color change or cyanosis may be an additional clue to respiratory failure. Children, who have oxygen saturations below 92%, moderate to severe respiratory distress, apnoea with or without feeding concerns, should be admitted and observed. The reasons for severity of symptoms and hospital admission are multi-factorial (Table 2- risk factors for acute viral bronchiolitis). Children with pre-existing medical conditions (Table 3), are at a risk of significant morbidity and higher mortality and should have a lower threshold for admission [12].

Of the previously healthy infants admitted to the hospital 4-15% require intensive care admission and 1-5 % require mechanical support [16]. The likelihood of PICU admission and mechanical support increases (Table 4) in those prematurely born with decreasing gestational age (GA) [16-18].

Table 1- Clinical presentation of acute viral bronchiolitis in children; may include all or a combination of some features listed below.

Preceding upper respiratory tract infection
Signs of lower respiratory tract infection
Cough
Fever
Tachypnoea
Increased work / Difficulty in breathing
Crackles + wheeze
Low oxygen saturations

Table 2- Risk factors for acute viral bronchiolitis in children.

Male sex
Age < six months
Birth during the first half of the RSV season
Overcrowding/ older siblings
Day care exposure
Low maternal education [low socioeconomic status]
Lack of breast feeding
Malnutrition
Passive smoke
High altitude

Table 3- Pre-existing medical conditions in children that increase the risk of acute viral bronchiolitis.

Prematurity
Low birth weight
Congenital lung abnormality
Chronic lung disease [neonatal, cystic fibrosis etc]
Haemodynamically significant congenital heart disease
Immunodeficiency

Table 4- Paediatric Intensive Care Unit admission rates in children hospitalized with respiratory syncytial virus bronchiolitis.

Gestation	PICU Admission rates	Mechanical support rates
Term	4-15%	1-5%
GA < 36 weeks	10-20%	8-27%
GA 32-35 weeks	20%	7%
GA < 32 weeks	100%	100%

GA - gestational age, PICU - paediatric intensive care unit, RSV - Respiratory Syncytial virus

Diagnosis

Acute viral bronchiolitis should be a straightforward clinical diagnosis. The problem however is that there is no consensual definition of the condition across the globe and this makes clinicians include children with purely viral induced wheezy episodes without crackles, those with crackles without wheeze and those with crackles and wheeze when diagnosing the condition [19]. This makes it difficult to analyze the epidemiology, clinical course and hence the response to treatment strategies.

Both the American academy of Pediatrics (AAP) and Scottish Intercollegiate guideline Network (SIGN) guidelines agree that the diagnosis should be made on the basis of history and physical examination [1, 2]. There is also agreement on the signs and symptoms which may include rhinorrhoea, tachypnoea, nasal flaring, increased respiratory effort, inspiratory crackles and wheeze [1,2]. While presence of wheezing is essential even in the absence of crackles to reach the diagnosis in US [1]. It is made in children who have crackles with or without wheeze in UK, Australia and New Zealand [20].

Complications

Acute complications

Apnea is reported in about 9% and respiratory failure in 14% of children hospitalized with RSV bronchiolitis and in those requiring intensive care support, apnea is noted in 20% [21]. Rare complications like pleural effusion and pneumothorax are all also reported in the literature. Otitis media is reported in up to 50% of children with RSV bronchiolitis but may be underestimated [22].

Infectious complications like bacterial pneumonia and sepsis are reported to be as high as 41% by some, however others including the major guidelines report secondary bacterial infection in less than 1% of children. In febrile infants less than 2 months of age, the recommendation however is to rule out sepsis. Also reported are electrolyte imbalances and cardiovascular complications like arrhythmias, more so in children with co-morbid conditions [21].

Chronic complications

Children who have had acute viral bronchiolitis are said to be at an increased risk for developing wheeze later in life [23-24]. Bronchiolitis obliterans is also seen as a sequelae in those who have had severe bronchiolitis especially that caused by adenovirus. Whether children who possibly have genetic predisposition and get acute viral bronchiolitis go on to develop these sequelae or it is purely the virus or virus-host interaction that leads to the development of the sequelae is debatable.

