Bronchiolitis in children: The Saudi initiative of bronchiolitis diagnosis, management, and prevention (SIBRO)

Adel S. Alharbi[1], Mansour Alqwaiee[1], Mohammed Y Al-Hindi[2], Rafat Mosalli[3], Abdullah Al-Shamrani[1], Saleh Alharbi[3], Abdullah Yousef[4], Amal Al Aidaroos[1], Turki Alahmadi[5], Aisha Alshammary[6], Abeer Miqdad[7], Yazan Said[8], Abdulrahman Alnemri[9]

[1]Department of Pediatrics, Prince Sultan Military City, Ministry of Defense, Riyadh, [2]King Abdullah International Medical Research Center/King Saud bin Abdulaziz University for Health Sciences, Department of Pediatric, Ministry of National Guard, Jeddah, [3]Department of Pediatrics, Umm Al Qura university, Makkah, [4]Department of Pediatrics, College of Medicine, Imam Abdulrahman bin Faisal University, Dammam, [5]King Abdulaziz University, College of Medicine, Department of Pediatrics, Jeddah, [6]Alyammamah Hospital, Ministry of Health, Riyadh, [7]Department of Pediatrics, Security forces hospital, Riyadh, [8]King Fahad Specialist Hospital, Ministry of Health, Dammam, [9]College of Medicine, Peadiatric Department, King Saud University, Riyadh, Saudi Arabia

Address for correspondence:
Dr. Adel S. Alharbi, Department of Pediatrics, Prince Sultan Military City, Riyadh, Saudi Arabia.
E-mail: dr.adelalharbi@gmail.com

Submission: 25-02-2018
Accepted: 09-05-2018

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/atm.ATM_60_18

Abstract:

Bronchiolitis is the leading cause of admissions in children less than two years of age. It has been recognized as highly debated for many decades. Despite the abundance of literature and the well-recognized importance of palivizumab in the high risk groups, and despite the existence of numerous, high-quality, recent guidelines on bronchiolitis, the number of admissions continues to increase. Only supportive therapy and few therapeutic interventions are evidence based and proved to be effective. Since Respiratory Syncytial Virus (RSV) is the major cause of bronchiolitis, we will focus on this virus mostly in high risk groups like the premature babies and children with chronic lung disease and cardiac abnormalities. Further, the prevention of RSV with palivizumab in the high risk groups is effective and well known since 1998; we will discuss the updated criteria for allocating infants to this treatment, as this medication is expensive and should be utilized in the best condition. Usually, diagnosis of bronchiolitis is not challenging, however there has been historically no universally accepted and validated scoring system to assess the severity of the condition. Severe RSV, especially in high risk children, is unique because it can cause serious respiratory sequelae. Currently there is no effective curative treatment for bronchiolitis. The utility of different therapeutic interventions is worth a discussion.

Keywords:

Bronchiolitis, guideline, palivizumab, prevention, respiratory syncitial virus

This guideline was prepared by the Saudi Pediatric Pulmonology Association - a subsidiary of the Saudi thoracic society - when noted how common are such conditions in the country and how urgent it is to have a national guideline according to the latest and best evidence-based practice. This guideline aims to help pediatricians and general practitioners when managing such conditions.

Abstract

Bronchiolitis is the leading cause of admissions in children <2 years of age. It has been recognized as highly debated for many decades. Despite the abundance of literature and the well-recognized importance of palivizumab in the high-risk groups, and despite the existence of numerous, high-quality, recent guidelines on bronchiolitis, the number of admissions continues to increase. Only supportive therapy and few therapeutic interventions are evidence-based and proved to be effective. Since respiratory syncytial virus (RSV) is the major cause of bronchiolitis, we will focus on this virus mostly in high-risk groups like the premature babies and children with chronic lung disease (CLD) and cardiac abnormalities. Further, the prevention of

How to cite this article: Alharbi AS, Alqwaiee M, Al-Hindi MY, Mosalli R, Al-Shamrani A, Alharbi S, *et al*. Bronchiolitis in children: The Saudi initiative of bronchiolitis diagnosis, management, and prevention (SIBRO). Ann Thorac Med 2018;13:127-43.

RSV with palivizumab in the high-risk groups is effective and well known since 1998; we will discuss the updated criteria for allocating infants to this treatment, as this medication is expensive and should be utilized in the best condition. Usually, diagnosis of bronchiolitis is not challenging. However, there has been historically no universally accepted and validated the scoring system to assess the severity of the condition. Severe RSV, especially in high-risk children, is unique because it can cause serious respiratory sequelae. Currently, there is no effective curative treatment for bronchiolitis. The utility of different therapeutic interventions is worth a discussion.

Definition

Bronchiolitis is the most common acute lower respiratory tract viral infection in infants <2 years of age.[1,2] This is a pathological description while bronchiolitis is a clinical description. Acutely, the inflammation is not limited to the bronchioles and is found in all parts of the airway further. In 2006, a subcommittee of the American Academy of Pediatrics (AAP) together with the European Respiratory Society (ERS) defined bronchiolitis as a constellation of clinical symptoms and signs including a viral respiratory prodrome followed by increased lower respiratory effort and wheezing in infants <2 years of age.[3] Children admitted for wheezing in the 2nd year of life are common; such could have different pathophysiology and different prognosis for this recent data limited bronchiolitis definition to the 1st year of life.[4] We reviewed numerous guidelines aiming to extract the best evidence in the management of bronchiolitis.[3,5-8]

Methods

We searched PubMed up to November 2015 using the following words in different combinations, bronchiolitis infant, guideline, pathophysiology, management, pharmacotherapy, acute, bronchodilator, steroid, oxygen, physiotherapy, hypertonic saline, intensive care, continuous positive airway pressure ventilation (CPAP), bi-level positive pressure ventilation, mechanical ventilation, antibiotic, and montelukast. The included studies where not systemically evaluated for the design and quality. Guidelines and Cochrane reviews were intensively reviewed.

To construct this guideline, the panel met twice. During the first meeting, the panel discussed the available evidence, while it graded the evidence during the second meeting. Grading the evidence was inspired from the recommendations in the center of evidence-based medicine website (www.cebm.net), listed by Burns *et al*.,[9] as below.

Level and corresponding type of evidence:

- 1A Systematic review (with homogeneity) of randomized controlled trials (RCTs)
- 1B Individual RCT (with narrow confidence intervals [CI])
- 1C All or none study
- 2A Systematic review (with homogeneity) of cohort studies
- 2B Individual Cohort study (including low quality RCT, e.g., <80% follow-up)
- 2C "Outcomes" research; ecological studies
- 3A Systematic review (with homogeneity) of case-control studies
- 3B Individual case–control study
- 4 Case series (and poor quality cohort and case–control study
- 5 Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles."

Epidemiology

Bronchiolitis is the most frequent disease in children <2 years and is the leading cause of hospital admissions in this age group; it is a seasonal disease, appearing most frequently as an epidemic during winter months.[10] Bronchiolitis is a well-recognized condition; it affects around 1%–3% of all healthy children and more than 10% in high-risk groups.[4] Bronchiolitis represents a large public health burden throughout the world where 2%–10% of cases require hospitalization.[11] About 5% of RSV bronchiolitis cases require Intensive Care Unit (ICU) admission.[12] Mortality is very low in developed countries, but reported high in the developing world possibly due to overcrowding, poor nutrition, high inoculation,[13,14] and low medical care. Mortality is high in the high-risk groups reaching 47% in CLD and 49.7% in congenital heart disease (CHD) infants.[15] RSV is the predominant organism responsible for around 70% of bronchiolitis cases worldwide, the prevalence in the kingdom of Saudi Arabia has wide variation 25%–88%.[16,17] RSV is a single-stranded RNA which belongs to the pneumoviridae family with two main subtypes, A and B.[18] RSV occurs in all parts of the world, especially during the winter time, and by the age of 2 years, the majority of children are already infected with RSV,[19,20] but only 40% of them develop lower respiratory tract symptoms.[19] Children may present with a wide range of symptoms ranging from simple upper respiratory tract infection (URTI) to respiratory failure requiring ventilator support.[21] RSV usually has a mild course but occasionally become severe, especially in high-risk groups such as premature neonates, children with CHD, children with CLD and children <2 months of age.[18,19,22] The peak incidence of RSV bronchiolitis occurs in infants between one and 6 months of age.[23,24]

The season on the northern hemisphere often starts in late October and continues to April, usually peaking in January.[25] The natural immunity is of short duration, thus repeated infection is common which could explain the recurrence of bronchiolitis, particularly in high-risk groups.[26] There are multiple other viral pathogens implicated in bronchiolitis, and co-infection with two or more agents could occur in up to 30% of cases usually with *Human metapneumovirus*, rhinovirus, parainfluenzavirus, bocavirus, and AdenoVirus.[4,27-30]

Global Respiratory Syncytial Virus Burden

RSV is found throughout the world and is responsible for a large proportion of infant morbidity and mortality, and is the leading cause of acute respiratory infections in children.[52]

The global burden of RSV in 2015 is estimated to be 33.1 million (uncertainty range 21·6–50·3) episodes of RSV-acute lower respiratory tract infection (LRTI), which resulted in about 3.2 million (2.7–3.8) hospital admissions, and 59,600 (48,000–74,500) in-hospital deaths in children younger than 5 years. About 45% of hospital admissions and in-hospital deaths due to RSV-ALRI occur in children younger than 6 months.[53]

Respiratory syncytial virus Burden in Saudi

During a 6-year study in Saudi, 643 hospitalized cases of ALRI were investigated.[54] Among all samples, respiratory viruses were detected in 309 samples. The overall detection rate was 48.1%. Of the positive samples, RSV was identified most frequently with 295 cases, which accounted for 95.5% of the total viral agents. Approximately 245 cases were younger than 1 year. The highest rate of RSV infection was identified in infants during the first 6 months of life ($P < 0.03$). Of the 309 virus-positive samples, bronchiolitis was detected in 264 (85%), and pneumonia in 45 (14.5%). RSV was the most often causative agent of both diseases (bronchiolitis in 251 and pneumonia in 44) ($P < 0.0001$).[54]

Furthermore in another Saudi study,[55] of 200 tested (nasopharyngeal aspirates) samples, 70 were positive for RSV infection (35%) typing of the positive samples using duplex real-time polymerase chain reaction (PCR) indicated that 57.1% were type A viruses and 42.9% were type B. These results validate the implication of both virus subtypes in RSV infection of Saudi Arabia children during the winter season, with a slight dominance of type A viruses. In this study, the samples were grouped into four main age groups as follows: 0–6; 6–12 months; 1–2 and 2–3 years. The results showed that 70% of the RSV-positive samples were collected from children younger than 1 year and then, the incidence decreased as the age increased (18.6% during the 1nd year and 11.4% during the third year). Risk factors including male gender, young age (<1 year), and asthma may be the underlying factors that favor RSV infection in Saudi Arabia children.[55]

A third Saudi study[56] with a total of 10,617 patient specimens screened for respiratory viruses there was a total of 883 (8.3%) positive patients. Of these, 733 were positive for RSV, 62 positive for influenza, 79 positive for parainfluenza, and nine positive for adenovirus. Age distribution of patients showed that 92% of infections occurred in children aged 1 year and under. RSV is an important cause of LRTIs in infants often causing hospitalization. RSV infections occur primarily during annual outbreaks during winter months. In the mentioned study, RSV infections occurred between November and February with a peak during January. Those results are in agreement with other studies carried out in Saudi Arabia[57] in which RSV was the most frequent cause of bronchiolitis.[55]

A fourth Saudi study[58] which included 282 specimens, 128 (45.4%) were found to be positive for RSV. Most of the positive specimens came from patients <1-year-old (51.3%), RSV was strongly associated with patients who were <2 years old (47.2%, $P = 0.019$). The clinical observations from 128 children positive for RSV showed that RSV infection was significantly associated with bronchopneumonia (56.7%, $P = 0.001$) and bronchiolitis (55.4%, $P = 0.002$). Of the infected children, 47% and 36.7% were hospitalized for 1–4 and 5–8 days, respectively. The frequency of the signs and symptoms of the 128 children positive for RSV a cough and tachypnea were the most frequent, occurring in 100% and 98% of the children, respectively, followed by fever (81%), wheezing, crepitation, and retraction, each representing 66%. Three deaths were reported.[58]

Furthermore in a fifth study,[59] 19.3% of the nasopharyngeal aspirate samples for 4575 inpatients and outpatients with acute respiratory symptoms were positive for RSV. About 55% of the cases were male and 45% were female. Most of the cases were in the age group 0–6 months (58.9%), followed by the age group >6–12 months (19.8%). Seasonal variation showed that most of the RSV cases were predominant during winter and early spring months.[60]

Furthermore in another study,[33] prematurity, CLDs, atopic dermatitis, pure formula feeding, passive smoking, and age of 1 year were significant predictors of admission. RSV was the most common frequent cause of admitted cases of bronchiolitis. RSV was isolated in 40% of the admitted cases. About 80% of bronchiolitis due to RSV were in children <6 months of age.[33]

Risk factors associated with RSV infection in Saudi children admitted to the pediatric ICU (PICU) of a tertiary university hospital were investigated[61] prematurity was associated with increased severity of RSV infection. Nearly 37% of infants admitted in the PICU were found to be of premature birth. Moreover, children with pulmonary pathology and cardiovascular abnormalities were also more prone to RSV infection. From a span of 5 years follow up, the earliest RSV cases appeared in October and the latest cases were documented as late as April. Peak RSV admissions were from December to February. Prematurity, pulmonary pathology, neurological, and cardiovascular abnormalities are associated with increased severity of RSV infection.[61]

Virology

RSV is a highly contagious respiratory virus that infects the lungs and breathing passages.[31]

Nearly all children are infected with RSV by the age of 2 years.[31] RSV is the number one cause of acute respiratory tract infection (such as bronchitis and pneumonia) among children under 5 years of age and severe RSV infection is the primary cause of bronchiolitis in infants ≤2 years.[11,31]

Healthy children infected with RSV generally experience disease of mild cold-like symptoms such as coughing, congestion, wheezing, sore throat, runny nose, and fever.[4,5,123] However, severe RSV disease can be fatal in infants and young children with the underlying conditions of prematurity, bronchopulmonary dysplasia (BPD), or CHD[5,32,33] Additional social and environmental risk factors associated with severe RSV infection include, but are not limited to, day care attendance, number of siblings, tobacco exposure, overcrowding, and a family history of asthma.[6]

Respiratory Syncytial Virus Nature

Human RSV, or RSV, is a member of the genus pneumovirus, of the family Paramyxoviridae. The virus is an enveloped, nonsegmented virus-containing a single negative-strand of ribonucleic acid (RNA).

The viral genome encodes ten proteins including two envelope proteins, F and G. The G protein mediates the attachment of the virus to the host cells and the F protein is involved in cell penetration and promotes cell-to-cell transmission through the formation of syncytia[47,50,51,104] RSV can be classified into two strains, RSV-A and RSV-B, based their reactivity with antibodies directed against the variable G protein.[53]

RSV is the most common cause of bronchiolitis and pneumonia in children younger than 1 year of age in the US[105] It is estimated that severe RSV infection causes as much as 90% of all childhood bronchiolitis (inflammation of the bronchioles) and up to 40% of all childhood pneumonias.[5]

RSV infections are commonly limited to the respiratory tract and generally manifest as URTIs or LRTIs. RSV attaches to and enters the epithelial cells of the upper respiratory tract, where the virus replicates. RSV is then spread down the respiratory tract through cell-to-cell transfer along the syncytia (or intracytoplasmic bridges) from the upper respiratory tract to the lower respiratory tract.[58,106]

The immunological response to RSV infection includes innate, cell-mediated, and humoral responses.[34] The innate immune system is the first-line of defense against infection and encompasses recruitment of phagocytic cells (neutrophils and macrophages) that initiate the release of a range of inflammatory cytokines.[35] Specifically, the F protein of RSV binds to Toll-like receptor 4 and CD14 on monocytes to stimulate the release additional cytokines. Among the components secreted by inflammatory cells, surfactant A is suggested to promote the clearance of RSV since surfactant A binds to and neutralizes RSV, while surfactant A-deficient in mice show impaired RSV clearance[36,37] Experiments with the cell-mediated immune response in mice indicate that an inactivated vaccine to RSV induces a Th2 allergy associated response over the Th1 delayed hypersensitivity-related response.[38,39]

In terms of nonimmunological factors, underdeveloped airways predispose infants to severe RSV disease. Lung development, i.e., its maturity, plays a major role in the development of RSV infections.[40]

Transmission of Respiratory Syncytial Virus

RSV is a highly transmissible virus and the only known reservoir for this virus is humans. However, RSV has been shown to survive on fomites (or objects or materials that are likely to carry infection), such as table tops for up to 6 h and on skin for up to 25 min[37,41] Infants with RSV infection can shed virus for 1–2 weeks and in immunocompromised infants, this can increase up to several weeks.[42]

During periods of active viral shedding, RSV is predominantly transmitted by the following methods:

Contact transmission

RSV-contaminated respiratory secretions are commonly transmitted by direct contact and therefore, the rates

of transmission may be greatly enhanced in crowded environments.[43]

Indirect transmission

RSV can be transmitted indirectly by contact with contaminated surfaces such as table tops or paper tissue. Furthermore, RSV can be transmitted indirectly by contaminated airborne droplets where particles are small enough to be inhaled into the respiratory tract. In 2009, aerosol samples were collected from an urgent care center in the United States and analyzed for viral RNA.[44] The study showed that RSV RNA was the most common virus detected in aerosol samples (32% in stationary samplers and 38% in personal samplers); these results support the hypothesis that RSV may be transmitted by airborne routes.[44]

Given that, RSV is highly transmissible through both direct and indirect contact with contaminated respiratory secretions, certain conditions can favor the rapid transmission of RSV, such as those in a pediatric hospital ward. A systematic review into nosocomial RSV infection showed that the risk of RSV transmission in neonatal or pediatric settings was between 6% and 56% (median: 28.5%) compared with 6% to 12% (median: 7%) in adult hospital units.[45]

Re-Infection of Respiratory Syncytial Virus

RSV infections are associated with high rates of re-infection. This high RSV re-infection rate is attributed to two strains of RSV (RSV-A and RSV-B) and the lack of long-term immunity. Infection with either strain can occur independently of the other, or both of them may occur simultaneously. The defining feature of the two RSV strains is in the variability of the G protein expressed on the surface of the virus. As such, neutralizing antibodies to one strain does not confer long-term immunity to the other[46] This lack of long-term immunity leaves infants susceptible to re-infection over time, as revealed by the Houston Family Study. During this study, it was observed that 98% of infants attending day care became infected with RSV during the 1st year of life, 74% were re-infected in year two and 65% in year three[47] A supportive study from Finland showed that the percentage of infants seropositive for RSV at 1, 2, and 3 years old was 37%, 68%, and 86%, respectively, indicating that younger infants are more likely to become re-infected due to low levels of antibody titers against RSV antigens.[48]

Although an infant's first RSV infection is usually the most severe and re-infection illnesses tend to be mild in healthy children, in some cases, re-infection can be severe, especially in high-risk infants.[49,50] An expert consensus panel commented that even after a documented RSV infection in high-risk infants, a second RSV infection may occur within the same RSV season and can be severe enough to require hospitalization.[51]

Clinical Presentation

The majority of RSV bronchiolitis present with congested nose, runny nose and cough for the first 2 days, and 40% of cases will develop lower respiratory signs such as tachypnea wheezing, and crackles.[62] Hypoxia and cyanosis are common manifestations.[10] Symptoms usually peak as of day 4 until end of the 1st week,[63] then children show clear signs of improvement in the second week.[63] Incidence of apnea or acute life-threatening event in previously healthy infants is ≤1%, but reported as high as 23% in high-risk groups with prematurity.[18,64] Clinicians should diagnose bronchiolitis and assess severity based on history and physical examination, and should assess the risk factors.[65] No single scoring system is used to assess the severity of bronchiolitis, nonetheless some suggestions for grading the severity of this disease is reported recently.[66] Recently, the Resvinet RSV expert network developed, validated and published a newly designed scoring system for severity of bronchiolitis named Resivnet scale. Its adoption in the clinical setting is likely to become frequent in the next years.[67]

Differential Diagnosis

In most cases, the diagnosis of bronchiolitis is clinically evident and further tests are not indicated,[10,68] however, other diagnoses may be considered in an infant with atypical presentation. Many viruses other than RSV are implicated in the diagnosis of acute bronchiolitis, especially *Human metapneumovirus*, Parainfluenza and rhinovirus, Less commonly reported in literature are Influenza, Boca, and Adeno viruses.[69] Pertussis and mycoplasma could be concomitant infections.[70,71] Aspiration is common in severe RSV bronchiolitis, attributed to the degree of respiratory distress.[72]

Bronchiolitis is difficult to distinguish from the first episode of asthma, especially in an atopic family or in a good responder to bronchodilator and steroids if used. Wheezes and crackles are common manifestations in multiple other respiratory conditions such as cystic fibrosis, ciliary dyskinesia, cardiac, or cases with immunodeficiency. In such conditions, detailed history and examination are enough to prioritize the differential diagnosis.