Differential diagnosis

It may be extremely difficult to differentiate between bronchiolitis and first wheezy episode secondary to viral infection. One should consider foreign body inhalation, congestive cardiac failure, gastro-esophageal reflux with secondary aspiration, cystic fibrosis, and congenital airway malacia and other abnormalities.

Diagnostic testing

Routine laboratory and radiologic investigations are not recommended by both of the above mentioned guidelines to confirm the diagnosis of bronchiolitis [1,2]. Rapid virologic identification by enzyme linked immunofluroscent assay (ELISA) in nasal swab or nasopharyngeal aspirate (NPA) is very sensitive and specific and may be useful in places where adequate isolation facilities are unavailable or to prevent unnecessary workup in very young infants. A positive test supports the clinical presentation; a negative result however does not negate the diagnosis. Viral genome amplification by polymerase chain reaction (PCR) and viral cultures can be used in addition to aid in the diagnosis. These tests are however not available in all hospitals and are very expensive.

Capillary or arterial blood gases may be useful in children with severe respiratory distress or who are getting exhausted and may be developing respiratory failure [1,2]. Chest X ray should be done in children only when there is a diagnostic difficulty or the patient is not responsive to supportive management or deteriorating and is heading towards intensive care requirement. Radiological findings typically seen hyperinflation with flattened diaphragms and areas of atelectasis may be seen in any lobe and may be difficult to differentiate from pneumonic infiltrates. RSV can itself cause viral pneumonia and there may also be co existing bacterial infection. The areas of atelectasis may change on a daily basis, hence using radiographs alone to base the diagnosis and management may not be appropriate.

Management

Supplemental oxygen therapy

Oxygen supplementation is indicated in children whose haemoglobin saturation level is below 92% according to SIGN [1] and 90% according to AAP [2] guidelines. Using pulse oximetry to guide the duration of the supplemental oxygen therapy has probably contributed to increased length of stays and increase in health care resource usage [25]. The supplemental oxygen should be weaned if the child is clinically improving and the haemoglobin saturation levels are consistently over 94%. The oxygen therapy can be discontinued if the baseline saturations are above those considered for the supplemental need.

Bronchodilators (β2 agonists, Racemic epinephrine)

There is insufficient evidence to support the routine use of bronchodilators in bronchiolitis [26], especially as sub-mucosal edema, mucus plugs and cellular debris cause the airway narrowing and there is very little, if any airway smooth muscle involvement. Racemic epinephrine may have a slight edge over salbutamol or placebo in emergency room setting [27], however there is little evidence to support its use in inpatient population [28]. The AAP guideline recommends that a careful trial of bronchodilators may be useful on an individual basis especially if there is a history of atopy in the patient or his/her family [1]. It should clearly be discontinued if there is no response

Corticosteroids

There is no evidence to support the use of either inhaled or systemic steroids [29, 30] and they should not be used in the management of patients with bronchiolitis.

Antibiotics

Secondary bacterial infection in bronchiolitis is unusual and the use of antibiotics is unnecessary unless there is clinical deterioration requiring PICU admission. There is one recent small study, which

showed significant benefit of using clarithromycin in reducing the duration of stay and readmission [31]. This finding was not replicated in a much larger trail using azithromycin [32]. As of now all the bronchiolitis management guidelines agree and do not recommend the routine use of antibiotics [1,2].

Antiviral agent

Ribavirin is the only specific antiviral drug used in small studies for treatment of acute viral bronchiolitis given its role in inhibition of viral replication [33]. Currently there is no guideline recommending its routine given the high cost, efficacy and also safety concerns and lack of large randomized controlled trials.

Hypertonic Saline

A Cochrane systematic review has shown that Nebulised hypertonic (3%) saline may significantly reduce the length of hospital stay and improve the clinical severity score in children with acute viral bronchiolitis [34].

There is evidence to suggest that 5% hypertonic saline may be better at reducing clinical severity scores in mild to moderate bronchiolitis [35].

Another study suggests that high volume normal saline nebulisation may be as good as hypertonic saline in reducing airway oedema and improving muco-ciliary clearance [36]. Although not included in the AAP and the SIGN guidelines, the hypertonic saline could be trialed in the patients with acute bronchiolitis given its lack of any significant side effects.