Investigation

Pulse oximetry

There is no clear international consensus regarding the lower accepted oxygen saturation in bronchiolitis.[73] Pulse oximetry should be included in the clinical assessment

of bronchiolitis, it can detect hypoxemia not suspected by clinical assessment.[7] In general, there is a need for hospitalization when the oxygen saturation is ≤90% on room air,[4,73,74] while children with oxygen saturation more than 94% may be considered safe for discharge.[69] However, the decision-making for hospitalization of patients with oxygen saturation ranging between 91% and 94% on room air should be supported by detailed history and physical examination.[68,69]

It is important to be aware that the adoption of different lower thresholds of saturation can highly impact on the hospitalization rates. Settings where hospitalization is mandatory for saturation levels of 92% or less will likely have lower hospitalization rates than settings where hospitalization is mandatory only – as an example for infants with saturation levels <94%. Therefore, it is mandatory to ensure at the very least-consistency, comparability and overall accuracy of the measurements, and (if possible) consistency between different settings of the criteria used to hospitalize.

With regard to the accuracy of measurements, the Panel recommends use of motion-tolerant instruments (level of evidence 1B). Furthermore, the Panel recommend accurate nasal suctioning (level of evidence 1B) before having the Saturation measurements taken.[75]

The panel recommends routine use of pulse oximetry for clinical assessment decision-making regarding hospitalization and discharge (level of evidence IB).

Management

Management of acute bronchiolitis is mainly supportive, where minimal handling approach seems to be beneficial in young age groups or in patients with significant respiratory distress.[4] All institutions caring for children with acute bronchiolitis should provide a clear treatment algorithm to their staff to minimize the burden of unnecessary procedure.

Oxygen therapy

Supplemental oxygen has not been studied adequately and it is difficult to choose a single point at which oxygen should be initiated.[78] The majority of investigators choose 92% rather 90% as reported recently by the APP. 2014.[78] Oxygen remains the mainstay of therapy in bronchiolitis, before initiating oxygen therapy, the accuracy of the initial reading should be verified by repositioning the probe and repeating the measurement[78,79] Appropriate use of oxygen is an essential part in treating bronchiolitis, and is considered as a pharmacological agent.[78,79] Oxygen can be delivered with different modalities according to the specific clinical needs. Oxygen needs always to be delivered heated and humidified. Use of nasal cannula, high-flow nasal cannula (HFNC), nasal CPAP can be considered. Initial rates of 0.5l/m for patients <6 m and at a rate of 1l/m for those more than 6 months are recommended[79] (level of evidence 1B). Severe cases may warrant intubation and mechanical ventilation. Some infants have abnormal baseline saturations, like in CLD, cardiac cases, and should be treated with caution.[80,81]

Airway clearance

Nasal suctioning

The published guidelines recommend gentle and superficial suction before feeding or inhalation, aiming to clear the nostril, and improve the airway patency[82] (level of evidence 1B). There is no evidence to support the use of deep pharyngeal suctioning of the airway in bronchiolitis.[47,82]

Chest physiotherapy and mist steam

Chest physiotherapy and mist steam does not improve the severity of the disease, respiratory parameters, nor reduce length of hospital stay or oxygen requirements in hospitalized infants with acute bronchiolitis not on mechanical ventilation.[83] There is insufficient evidence to show any benefit from steam inhalation.[83]

Feeding and hydration

Maintaining hydration is an important part in the management of acute bronchiolitis.[6] Children with mild respiratory distress can usually continue enteral feeds and only need observation. In patients with moderate respiratory distress and a respiratory rate that exceeds 60/min, feeding becomes compromised,[6] particularly in young age groups or in patients who have copious secretion, where the risk of incoordination and aspiration increases.[6,84] Enteral feeding through oral gastric tube or nasogastric tube is recommended, and some kids benefit more from small frequent boluses or continuous feeding to minimize the risk of aspiration However, feeding increases basal metabolic rate, and puts patients at risk of dehydration.[6] In patients with severe respiratory distress, enteral feeding should be discontinued and parenteral fluids, such as sodium chloride and dextrose 5%, should be started[84] The AAP updates guidelines on bronchiolitis recommends nasogastric or intravenous fluid for moderate or severe cases who cannot maintain hydration orally.[6,47]

Bronchodilators

Clinicians are still commonly using bronchodilators in bronchiolitis in 59%–100% of cases.[84,85] However, there is a strong statement by the recent AAP Updates Guidelines on Bronchiolitis for not using salbutamol or adrenaline in bronchiolitis.[6,86] Nonetheless, clinicians are often showing difficulty in complying with this recommendation.

The panel recommends the following (level of evidence 1B):

1. Bronchodilator should not be used routinely in bronchiolitis
2. On a case-by-case basis, a trial of bronchodilators may be performed, and the same drugs may not be discontinued only if there is a documented positive response from the treating team or if a scoring system is used, then more than one is needed to get a clear decision about continuing bronchodilators.

There is modest benefit from using racemic compared to salbutamol.[40,87-89]

Hypertonic saline

There is growing evidence supporting the use of hypertonic saline in bronchiolitis. This idea started since 2002 by Sarell, Mendelberg[36,90] as hypertonic saline improves mucociliary function in both diseased and healthy lungs.[38,91] Hypertonic saline significantly reduces the length of hospitalization by 26% and improves illness severity;[37,92] however, these points cannot be generalized at the level of the emergency department.[37] Hypertonic saline is generally administered in preparations containing a small amount of bronchodilator.

Due to the high safety profile,[41] low cost and noninvasive modality of administration, it looks reasonable to use hypertonic saline in the management of the bronchiolitis[37] as displayed by recent guidelines[6] (level of evidence 1B).

Glucocorticoid (inhaled and systemic)

Steroids are commonly used in the treatment of bronchiolitis, because of their anti-inflammatory effect. It is postulated that steroids decrease symptoms severity by minimizing airway edema and mucosal swelling. However, the Cochrane database, APP concludes that there is no clinical benefit of both systemic and inhaled steroids in reducing neither the rate of admission nor length of hospitalization.[44] In addition, inhaled steroids given in the acute phase are not beneficial in reducing the rate of postviral wheeze.[44] Their use is not routinely recommended in previously healthy infants with acute bronchiolitis.[45,46,48,78,93]

Combined inhaled steroid and bronchodilators

A large multicenter randomized trial which compared a combination of dexamethasone and nebulized epinephrine to placebo, and found that the investigation mixture may reduce the risk of admission on the 7th day of emergency visit; however, more evidence is still needed[94] (level of evidence 1B).

Antiviral

Ribavirin, a synthetic guanosine analog, is the only antiviral licensed medication that so far has been studied for the treatment of bronchiolitis.

Its use is highly controversial due to uncertainty about efficacy, safety, and high costs (CPS statement 2017). There are few reports that state that it could minimize the duration of illness in the ICU. The panel adopts the current Cochrane and APP recommendations, i.e., this drug should not be used routinely but might be considered only in specific patients affected by severe immunodeficiency syndromes, or severe CLD, or hemodynamically significant CHD[3,49] (level of evidence 1A).

Antibiotics

Serious bacterial infection is rare in bronchiolitis where it accounts for an average of ≤2% of cases.[50,51,95] However, antibiotics are commonly prescribed in hospitalized patients, with rates comprised between 34%,[96] 45%[97] 2005, and even up to 95% in the ICUs as reported by Kneyber.[98]

Even for outpatients, antibiotics are excessively prescribed according to many reports from 53% to 99%.[96-101]

Indications for antibiotics in bronchiolitis include cases complicated with otitis media or urinary tract infections.[3]

The use of antibiotics in very sick patients with CLD admitted in the ICU warrants further research, considering that bacterial colonization of the airways is frequently occurring in such patients.[97,102]

The use of macrolides as anti-inflammatory agents is still debated and has no solid evidence so far.[103-105]

As a whole, there is no sufficient evidence to support the use of antibiotics in acute bronchiolitis. A recent Cochrane review recommends further research to determine the reasons for prescribing antibiotics, the correct indications, and how to reduce their use.[106,107] The panel recommends that antibiotics should not be routinely used in the management of bronchiolitis unless there is a strong clinical suspicion of concomitant bacterial Infection or aspiration (level of evidence 1B). Antibiotic therapy may be considered in children with respiratory failure who require invasive ventilatory support.[102,103]

Heliox

Heliox may improve the severity score in infants with acute RSV bronchiolitis, especially in the 1st h after commencing inhalation therapy. A systematic review of seven heterogeneous randomized trials of heliox for the treatment of moderate or severe bronchiolitis concluded that heliox did not reduce the rate of intubation, the rate of discharge from the emergency department, or the length of treatment for respiratory distress in PICU.[108] The panel

states that heliox may be used as adjunctive therapy in critically ill children with RSV bronchiolitis (level of evidence 1A). However, further clinical studies are required to assess the efficacy of this therapy.

Noninvasive ventilation

CPAP can decrease the work of breathing and prevent endotracheal intubation in children with progressive hypoxemia or hypercarbia or in children who fail HFNC.[74]

Several studies showed that nasal CPAP is efficient in infants with bronchiolitis and severe respiratory distress, where it improves the breathing pattern and may be associated with decreased length of PICU stay.

The panel therefore highly recommends the use of CPAP to avoid endotracheal intubation in infants and children with bronchiolitis and severe respiratory distress or impending respiratory failure (level of evidence 2A).

Mechanical ventilation

Endotracheal intubation and mechanical ventilation are indicated in infants who have apnea or hypoxemia despite oxygen supplementation or in infants with worsening respiratory distress despite being on noninvasive ventilations such as CPAP or HFNC.

Endotracheal intubation and mechanical ventilation may also be required in cases with respiratory failure who failed other modalities and in high-risk groups, especially in patients younger than 3 months or those who had history of prematurity.[89] There is no consensus on which ventilator technique is the best for children with bronchiolitis[89] (level of evidence 2A).

Phenylephrine

There is no evidence that nasal phenylephrine 0.5% is effective in infants with acute bronchiolitis.[109]

The panel thus does not recommend the use of phenylephrine in the management of acute bronchiolitis (level of evidence 1B).

Anti-cholinergics

The role of anticholinergics in the management of bronchiolitis is uncertain.[110]

The panel thus does not recommend the use of anticholinergics in the management of acute bronchiolitis (level of evidence 1A).

Dornase Alfa (rhDNase Pulmozyme)

Although it might aid in the clearance of mucus and in relieving peripheral airway obstruction, a Cochrane review showed however that the administration of rhDNase does not reduce the length of hospital stay or the duration of supplemental oxygen in oxygen-dependent infants with RSV bronchiolitis.[111]

The panel thus does not recommend the use of rhDNase in the management of acute bronchiolitis (level of evidence 1B).

Surfactant

Abnormalities of surfactant quantity or quality have been observed in selected, severe cases of bronchiolitis.[112] Use of surfactant may be associated with a decrease in duration of mechanical ventilation and a decrease in ICU length of stay.[112] Some studies have also reported short-term benefit of surfactant on pulmonary mechanics and gas exchange[49] No adverse effects were found.[113] However, the studies are few and small, therefore the available evidence is still not sufficient to provide reliable evidence regarding positive effects of surfactant use in mechanically ventilated infants and children with severe bronchiolitis[112] (level of evidence 1A).

Anti-leukotriene (montelukast)

Bronchiolitis is an inflammation where the leukotriene pathway has been reported to be involved in the pathogenesis of the disease.[114] Accordingly, leukotriene inhibitors, such as montelukast, have been used in infants and young children with bronchiolitis[115,116] The current evidence, however, does not show a clear benefit on the length of admission or on decreasing the chance of recurrent wheezing.[114-116] Based on this evidence, the panel does not recommend routine use of montelukast in the treatment of acute bronchiolitis (level of evidence 1B).

Identifying the causative virus

There are several methods to identify the virus

a. Rapid antigenic detection tests (RADTs): Widely used, inexpensive, quick, practical at the bedside, does not need laboratory-trained personnel and with a sensitivity of 80%–85%[76]
b. Direct fluorescent antibodies (DFA): This test is based on microscopic deletion of viral proteins on host cells via labeled antibodies, results take 2–4 h with sensitivity of 80%–97%[71,72]
c. PCR: Expensive, not widely available, it is getting more popular, better than DFA[68,72] and results take 2–24 h with sensitivity exceeding 90%[70,77]
d. Viral culture: Rarely used, expensive and the results take 4 days to 2 weeks.[74]

The panel recommends using RADTs as first-line diagnostic tool (level of evidence 1B).

The sample for the RADT should be taken preferably through the nasal wash, rather than through nasal swab. Noteworthy, RADTs carry significant limitations due to their suboptimal sensitivity. Thus, confirmatory testing

with PCR may be required for negative results in the presence of strong clinical suspicion and/or depending on surveillance reasons. PCR might be preferable also when nosocomial outbreaks need to 6 NRbe investigated/ruled out, and in episodes occurring in patients with primary or secondary immunodeficiency.

Radiological imaging

Chest X-rays are commonly requested for patients with bronchiolitis.[57,74] The usual finding on X-ray includes hyperinflation and peribronchial wall infiltrates.[57,74] In general, X-rays are not useful in bronchiolitis, and their use is associated with more prescription of antibiotics.[57,74] However, the median recovery is the same at the end of the 1st week regardless of the X-ray findings.[57,74] Hence, it is better not to use chest X-ray routinely in bronchiolitis, as recently published by AAP.[6]

The panel does not recommend routine use of chest X-ray as part of bronchiolitis management and recommends to reserve it for patients with complicated bronchiolitis such as secondary bacterial infection, aspiration or presence of other comorbidities (level of evidence 2B).

Laboratory investigation

Full blood count is commonly requested in bronchiolitis, but should not be performed in typical acute bronchiolitis.[6] Routine bacteriological testing (blood and urine) should be limited to the febrile patient or for atypical presentation.[8] Electrolytes, urea, and creatinine are usually normal and should not be measured.[3] Implementation of the guideline has shown the reduced use of diagnostic tests and therapeutic options with further reduction in the cost and length of stay.[4,78]

Isolation

RSV inoculates mucous membranes and can survive up to 7 h on all hard surfaces, and can be transmitted directly or indirectly by touch.[86] It can be identified in the air as much as 22 feet from the patient bed.[68] Shedding of the virus can continue for 3 weeks in immunocompetent patients and for several months in immunocompromised ones.[86] Hygiene measures are therefore the cornerstone of any preventive strategy. Personal protective equipment, gloves, gown, and mask, should be used during the patient encounter. Of note, hand washing alone can decrease nosocomial RSV by 39%–50%.[117-119] Hospital inpatients with confirmed or suspected RSV should be placed in a private room under strict contact and droplet precautions. Contact and droplet precautions require the use of gowns, gloves, and surgical mask, and use of personalized stethoscopes. Accordingly, the panel recommends strict isolation of all patients presenting with suspected bronchiolitis. The panel stresses on the importance of strict hand washing practices and use of personal protective equipment (i.e., gloves and gowns) for preventing disease transmission. Among healt-hcare providers, the panel also recommends wearing masks during patient care encounters as exposure to aerosolized secretions is likely expected.

Prevention

Since effective anti-viral treatment for RSV is still lacking, RSV prevention remains of key importance. Comprehensive hygiene etiquettes are efficacious and cost-effective in preventing RSV spread, and should always be advocated as prophylactic measures.[1] In addition, secondhand smoking heightens risk for severe RSV infection requiring hospitalization, especially in late-preterm infants.[2] Accordingly, measures to reduce and prevent second-hand smoking are another cornerstone in RSV prevention. On a different note, breastfeeding, even in association with formula milk, reduces the risk of hospitalization for bronchiolitis during the 1st year of life (Lanari, 2013 #235). Thus, it is essential to encourage breastfeeding.

PaIivizumab

Palivizumab is a humanized monoclonal antibody produced by recombinant DNA technology that is a composite of human (95%) and murine (5%) antibody sequences.[120] It binds to the F protein of RSV F protein, which plays a role in virus attachment and mediates fusion, effectively neutralizing the virus and preventing its entry into the cell. Palivizumab was licensed in June 1998 by the US Food and Drug Administration for the reduction of severe LRTIs caused by the RSV in certain risk groups.

The efficacy and safety of palivizumab have been revealed in many prospective, retrospective, cohort and registry studies (Manzoni, 2017 #228). Among all the clinical studies, the most reliable evidence comes from three Phase III RCTs: The IMpact-RSV trial (1998),[100] the Feltes *et al*. study on critical congenital heart disease[15] the Blaanken *et al*. study (NEJM 2014).[128] These studies highlighted that Palivizumab is an effective form of prophylaxis that significantly reduces RSV-related hospitalization rates by 38%–80%, positively affecting a number of outcomes such as length of hospital stays, progression to ICU admission, duration of oxygen support, occurrence of wheezing episodes during the 1st year of age, mortality in high-risk populations.[15,71,72,121]

In the first multi-center randomized double-blinded placebo-controlled trial (IMpact-RSV study), palivizumab showed 55% reduction (10.6% placebo vs. 4.8% palivizumab) in hospitalization as a result of RSV infection in premature babies.[15] In children with CHD, palivizumab was associated with a 45% reduction in RSV hospitalizations. Since then, AAP had updated

the guidelines four times for better usage of this medication.[3,122-124]

Palivizumab is administered intramuscularly at a dosage of 15 mg/kg, packaged in 100 mg vials, and the opened vials should be used within 6 h.[125]

Palivizumab is administered once per month. The regime continues for a total of five doses, sufficient to provide protection during the entire RSV season which in Saudi Arabia usually extends from middle to late October and ends in early to mid-March.[121,126]

This is different from the polyclonal RSV immune globulin intravenous (RSV-IGIV; RespiGamTM, MedImmune Inc., Gaithersburg, MD, USA) which is a hyper-immune polyclonal human intravenous antibody agent prepared from multiple donors. It used to be given as a monthly infusion at a dose of 750 mg/kg. Some disadvantages of prophylaxis with RSV-IGIV included the need for intravenous access; the fluid load (15 mL/kg) required to deliver the drug, the potential for transmission of blood-borne pathogens, and the interference with the antibody response to live-virus vaccines. Moreover, a significant increase in cyanotic episodes and cardiac surgery-related deaths was reported among children with cyanotic CHD and right to left shunt who were given RSV-IGIV,[134] thus limiting its use in children with CHD. RSV-IGIV is no longer marketed in the USA, and its use has been replaced by palivizumab.

Adherence to infection control practices is the basis for reducing healthcare-associated RSV disease. Till date, passive immune-prophylaxis against RSV infection with monoclonal antibodies is the only strategy that has demonstrated efficacy in reducing RSV hospitalizations in high-risk children. The lack of effective therapy against RSV infection makes prophylactic interventions the best strategy to avoid the acute and chronic complications of the disease.[127]

Palivizumab reduces RSV hospitalizations

Monthly administration of palivizumab throughout the RSV season was associated with reductions in RSV-related hospitalizations in all premature patient groups as revealed in the IMpact-RSV study.[100] It was observed that there was a significant reduction of 55% (95% CI: 38–72; $P < 0.0001$) in RSV-related hospitalizations in all infants and young children who received palivizumab versus those who received placebo (4.8% vs. 10.6%, respectively). A *post hoc* analysis of the original IMpact-RSV study was performed in 11 gestational age groups from the cohort of 724 premature infants and young children without CLD.[30] This analysis revealed that palivizumab significantly decreased the relative risk of RSV-related hospitalization (73%–82%, $P < 0.05$) compared with placebo in the 28wGA–31wGA, 29wGA–32wGA, 29wGA–33wGA, 32wGA–34wGA, and 32wGA–35wGA subgroups. Furthermore, the use of palivizumab consistently reduced RSV-related hospitalizations (64.5%–100%) compared with placebo in all 11 gestational age groups evaluated. Notably, relative reductions in risk for RSV-related hospitalizations were substantial for the moderate/late preterm infants and young children (82% for both the 32wGA–34wGA and 32wGA–35wGA groups).[30]