Ventilatory Support

Early use of continuous positive pressure (CPAP) or high-flow oxygen therapy may be sufficient for children who develop with apneas and /or respiratory failure and may reduce need for more intubation and invasive ventilatory support.

Pressure support should be as minimal as possible to provide adequate oxygenation and permissive hypercapnia should be given preference over aggressive ventilatory support strategy. Infants who do not respond to conventional support may need inhaled nitric oxide in addition to high frequency ventilation or even ECMO (extra corporeal membrane oxygenation).

Other therapies

Exogenous surfactant, leukotriene receptor antagonists, intravenous immunoglobulin, furosemid and heliox have not shown to be of any significant benefit and are not recommended to be used in routine management of bronchiolitis.

Supportive and non-pharmacologic management

Hydration/Nutrition

Children with bronchiolitis commonly present with difficulty in feeding; assessment and management of their hydration status is paramount. Intravenous fluid management may be needed if the child is unable to feed or too tachypneic or ill for hydration through a nasogastric tube. Severe pulmonary involvement may be associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH), and a close eye should be kept on serum electrolytes and the IV fluids need to be restricted to two-thirds of the daily maintenance. There is lack of evidence to support any one route of hydration over the other and both may be equally suitable [37].

Chest Physiotherapy

It is best if children with acute bronchiolitis are minimally handled. All guidelines support this and only advocate minimal nasal suctioning to provide relief to nasal congestion/blockage. They do not recommend the use of chest physiotherapy in management, as there is no proven benefit in reducing

the clinical severity scores, oxygen requirement or duration of stay [38].

Prevention

Control precautions

Viral testing can be invaluable in helping to cohort patients, however given the limited availability of the techniques and also limited number of virus screened in the nasal swabs or aspirates, it becomes impossible to detect other agents that can co-infect or cause bronchiolitis on their own.

Respiratory viruses primarily spread through large-particle aerosols that traverse distances of up to 3 feet or by coming in direct contact with fomites contaminated by infectious secretions or by coming in close contact with an infected individual. Comply with appropriate precautions such as the cleansing of hands and fomites, separating infant beds in bays by at least 3 feet, and other recommended infection-control procedures [39]. Except for hand sanitation, the efficacy of specific additional precautions, such as use of gowns, gloves, and masks, are not entirely clear [39].

Vaccination/immuno-prophylaxis

Polyclonal RSV hyperimmune globulin (RSV IVIG-Respigam) and humanized monoclonal antibody (mAb – Palivizumab) are the two presently available therapies aimed at preventing RSV bronchiolitis

Although Palivizumab is 50 times more potent than RSV-IVIG, and has been used extensively to help prevent severe RSV disease in high-risk infants and children, a very small number of patients receiving it does not appear to be adequately protected. It is recommended for use as prophylaxis in high-risk children (Table 3) and has been shown to be beneficial. The prescribed regimen is an intramuscular injection at monthly intervals during the 5 months of RSV season.

A more potent second-generation mAb, Motavizumab, which is supposedly 20 times more potent than Palivizumab was undergoing phase III clinical trials [40]. Development of this as a successor to Palivizumab has however been put on hold.

CONCLUSION

Acute viral bronchiolitis continues to poses a major worldwide health burden more so to the high-risk infants. It is usually a self-limiting disease, which resolves in about a week in healthy infants. Infants are generally noted to get worse clinically before showing signs of improvement. Despite advances in various medical technologies, available evidence suggests that supportive care is still the mainstay of treatment. Till there is an effective vaccine for preventing RSV bronchiolitis, we only have the monoclonal antibodies in our armamentarium for prevention of the condition in high-risk children. Adherence to clinical practice guidelines based on best available clinical evidence will hopefully avoid unnecessary investigations and unbeneficial strategies in the diagnosis and management of acute viral bronchiolitis.