Results from the study by Feltes *et al*.[15] were consistent with those observed in the IMpact-RSV study. In young children with CHD, monthly prophylaxis with Palivizumab was associated with a significant reduction of 45% (95% CI: 23–67) in RSV-related hospitalizations following prophylaxis with Palivizumab compared with placebo (5.3% vs. 9.7%, respectively; $P < 0.005$).[15]

A systematic literature review and meta-analysis[128] conducted in 2014 combined the results from five randomized, placebo-controlled trials of palivizumab and assessed the safety and efficacy of palivizumab. The five studies included in the review were the IMpact-RSV trial,[121] the Feltes *et al*. study,[15] and three supplementary, nonpivotal trials, MAKI,[129] Subramanian[60] and Tasyo.[128] MAKI trial (2013) focused on the development of recurrent wheezing in preterm infants (33wGA to 35wGA) following the use of palivizumab for the prevention of RSV infection.[129] Subramanian (1998) was a Phase I/II multicenter, randomized, double-blind, placebo-controlled, dose-escalation trial of palivizumab on preterm infants (≤35wGA), and young children with BPD.[60] Tavsu (2014) assessed RSV-related hospitalization of preterm infants (<32wGA) following RSV prophylaxis with palivizumab.[130]

In the combined analysis, it was observed that palivizumab was highly effective at reducing RSV-related hospitalizations compared with placebo (odds ratio [OR]: 0.41; 95% CI: 0.31–0.55; $P < 0.00001$).[128]

Palivizumab reduces length of hospital stay

Although prophylaxis with palivizumab significantly reduces the incidence of RSV hospitalizations, some infants, and young children may still develop the breakthrough disease and require hospitalization. In the IMpact-RSV study, infants and young children randomized to palivizumab spent significantly fewer days in the hospital, required less supplemental oxygen and spent fewer days with a moderate or severe LRTI ($P < 0.001$ for all).[121]

Similar to the IMpact-RSV study, young children with HS-CHD receiving palivizumab prophylaxis had

significantly fewer days of RSV hospitalization ($P < 0.005$) and increased oxygen requirement ($P < 0.05$).[15]

Palivizumab reduces rates of wheezing and/asthma

RSV infection is implicated in the development of recurrent wheezing and asthma in early childhood and later life.[39,129,131-136]

As such, it is speculated that prevention of RSV infection should reduce the rate of development of childhood recurrent wheezing and asthma. A double-blind, placebo-controlled trial from The Netherlands was performed to investigate the potential of Palivizumab in preventing the development of RSV-related wheezing during an infant's 1st year of life[129] RSV prophylaxis was shown to confer a relative reduction of 61% (95% CI: 56-65) in the total number of wheezing days during the 1st year of life (1.8% vs. 4.5%).[129]

During the 1-year follow-up period, the proportion of infants with recurrent wheeze was 10% lower in infants who received palivizumab compared with infants who did not ($P < 0.05$).

These data confirm that early RSV disease is an important mechanism in the pathogenesis of wheezing morbidity in this specific population and that prevention of early RSV disease may impact beneficially on the odds of developing wheezing during the 1st year of age.[129]

To determine whether immune-prophylaxis with palivizumab during infancy was associated with decreased childhood asthma, a retrospective cohort investigation was performed between 1996 and 2003.[137] Asthma was defined as 4.5–6 years of age and by using data from asthma-specific health-care visits and medication fills. Using multivariate logistic regression and propensity-score matched analysis, it was shown that infants who had 70% or greater adherence to palivizumab had decreased odds of developing asthma compared with infants with 20% or less adherence (OR: 0.62; 95% CI: 0.50–0.78).[137] RSV infections have been most frequently documented about asthma inception; it is possible that immune responses unique to this virus might also play a role in these outcomes.[138]

Recurrent wheezing may also develop in young children following RSV infection in infancy.[39,129,131-136]

A prospective multicenter international cohort study of preterm infants was conducted to examine the relationship between RSV-related LRTIs in early life and rates of subsequent recurrent wheezing.[127] The study enrolled 191 preterm infants (≤35wGA) who had previously received palivizumab before 6 months of age and 230 who had never received palivizumab (76 who had been hospitalized due to RSV and 154 who had not). This study did not include infants with CLD or CHD. During the 2-year follow-up period, beginning at a mean age of 19 months, the incidence of reported recurrent wheezing was assessed according to the following definitions:[127]

- An episode of wheezing: One or more consecutive days of wheezing, preceded and followed by a healthy period of at least 1 week
- Recurrent wheezing: Three or more episodes of wheezing in a 12-month period, not necessarily documented by a physician
- Physician-diagnosed recurrent wheezing: Three or more physician-diagnosed episodes of wheezing in a 12-month period.

A reduced incidence of recurrent wheezing was observed to be statistically significant in young children who previously received palivizumab compared with young children who have never received palivizumab (13% and 26%, respectively; $P < 0.005$)[127]

Safety

Safety data revealed that palivizumab at a dose of 15 mg/kg IM is safe and well tolerated.[139] In general, there were few differences in adverse event (AE) incidence among patients who had received palivizumab and those who had received placebo.[139]

The most common adverse effects were erythema at the injection site, fever, or diarrhea.[139] Discontinuation of palivizumab due to a drug-related AE is rare.

At a local level, a Phase II, single-arm, single-center, noncomparative, open-label, prospective study conducted in Saudi Arabia (Al-Alaiyan, 2015 [125]), enrolled children at high risk for RSV infection and introduced up to seven monthly injections of palivizumab (15 mg/kg) during the 2000–2001 RSV season. Key enrollment criteria were no previous exposure to palivizumab and gestational age ≤35 weeks, ≤6 months of age at enrollment, or CLD and ≤24 months of age at enrollment. The aim of the study was to assess the safety, immunogenicity, and pharmacokinetics of palivizumab as an extended seven-dose regimen. Of 18 enrolled patients, 17 patients received seven palivizumab injections. The study concluded that an extended palivizumab regimen of up to seven monthly doses during the RSV season exhibited an acceptable safety profile in children at high risk for RSV infection in Saudi Arabia.[125]

Palivizumab reduces all-cause mortality rates

Prophylaxis with palivizumab has been shown to be associated with a reduction in all-cause mortality among preterm infants at high risk. A systematic review

and meta-analysis of published literature between 1990 and 2007 was performed, including all RCTs, and prospective or retrospective cohort studies[140] Overall, it was observed that the all-cause mortality due to severe RSV disease was 0.19% in infants who received Palivizumab compared with 0.53% for infants without prophylaxis (OR: 0.30; 95% CI: 0.17-0.55).[140]

Cost benefit analysis

Several economic analyses of RSV immune-prophylaxis have been published and reviewed.[140-142] In general, cost-effectiveness studies are challenging to design and to compare since the items involved in the cost-effectiveness analysis vary considerably among Countries, social health-care systems, and pricing of the drug in different areas of the world.

For all the above-mentioned benefits of palivizumab the panel recommends the use of palivizumab for the immune-prophylaxis against RSV as per Table 1 and documentation as per Table 2.

Also, the below considerations should be well noted

- RSV clinics shall dispense RSV prophylaxis from the beginning of October until the end of March
- Palivizumab should be administered up to a maximum of 5 monthly doses (15 mg/kg/dose administered intramuscularly once every 28 days) during the RSV season to infants who qualify for prophylaxis. A child with a history of a severe allergic reaction following a dose of palivizumab should not receive additional doses
- Qualified infants born during the RSV season must receive fewer doses according to their month of birth. For example, infants born in January would receive their last dose in March
- Injection palivizumab should be stored in a refrigerator at 2°C–8°C
- To reduce the risk for RSV and other viral infections, all infants, especially preterm infants, should be offered breast milk. The parents should be instructed to avoid smoke exposure, attendance at large group childcare during the first winter season and contact with ill people
- It is recommended that household members should be immunized against influenza and practice good hand and cough hygiene
- Palivizumab does not interfere with routine childhood immunizations.

Conclusion

In summary, bronchiolitis is the most common reason for hospital admission in the infancy period and is a major burden for any healthcare system.

According to the current evidence, management of bronchiolitis is mainly supportive and consists of oxygen

Table 1: Recommendations on using Palivizumab across different patients categories.

Patient segment	Recommendations	Level of evidence
Early preterm (≤28 weeks, 6 days GA)	≤12 months of age	1B
Mid preterm (29 weeks GA, 0 days to 32 weeks, 6 days GA)	≤6 months of age	1B
Late preterm (33 weeks, 0 days weeks GA to 35 weeks, 0 days GA)	≤6 months of age at the start of the RSV season OR born during RSV season with at least one of the following risk factors Attendance at child care Children <5 years of age who live permanently in the same household (including siblings) Exposure to environmental air pollutants	1B
Infants and children with CLD	<12 months for all; <24 months if still receiving medications for CLD within 6 months from the beginning of the epidemic season	1B
Infants and children with hemodynamically significant CHD	<12 months for all; <24 months if still receiving medications for the cardiac condition <6 months from the beginning of the epidemic season. Postoperative dose after cardio bypass	1B
Children with anatomic pulmonary abnormalities or neuromuscular disorder	<24 months may be considered for infants with impaired ability to handle respiratory secretions	3B
Immunocompromised children	<24 months may be considered for children who are profoundly immunocompromised during the RSV season	2B
Children with down syndrome	Recommended in children with accompanying qualifying heart disease, CLD, airway clearance issues, or prematurity (<35 weeks, 0 days GA)	2B
Children with cystic fibrosis	<12 months with clinical evidence of CLD and/or nutritional compromise <24 months with manifestations of severe lung disease OR weight for length <10th percentile	2A
Special situations: If an infant who is receiving prophylaxis experiences a breakthrough of RSV	If an infant who is receiving prophylaxis experiences a breakthrough of RSV, the monthly prophylaxis should continue as planned until a maximum of 5 doses have been administered	3B

RSV=Respiratory Syncytial Virus, OR=Odds ratio, CLD=Chronic lung disease

Table 2: Respiratory syncytial virus prophylaxis program

Referral form

Part A and B to be filled by referring physician and to be sent to Email: email of the coordinator

Contact info of the coordinator (extension)

A. Patient information

Patient's name MRN

Patient's date of birth / / Gestational age

Day Month Year

Gender □ Male □ Female Contact number

Referring team/physician Bleep Ext

B. Criteria for prophylaxis

□ Born <29 weeks gestation and aged ≤12 months at the start of, or during the local RSV season (after October 1, year)

□ Infants born prematurely at 29-32 weeks gestation and aged ≤6 months at the start of, or during the local RSV season. (born after May 1,year) Gestational age:

□ 29 weeks □ 30 weeks □ 31 weeks □ 32 weeks

□ Infants 33-35 weeks gestation and aged ≤6 months (born after May 1, Year) at the start of, or during the local RSV season with one or more risk factors: □ Child care attendance

□ School – aged siblings (<5 years)

□ Exposure to environmental air pollutants

□ Children <24 months of age at the start of, or during the local RSV season with BPD/CLD and who required oxygen and/or medical therapy within the 6 months preceding the RSV season

Diagnosis : Treatment

□ Children <24 month of age at the start of, or during the local RSV season who require daily respiratory treatments for conditions that adversely affect respiratory function such neuromuscular conditions and GE reflux disease with recurrent aspiration

□ Children <24 months of age at the start of, or during the local RSV season with hemodynamically significant congenital heart disease

Diagnosis Treatment

Children with cystic fibrosis as below

□ <12 months of age at the start of, or during the local RSV season with clinical evidence of CLD and/or nutritional compromise

□ <24 months of age at the start of, or during the local RSV season with manifestations of severe lung disease OR weight for length <10th percentile

Diagnosis Treatment

□ Children <24 months of age at the start of, or during the local RSV season who are profoundly immunocompromised during the RSV season

Diagnosis Treatment

C. RSV immunoprophylaxis doses "This part to be filled by RSV Team"

Please enter the patient's current body weight in kilograms and the date of injection in the appropriate boxes below·

Complete only the boxes for the current injection request

Date of injection #1	Date of injection #2	Date of injection #3	Date of injection #4	Date of injection #5	Date of injection #6]	Date of injection #7
Body weight (kg)	Body weight (kg)	Body weight (kg)	Body weight (kg)	Body weight (kg)	Body weight (kg)	Body weight (kg)
Dose (mg)	Dose (mg)	Dose (mg)	Dose (mg)	Dose (mg)	Dose (mg)	Dose (mg)
Doctor signature	Doctor signature	Doctor signature	Doctor signature	Doctor signature	Doctor signature	Doctor signature

RSV=Respiratory Syncytial Virus, CLD=Chronic lung disease, BPD=Bronchopulmonary dysplasia

administration, clearing the nasal airway secretions, and fluid balance maintenance.

Clinicians should pay special attention to the infants belonging to the high-risk groups for severe bronchiolitis.

There is growing evidence that hypertonic saline is an effective modality for treatment of inpatients as it is found to reduce the length of hospital stay. The available data does not support the routine use of bronchodilators, thus clinicians should limit their use to those cases with positive response only. There is modest benefit of using racemic epinephrine, and steroids whether inhaled or systemic are not effective. Some promising data exist for the use of Heliox and of noninvasive strategies of ventilation in severe cases, but more research is needed before a clear recommendation can be issued.

Currently, there is no available vaccine for RSV, the major causative pathogen of bronchiolitis, and immune-prophylaxis with palivizumab remains the mainstay of prevention in high-risk groups who qualify for this treatment. Cohorting, isolation, strict hygiene measures including accurate hand washing and use of personal equipment measures are crucial.

Acknowledgments

We would like to thank the two international experts Paolo Manzoni, MD, PhD and Xavier Carbonell-Estrany, MD, PhD for reviewing this manuscript.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Bronchiolitis Guideline Team, Cincinnati Children's Hospital Medical Center: Evidence based clinical practice guideline for medical management of bronchiolitis in infants 1 year of age or less presenting with a first time episode. 2005. p. 1-13. Available from: http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/bronchiolitis.htm.
2. Nicolai A, Ferrara M, Schiavariello C, Gentile F, Grande ME, Alessandroni C, *et al*. Viral bronchiolitis in children: A common condition with few therapeutic options. Early Hum Dev 2013;89 Suppl 3:S7-11.
3. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. Pediatrics 2006;118:1774-93.
4. Zorc JJ, Hall CB. Bronchiolitis: Recent evidence on diagnosis and management. Pediatrics 2010;125:342-9.
5. Nagakumar P, Doull I. Current therapy for bronchiolitis. Arch Dis Child 2012;97:827-30.
6. Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, *et al*. Clinical practice guideline: The diagnosis, management, and prevention of bronchiolitis. Pediatrics 2014;134:e1474-502. [Erratum in: Pediatrics 2014;136:782].
7. Baumer JH. SIGN guideline on bronchiolitis in infants. Arch Dis Child Educ Pract Ed 2007;92:ep149-51.
8. Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, *et al*. Clinical practice guideline: The diagnosis, management, and prevention of bronchiolitis. Pediatrics. 2014:peds-2014.
9. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011;128:305-10.
10. Øymar K, Skjerven HO, Mikalsen IB. Acute bronchiolitis in infants, a review. Scand J Trauma Resusc Emerg Med 2014;22:23.
11. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, *et al*. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: A systematic review and meta-analysis. Lancet 2010;375:1545-55.
12. Stockman LJ, Curns AT, Anderson LJ, Fischer-Langley G. Respiratory syncytial virus-associated hospitalizations among infants and young children in the United States, 1997-2006. Pediatr Infect Dis J 2012;31:5-9.
13. Zhang Q, Guo Z, Langley JM, Bai Z. Respiratory syncytial virus-associated Intensive Care Unit admission in children in Southern China. BMC Res Notes 2013;6:447.
14. Bakir TM, Halawani M, Ramia S. Viral aetiology and epidemiology of acute respiratory infections in hospitalized Saudi children. J Trop Pediatr 1998;44:100-3.
15. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH Jr., *et al*. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003;143:532-40.
16. Leung AK, Kellner JD, Davies HD. Respiratory syncytial virus bronchiolitis. J Natl Med Assoc 2005;97:1708.
17. Al-Hajjar S, Akhter J, al Jumaah S, Hussain Qadri SM. Respiratory viruses in children attending a major referral centre in Saudi Arabia. Ann Trop Paediatr 1998;18:87-92.
18. Ralston S, Hill V. Incidence of apnea in infants hospitalized with respiratory syncytial virus bronchiolitis: A systematic review. J Pediatr 2009;155:728-33.
19. Meissner HC. Selected populations at increased risk from respiratory syncytial virus infection. Pediatr Infect Dis J 2003;22:S40-4.
20. Tregoning JS, Schwarze J. Respiratory viral infections in infants: Causes, clinical symptoms, virology, and immunology. Clin Microbiol Rev 2010;23:74-98.
21. Lambert L, Sagfors AM, Openshaw PJ, Culley FJ. Immunity to RSV in early-life. Front Immunol 2014;5:466.
22. Flaherman VJ, Ragins AI, Li SX, Kipnis P, Masaquel A, Escobar GJ, *et al*. Frequency, duration and predictors of bronchiolitis episodes of care among infants ≥32 weeks gestation in a large integrated healthcare system: A retrospective cohort study. BMC Health Serv Res 2012;12:144.
23. Horn SD, Smout RJ. Effect of prematurity on respiratory syncytial virus hospital resource use and outcomes. J Pediatr 2003;143:S133-41.
24. Panozzo CA, Fowlkes AL, Anderson LJ. Variation in timing of respiratory syncytial virus outbreaks: Lessons from national surveillance. Pediatr Infect Dis J 2007;26:S41-5.
25. Chen ZR, Ji W, Wang YQ, Yan YD, Shao XJ, Zhang XL, *et al*. Etiology of acute bronchiolitis and the relationship with meteorological conditions in hospitalized infants in china. J Formos Med Assoc 2014;113:463-9.
26. McNamara PS, Flanagan BF, Smyth RL, Hart CA. Impact of human metapneumovirus and respiratory syncytial virus co-infection in severe bronchiolitis. Pediatr Pulmonol 2007;42:740-3.
27. Williams JV, Harris PA, Tollefson SJ, Halburnt-Rush LL, Pingsterhaus JM, Edwards KM, *et al*. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. N Engl J Med 2004;350:443-50.
28. Budhiraja S, Verma R, Shields MD. The management of acute bronchiolitis in infants. Paediatr Child Health 2013;23:296-300.
29. Notario G, Vo P, Gooch K, Deaton R, Wu X, Harris B, *et al*. Respiratory syncytial virus-related hospitalization in premature infants without bronchopulmonary dysplasia: subgroup efficacy analysis of the IMpact-RSV trial by gestational age group. Pediatric Health, Medicine and Therapeutics 2014;5:43-8.
30. Perlstein PH, Kotagal UR, Bolling C, Steele R, Schoettker PJ, Atherton HD, *et al*. Evaluation of an evidence-based guideline for bronchiolitis. Pediatrics 1999;104:1334-41.
31. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA, *et al*. Incubation periods of acute respiratory viral infections: A systematic review. Lancet Infect Dis 2009;9:291-300.
32. Willwerth BM, Harper MB, Greenes DS. Identifying hospitalized infants who have bronchiolitis and are at high risk for apnea. Ann Emerg Med 2006;48:441-7.
33. Fleming DM, Pannell RS, Cross KW. Mortality in children from influenza and respiratory syncytial virus. J Epidemiol Community Health 2005;59:586-90.
34. Ramos Fernández JM, Cordón Martínez A, Galindo Zavala R, Urda Cardona A. Validation of an acute bronchiolitis severity scale. An Pediatr (Barc) 2014;81:3-8.
35. Justicia-Grande AJ, Pardo-Seco J, Cebey-López M, Vilanova-Trillo L, Gómez-Carballa A, Rivero-Calle I, *et al*. Development and validation of a new clinical scale for infants with acute respiratory infection: The ReSVinet scale. PLoS One 2016;11:e0157665.
36. Aintablian N, Walpita P, Sawyer MH. Detection of bordetella pertussis and respiratory synctial virus in air samples from hospital rooms. Infect Control Hosp Epidemiol 1998;19:918-23.
37. McCulloh R, Koster M, Ralston S, Johnson M, Hill V, Koehn K, *et al*. Use of intermittent vs. continuous pulse oximetry for nonhypoxemic infants and young children hospitalized for bronchiolitis: A randomized clinical trial. JAMA Pediatr 2015;169:898-904.
38. Freymuth F, Vabret A, Cuvillon-Nimal D, Simon S, Dina J, Legrand L, *et al*. Comparison of multiplex PCR assays and conventional techniques for the diagnostic of respiratory