REFERENCES

1. Scottish Intercollegiate Guidelines Network (SIGN). Bronchiolitis in children. A national clinical guideline. Report No 91. SIGN, 2006
2. American Academy of Pediatrics. Diagnosis and management of bronchiolitis. Pediatrics 2006;118:1774–93
3. Jartti T, Lehtinen P, Vuorinen T, Österback R, Van den Hoogen B , Osterhaus ADME et al, Respiratory Picornaviruses and Respiratory Syncytial Virus as Causative Agents of Acute Expiratory Wheezing in Children Emerging Infectious Diseases 2004; Vol 10(6): 1095-1101
4. Sezer GM, Ünsür EK, Kayaoğlu S and Akçay F The respiratory syncytial virus may not always be responsible for Bronchiolitis in children. African Journal of Microbiology Research 2011 Vol. 5(14): 1808-1812.
5. Tristram DA, Welliver RC. Bronchiolitis. In: Long SS, Pickering LK, Prober CG, ed Principles and practice of Pediatric Infectious Diseases. (2nd ed). New York: Churchill Livingstone; 2003:213-219.
6. McNamara PS, Flanagan BF, Baldwin LM, Newland P, Hart CA, Smyth RL.. Interleukin 9 production in the lungs of infants with severe respiratory syncytial virus bronchiolitis. Lancet. 2004;363(9414):1031-7.
7. McNamara PS, Flanagan BF, Hart CA, Smyth RL. Production of chemokines in the lungs of infants with severe respiratory syncytial virus bronchiolitis. J Infect Dis. 2005;191(8):1225-32.
8. Miller AL, Streiter RM, Gruber AD, Ho SB, Lukas NW, CXRC@ regulates respiratory syncytial virus induced airway hyperactivity and mucus production. J Immunology. 2003; 3348-3356.
9. Hall, W.J., C.B. Hall, and D.M. Speers. . Respiratory syncytial virus infections in adults: clinical, virologic, and serial pulmonary function studies. Ann. Intern. Med. 1978; 88:203–205.
10. Caroline Breese Hall, R. Gordon Douglas Jr., Joyce M. Geiman, Respiratory syncytial virus infections in infants: Quantitation and duration of shedding, The Journal of Pediatrics. 1976 Vol 89, (1): 11-15.
11. Hall, C.B. Respiratory syncytial virus and Para influenza virus. N. Engl. J.Med. 2001; 344:1917–1928
12. Simoes EA: Respiratory syncytial virus infection. Lancet 1999, 354(9181): 847-852.
13. Deshpande SA, Northern V. The clinical and health economic burden of respiratory syncytial virus disease among children under 2 years of age in a defined geographical area. Arch Dis Child 2003; 88(12): 1065-9.
14. Zaw W, McDonald J. Respiratory syncytial virus bronchiolitis in ex-preterm infants in the Scottish highlands: review of hospital admissions and an analysis of hospital cost. Scott Med J. 2003; 48(4): 108-10.
15. Figueras-Aloy J, Carbonell-Estrany X, Quero-Jimenez J, Fernandez-Colomer B, Guzman-Cabanas J, Echaniz-Urcelay i, et al: Iris study group. Flip-2 study: risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born in spain at a gestation age of 32 to 35 weeks. Pediatr Infect Dis J. 2008; 27:788-793.
16. Law BJ, Wang EE, MacDonald N, MacDonald J, Boucher F, Langley et al. Does ribavirin impact on the hospital course of children with respiratory syncytial virus (RSV) infection? An analysis using the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) RSV database. Pediatrics. 1997; 99:E7
17. Carbonell-Estrany X, Bont L, Doering G,Gouyon JB and Lanari M. Clinical relevance of prevention of respiratory syncytial virus lower respiratory tract infection in preterm infants born between 33 and 35 weeks gestational age. Eur J Clin Microbiol Infect Dis 2008; 27:891-899.
18. Greenough A, Cox S, Alexander J, Lenney W, Turnbull F, Burgess S et al. Health care utilisation of infants with chronic lung disease, related to hospitalisation for RSV infection. Arch Dis Child 2001; 85: 463-468.
19. Bordley WC, Viswanathan M, King VJ Sutton SF, Jackman AM, Sterling L et al Diagnosis and testing in bronchiolitis: a systematic review. Arch Pediatr Adolesc Med 2004; 158:119-26.
20. Fitzgerald DA, Kilham HA. Bronchiolitis: assessment and evidence-based management. Med J Aust 2004; 180: 399-404.
21. Wilson DF, Landrigan CP, Horn SD, and Smout. RJ. Complications in infant hospitalized with bronchiolitis or respiratory virus pneumonia. J Pediatr. 2003; 43:S142-S149.
22. Smyth, Rosalind L; Openshaw, Peter JM. Bronchiolitis.. The Lancet vol. 368 issue 9532 July 22 - 28 2006. p. 312-322.
23. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. Am J Respir Crit Care Med. 2005 Jan 15; 171(2): 137-41
24. Piippo-Savolainen E, Korppi M, Korhonen K, and Remes S. Adult asthma after non-respiratory syncytial virus bronchiolitis in infancy: subgroup analysis of the 20-year prospective follow-up study. Pediatr Int. 2007 Apr; 49(2): 190-5