virus infections in children admitted to hospital with an acute respiratory illness. J Med Virol 2006;78:1498-504.
39. Antunes H, Rodrigues H, Silva N, Ferreira C, Carvalho F, Ramalho H, *et al*. Etiology of bronchiolitis in a hospitalized pediatric population: Prospective multicenter study. J Clin Virol 2010;48:134-6.
40. Kuypers J, Wright N, Ferrenberg J, Huang ML, Cent A, Corey L, *et al*. Comparison of real-time PCR assays with fluorescent-antibody assays for diagnosis of respiratory virus infections in children. J Clin Microbiol 2006;44:2382-8.
41. Shaw KN, Bell LM, Sherman NH. Outpatient assessment of infants with bronchiolitis. Am J Dis Children 1991;145:151-5.
42. Schuh S, Lalani A, Allen U, Manson D, Babyn P, Stephens D, *et al*. Evaluation of the utility of radiography in acute bronchiolitis. J Pediatr 2007;150:429-33.
43. Moschino L, Mario F, Carraro S, Visentin F, Zanconato S, Baraldi E, *et al*. Is nasal suctioning warranted before measuring O2 saturation in infants with bronchiolitis? Arch Dis Child 2016;101:114-5.
44. Lehtinen P, Jartti T, Virkki R, Vuorinen T, Leinonen M, Peltola V, *et al*. Bacterial coinfections in children with viral wheezing. Eur J Clin Microbiol Infect Dis 2006;25:463-9.
45. Cruz AT, Cazacu AC, Greer JM, Demmler GJ. Performance of a rapid assay (Binax NOW) for detection of respiratory syncytial virus at a children's hospital over a 3-year period. J Clin Microbiol 2007;45:1993-5.
46. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, *et al*. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009;360:588-98.
47. Parikh K, Hall M, Teach SJ. Bronchiolitis management before and after the AAP guidelines. Pediatrics 2014;133:e1-7.
48. Unger S, Cunningham S. Effect of oxygen supplementation on length of stay for infants hospitalized with acute viral bronchiolitis. Pediatrics 2008;121:470-5.
49. Fitzgerald DA, Kilham HA. Bronchiolitis: assessment and evidence-based management. Med J Aust 2004;180:399.
50. Landau LI. Current pharmacological treatments for bronchiolitis are useless. The case for the con's. Paediatr Respir Rev 2006;7 Suppl 1:S101-3.
51. Da Dalt L, Bressan S, Martinolli F, Perilongo G, Baraldi E. Treatment of bronchiolitis: State of the art. Early Hum Dev 2013;89 Suppl 1:S31-6.
52. Roqué i Figuls M, Giné-Garriga M, Granados Rugeles C, Perrotta C. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. Cochrane Database Syst Rev 2012:CD004873.
53. Umoren R, Odey F, Meremikwu MM. Steam inhalation or humidified oxygen for acute bronchiolitis in children up to three years of age. Cochrane Database Syst Rev 2011:CD006435.
54. Plint AC, Grenon R, Klassen TP, Johnson DW. Bronchodilator and steroid use for the management of bronchiolitis in Canadian pediatric emergency departments. CJEM 2015;17:46-53.
55. Hodge D, Chetcuti PA. RSV: Management of the acute episode. Paediatr Respir Rev 2000;1:215-20.
56. Hall CB, Douglas RG Jr., Geiman JM. Possible transmission by fomites of respiratory syncytial virus. J Infect Dis 1980;141:98-102.
57. Hartling L, Wiebe N, Russell K, Patel H, Klassen TP. Epinephrine for bronchiolitis. Cochrane Database Syst Rev 2004: CD003123.
58. King VJ, Viswanathan M, Bordley WC, Jackman AM, Sutton SF, Lohr KN, *et al*. Pharmacologic treatment of bronchiolitis in infants and children: A systematic review. Arch Pediatr Adolesc Med 2004;158:127-37.
59. Turner T, Wilkinson F, Harris C, Mazza D, Health for Kids Guideline Development Group. Evidence based guideline for the management of bronchiolitis. Aust Fam Physician 2008;37:6-13.
60. Greenough A. Role of ventilation in RSV disease: CPAP, ventilation, HFO, ECMO. Paediatr Respir Rev 2009;10 Suppl 1:26-8.
61. Sarrell EM, Tal G, Witzling M, Someck E, Houri S, Cohen HA, *et al*. Nebulized 3% hypertonic saline solution treatment in ambulatory children with viral bronchiolitis decreases symptoms. Chest 2002;122:2015-20.
62. Mandelberg A, Tal G, Witzling M, Someck E, Houri S, Balin A, *et al*. Nebulized 3% hypertonic saline solution treatment in hospitalized infants with viral bronchiolitis. Chest 2003;123:481-7.
63. Mandelberg A, Amirav I. Hypertonic saline or high volume normal saline for viral bronchiolitis: Mechanisms and rationale. Pediatr Pulmonol 2010;45:36-40.
64. Daviskas E, Anderson SD, Gonda I, Eberl S, Meikle S, Seale JP, *et al*. Inhalation of hypertonic saline aerosol enhances mucociliary clearance in asthmatic and healthy subjects. Eur Respir J 1996;9:725-32.
65. Kuzik BA, Al-Qadhi SA, Kent S, Flavin MP, Hopman W, Hotte S, *et al*. Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. J Pediatr 2007;151:266-70, 270.e1.
66. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev 2008: CD006458.
67. Ralston S. Repeated dosing of nebulised 5% saline improves respiratory scores in inpatients with mild to moderate bronchiolitis at 48 h. Evid Based Med 2011;16:82-3.
68. Blom DJ, Ermers M, Bont L, van Woensel JB, Van Aalderen WM. WITHDRAWN: Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitic wheezing. Cochrane Database Syst Rev 2011: CD004881.
69. Sumner A, Coyle D, Mitton C, Johnson DW, Patel H, Klassen TP, *et al*. Cost-effectiveness of epinephrine and dexamethasone in children with bronchiolitis. Pediatrics 2010;126:623-31.
70. Plint AC, Johnson DW, Patel H, Wiebe N, Correll R, Brant R, *et al*. Epinephrine and dexamethasone in children with bronchiolitis. N Engl J Med 2009;360:2079-89.
71. Alansari K, Sakran M, Davidson BL, Ibrahim K, Alrefai M, Zakaria I, *et al*. Oral dexamethasone for bronchiolitis: A randomized trial. Pediatrics 2013;132:e810-6.
72. Bialy L, Foisy M, Smith M, Fernandes RM. The Cochrane Library and the treatment of bronchiolitis in children: An overview of reviews. Evid Based Child Health Cochrane Rev J 2011;6:258-75.
73. Ochoa Sangrador C, González de Dios J, Research Group of the aBREVIADo Project. Overuse of bronchodilators and steroids in bronchiolitis of different severity: Bronchiolitis-study of variability, appropriateness, and adequacy. Allergol Immunopathol (Madr) 2014;42:307-15.
74. Ventre K, Randolph A. WITHDRAWN: Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. Cochrane Database Syst Rev 2010: CD000181.
75. Kuppermann N, Bank DE, Walton EA, Senac MO Jr., McCaslin I. Risks for bacteremia and urinary tract infections in young febrile children with bronchiolitis. Arch Pediatr Adolesc Med 1997;151:1207-14.
76. Greenes DS, Harper MB. Low risk of bacteremia in febrile children with recognizable viral syndromes. Pediatr Infect Dis J 1999;18:258-61.
77. Purcell K, Fergie J. Concurrent serious bacterial infections in 912 infants and children hospitalized for treatment of respiratory syncytial virus lower respiratory tract infection. Pediatr Infect Dis J 2004;23:267-9.
78. Vogel AM, Lennon DR, Harding JE, Pinnock RE, Graham DA, Grimwood K, *et al*. Variations in bronchiolitis management between five New Zealand hospitals: Can we do better? J Paediatr Child Health 2003;39:40-5.
79. Thorburn K, Harigopal S, Reddy V, Taylor N, van Saene HK. High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. Thorax

2006;61:611-5.
80. Kneyber MC, Blussé van Oud-Alblas H, van Vliet M, Uiterwaal CS, Kimpen JL, van Vught AJ, *et al*. Concurrent bacterial infection and prolonged mechanical ventilation in infants with respiratory syncytial virus lower respiratory tract disease. Intensive Care Med 2005;31:680-5.
81. Kabir ML, Haq N, Hoque M, Ahmed F, Amin R, Hossain A, *et al*. Evaluation of hospitalized infants and young children with bronchiolitis – A multi centre study. Mymensingh Med J 2003;12:128-33.
82. Christakis DA, Cowan CA, Garrison MM, Molteni R, Marcuse E, Zerr DM, *et al*. Variation in inpatient diagnostic testing and management of bronchiolitis. Pediatrics 2005;115:878-84.
83. El Sayed MF, Tamim H, Jamal D, Mumtaz G, Melki I, Yunis K, *et al*. Prospective study on antibiotics misuse among infants with upper respiratory infections. Eur J Pediatr 2009;168:667-72.
84. Levin D, Tribuzio M, Green-Wrzesinki T, Ames B, Radwan S, Jarvis JD, *et al*. Empiric antibiotics are justified for infants with respiratory syncytial virus lower respiratory tract infection presenting with respiratory failure: A prospective study and evidence review. Pediatr Crit Care Med 2010;11:390-5.
85. McCallum GB, Morris PS, Chatfield MD, Maclennan C, White AV, Sloots TP, *et al*. A single dose of azithromycin does not improve clinical outcomes of children hospitalised with bronchiolitis: A randomised, placebo-controlled trial. PLoS One 2013;8:e74316.
86. Tahan F, Ozcan A, Koc N. Clarithromycin in the treatment of RSV bronchiolitis: A double-blind, randomised, placebo-controlled trial. Eur Respir J 2007;29:91-7.
87. Kneyber MC, van Woensel JB, Uijtendaal E, Uiterwaal CS, Kimpen JL; Dutch Antibiotics in RSV Trial (DART) Research Group, *et al*. Azithromycin does not improve disease course in hospitalized infants with respiratory syncytial virus (RSV) lower respiratory tract disease: A randomized equivalence trial. Pediatr Pulmonol 2008;43:142-9.
88. Farley R, Spurling GK, Eriksson L, Del Mar CB. Antibiotics for bronchiolitis in children under two years of age. Cochrane Database Syst Rev 2014: CD005189.
89. Spurling GK, Doust J, Del Mar CB, Eriksson L. Antibiotics for bronchiolitis in children. Cochrane Database Syst Rev 2011:CD005189.
90. Liet JM, Ducruet T, Gupta V, Cambonie G. Heliox inhalation therapy for bronchiolitis in infants. Cochrane Database Syst Rev 2010: CD006915.
91. Ralston S, Roohi M. A randomized, controlled trial of nasal phenylephrine in infants hospitalized for bronchiolitis. J Pediatr 2008;153:795-8.
92. Everard ML, Bara A, Kurian M, Elliott TM, Ducharme F, Mayowe V, *et al*. Anticholinergic drugs for wheeze in children under the age of two years. Cochrane Database Syst Rev 2005: CD001279.
93. Boogaard R, Hulsmann AR, van Veen L, Vaessen-Verberne AA, Yap YN, Sprij AJ, *et al*. Recombinant human deoxyribonuclease in infants with respiratory syncytial virus bronchiolitis. Chest 2007;131:788-95.
94. Jat KR, Chawla D. Surfactant therapy for bronchiolitis in critically ill infants. Cochrane Database Syst Rev 2015;???: CD009194.
95. Ventre K, Haroon M, Davison C. Surfactant therapy for bronchiolitis in critically ill infants. Cochrane Database Syst Rev 2006: CD005150.
96. Liu F, Ouyang J, Sharma AN, Liu S, Yang B, Xiong W, *et al*. Leukotriene inhibitors for bronchiolitis in infants and young children. Cochrane Database Syst Rev 2015: CD010636.
97. Bisgaard H; Study Group on Montelukast and Respiratory Syncytial Virus. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. Am J Respir Crit Care Med 2003;167:379-83.
98. Amirav I, Luder AS, Kruger N, Borovitch Y, Babai I, Miron D, *et al*. A double-blind, placebo-controlled, randomized trial of montelukast for acute bronchiolitis. Pediatrics 2008;122:e1249-55.
99. Karanfil LV, Conlon M, Lykens K, Masters CF, Forman M, Griffith ME, *et al*. Reducing the rate of nosocomially transmitted respiratory syncytial virus. Am J Infect Control 1999;27:91-6.
100. Isaacs D, Dickson H, O'Callaghan C, Sheaves R, Winter A, Moxon ER, *et al*. Handwashing and cohorting in prevention of hospital acquired infections with respiratory syncytial virus. Arch Dis Child 1991;66:227-31.
101. Hall CB, Douglas RG Jr., Geiman JM, Messner MK. Nosocomial respiratory syncytial virus infections. N Engl J Med 1975;293:1343-6.
102. Paes BA, Mitchell I, Banerji A, Lanctôt KL, Langley JM. A decade of respiratory syncytial virus epidemiology and prophylaxis: Translating evidence into everyday clinical practice. Can Respir J 2011;18:e10-9.
103. Scheltema NM, Gentile A, Lucion F, Nokes DJ, Munywoki PK, Madhi SA, *et al*. Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): A retrospective case series. Lancet Glob Health 2017;5:e984-91.
104. Al-Shehri MA, Sadeq A, Quli K. Bronchiolitis in Abha, Southwest Saudi Arabia: Viral etiology and predictors for hospital admission. West Afr J Med 2005;24:299-304.
105. Murawski MR, Bowen GN, Cerny AM, Anderson LJ, Haynes LM, Tripp RA, *et al*. Respiratory syncytial virus activates innate immunity through toll-like receptor 2. J Virol 2009;83:1492-500.
106. Wark PA, McDonald V, Jones AP. Nebulised hypertonic saline for cystic fibrosis. Cochrane Database Syst Rev 2005: CD001506.
107. Simoes EA, Groothuis JR, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick LM, *et al*. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. J Pediatr 2007;151:34-42, 42.e1.
108. Al-Ansari K, Sakran M, Davidson BL, El Sayyed R, Mahjoub H, Ibrahim K, *et al*. Nebulized 5% or 3% hypertonic or 0.9% saline for treating acute bronchiolitis in infants. J Pediatr 2010;157:630-4, 634.e1.
109. Jacobs JD, Foster M, Wan J, Pershad J. 7% hypertonic saline in acute bronchiolitis: A randomized controlled trial. Pediatrics 2014;133:e8-13.
110. Simoes EA, Carbonell-Estrany X. Impact of severe disease caused by respiratory syncytial virus in children living in developed countries. Pediatr Infect Dis J 2003;22:S13-8.
111. Shi T, McAllister DA, O'Brien KL, Simoes EA, Madhi SA, Gessner BD, *et al*. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: A systematic review and modelling study. Lancet 2017;390:946-58.
112. Bukhari EE, Elhazmi MM. Viral agents causing acute lower respiratory tract infections in hospitalized children at a tertiary care center in Saudi Arabia. Saudi Med J 2013;34:1151-5.
113. Al-Majhdi FN, Al-Jarallah A, Elaeed M, Latif A, Gissmann L, Amer HM. Prevalence of respiratory syncytial virus infection in Riyadh during the winter season 2007-2008 and different risk factors impact. Int J Virol 2009;5:154-63.
114. Akhter J, Al-Johani S, Dugaishm F, Al-Hefdi R, Al-Hassan I. Etiology of respiratory viral infections using rapid virus isolation methods at a tertiary care center in Riyadh, Saudi Arabia. Saudi Pharm J 2009;17:177-81.
115. Meqdam MM, Subaih SH. Rapid detection and clinical features of infants and young children with acute lower respiratory tract infection due to respiratory syncytial virus. FEMS Immunol Med Microbiol 2006;47:129-33.
116. Shier M, Badr MA. Respiratory syncytial virus infection in patients visiting King Khaled university hospital. Minoufia Med J 2005;18:11-8.
117. Subramanian KN, Weisman LE, Rhodes T, Ariagno R, Sánchez PJ, Steichen J, *et al*. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in

premature infants and infants with bronchopulmonary dysplasia. MEDI-493 study group. Pediatr Infect Dis J 1998;17:110-5.
118. Al-Muhsen SZ. Clinical profile of respiratory syncytial virus (RSV) bronchiolitis in the intensive care unit at a tertiary care hospital. Curr Pediatr Res 2010;14.
119. Huang K, Incognito L, Cheng X, Ulbrandt ND, Wu H. Respiratory syncytial virus-neutralizing monoclonal antibodies motavizumab and palivizumab inhibit fusion. J Virol 2010;84:8132-40.
120. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998;102:531-7.
121. ABIM Foundation. American Board of Internal Medicine, ACP-ASIM Foundation. American College of Physicians-American Society of Internal Medicine, European Federation of Internal Medicine. Medical professionalism in the new millennium: A physician charter. Ann Intern Med 2002;136:243-6.
122. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics 2003;112:1442-6.
123. Romero JR. Palivizumab prophylaxis of respiratory syncytial virus disease from 1998 to 2002: Results from four years of palivizumab usage. Pediatr Infect Dis J 2003;22:S46-54.
124. Al-Alaiyan S, Pollack P, Notario GF. Safety and pharmacokinetics of extended use of palivizumab in Saudi Arabian infants and children. Drugs Context 2015;4. pii: 212270.
125. Lacaze-Masmonteil T, Rozé JC, Fauroux B, French Pediatricians' Group of Sunagis Patients' Name-Based Programs. Incidence of respiratory syncytial virus-related hospitalizations in high-risk children: Follow-up of a national cohort of infants treated with palivizumab as RSV prophylaxis. Pediatr Pulmonol 2002;34:181-8.
126. Simoes EA, Sondheimer HM, Top FH Jr., Meissner HC, Welliver RC, Kramer AA, *et al*. Respiratory syncytial virus immune globulin for prophylaxis against respiratory syncytial virus disease in infants and children with congenital heart disease. The cardiac study group. J Pediatr 1998;133:492-9.
127. Wegzyn C, Toh LK, Notario G, Biguenet S, Unnebrink K, Park C, *et al*. Safety and effectiveness of palivizumab in children at high risk of serious disease due to respiratory syncytial virus infection: A systematic review. Infect Dis Ther 2014;3:133-58.
128. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, *et al*. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med 2013;368:1791-9.
129. Tavsu I, Gursoy T, Dirman S, Erbil N, Ovali F. Palivizumab prophylaxis: Does it have any influence on the growth and development of the infants? Am J Perinatol 2014;31:667-72.
130. Gelfand EW. Pediatric asthma: A different disease. Proc Am Thoracic Soc 2009;6:278-82.
131. Singh AM, Moore PE, Gern JE, Lemanske RF Jr., Hartert TV. Bronchiolitis to asthma: A review and call for studies of gene-virus interactions in asthma causation. Am J Respir Crit Care Med 2007;175:108-19.
132. Resch B. Burden of respiratory syncytial virus infection in young children. World J Clin Pediatr 2012;1:8-12.
133. Martinez FD. Respiratory syncytial virus bronchiolitis and the pathogenesis of childhood asthma. Pediatr Infect Dis J 2003;22:S76-82.
134. Régnier SA, Huels J. Association between respiratory syncytial virus hospitalizations in infants and respiratory sequelae: Systematic review and meta-analysis. Pediatr Infect Dis J 2013;32:820-6.
135. Yoshihara S, Kusuda S, Mochizuki H, Okada K, Nishima S, Simões EA, *et al*. Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants. Pediatrics 2013;132:811-8.
136. Carroll KN, Gebretsadik T, Escobar GJ, Wu P, Li SX, Walsh EM, *et al*. Respiratory syncytial virus immunoprophylaxis in high-risk infants and development of childhood asthma. J Allergy Clin Immunol 2017;139:66-71.e3.
137. Lemanske RF. Viral infections and asthma inception. J Allergy Clin Immunol 2004;114:1023-6.
138. Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Vrca VB, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Evid Based Child Health Cochrane Rev J 2013;8:2243-376.
139. Checchia PA, Nalysnyk L, Fernandes AW, Mahadevia PJ, Xu Y, Fahrbach K, *et al*. Mortality and morbidity among infants at high risk for severe respiratory syncytial virus infection receiving prophylaxis with palivizumab: A systematic literature review and meta-analysis. Pediatr Crit Care Med 2011;12:580-8.
140. Wang D, Bayliss S, Meads C. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: A systematic review and additional economic modelling of subgroup analyses. Health Technol Assess 2011;15:iii-iv, 1-124.
141. Mesquita FD, Oliveira DB, Crema D, Pinez CM, Colmanetti TC, Thomazelli LM, *et al*. Rapid antigen detection test for respiratory syncytial virus diagnosis as a diagnostic tool. J Pediatr (Rio J) 2017;93:246-52.
142. Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie 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;154:55-61.