25. Zorc JJ, Hall CB. Bronchiolitis: Recent evidence on diagnosis and management. Pediatrics 2010; 125: 342-9.
26. Gadomski AM, Brower M. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev. 2010 Dec 8;(12): CD001266
27. Hartling L, Russell KF, Patel H, Klassen TP, Liang Y. Epinephrine for bronchiolitis. Cochrane Database Syst Rev 2004; 1: CD003123
28. Wainwright C, Altamirano L, Cheney M, Cheney J, Barber S, Price D et al. A multicenter, randomized, double blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. N Engl J Med 2003; 349: 27-35.
29. Ermers MJJ, Rovers MM, van Woensel JB, Kimpen JLL,and Bont LJ, on behalf of the RSV Corticosteroid Study Group. The effect of high dose inhaled corticosteroids on wheeze in infants after respiratory syncytial virus infection: randomized double blind placebo controlled trial. BMJ 2009; 338: b897.
30. Patel H, Platt R, Lozano JM, Wang EE. Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Data- base Syst Rev 2004; 3: CD00487
31. Tahan F, Ozcan A, and Koc N. Clarithromycin in the treatment of RSV bronchiolitis: a double-blind, randomised, placebo-controlled trial. Eur Respir J 2007; 29: 91-7
32. Kneyber MC, van Woensel JB, Uijtendaal E, Uiterwaal CS,and Kim- pen JL; Dutch Antibiotics in RSV Trial (DART) Research Group. Azithromycin does not improve disease course in hospitalized in- fants with respiratory syncytial virus (RSV) lower respiratory tract disease: a randomized equivalence trial. Pediatr Pulmonol 2008; 43: 142-9.
33. Ventre K, and Randolph A. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. Cochrane Database Syst Rev 2004; 4:CD000181
34. Zhang L, Mendoza-Sassi RA, Wainwright C, and Klassen TP. Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev 2008; 4: CD006458
35. Al-Ansari K, Sakran M, Davidson BL, El Sayyed R, Mahjoub H,and Ibrahim K. Nebulized 5% or 3% hypertonic or 0.9% saline for treating acute bronchiolitis in infants. J Pediatr. 2010 ; 157(4):630-4
36. Anil AB, Anil M, Saglam AB, Cetin N, Bal A, and Aksu N. High volume normal saline alone is as effective as nebulized salbutamol- normal saline, epinephrine-normal saline, and 3% saline in mild bronchiolitis. Pediatric Pulmonology 2010; 45: 41-7
37. Babl FE, Sheriff N, Neutze J, Borland M, and Oakley E. Bronchiolitis management in pediatric emergency departments in Australia and New Zealand: a PREDICT study. Pediatr Emerg Care 2008; 24: 656-8.
38. Perrotta C, Ortiz Z, Roqué I, and Figuls M. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. Cochrane Database Syst Rev 2007; 1: CD004873.
39. Hall CB and Lieberthal AS. Viral Testing and Isolation of Patients With Bronchiolitis. Pediatrics 2007; 120; 893 DOI: 10.1542/peds.2007-1634
40. Carbonell-Estrany X, Simoes EA, Dagan R, Hall, C. B., Harris, B., Hultquist , M et al. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a noninferiority trial. Pediatrics 2010; 125:e35–51.