Recent advances in the management of acute bronchiolitis
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Abstract
Acute bronchiolitis is characterized by acute wheezing in infants or children and is associated with signs or symptoms of respiratory infection; it is rarely symptomatic in adults and the most common etiologic agent is respiratory syncytial virus (RSV). Usually it does not require investigation, treatment is merely supportive and a conservative approach seems adequate in the majority of children, especially for the youngest ones (<3 months); however, clinical scoring systems have been proposed and admission in hospital should be arranged in case of severe disease or a very young age or important comorbidities. Apnea is a very important aspect of the management of young infants with bronchiolitis. This review focuses on the clinical, radiographic, and pathologic characteristics, as well as the recent advances in management of acute bronchiolitis.

Introduction
Bronchiolitis is a general term used to describe a non-specific inflammatory injury that primarily affects the small airways (less than 2 mm in diameter). The term can describe a clinical syndrome or a constellation of histological abnormalities that may occur in a variety of disorders [1–3]. Primary bronchiolitis can develop into acute bronchiolitis, but also into constrictive bronchiolitis, respiratory bronchiolitis, follicular bronchiolitis, mineral dust airway disease and diffuse panbronchiolitis (Table 1); not all of them are associated with airflow limitation.

Definition and etiology
Acute bronchiolitis is rarely symptomatic in adults because total pulmonary resistance is influenced to a lesser extent by small airways. Inhalation injury, infections, drug-induced processes or known exposure to a predisposing factor before the onset of the disease are associated with acute bronchiolitis [4–9]. Examples of predisposing factors include inhalation of nitrogen oxides, ammonia, welding fumes, or food flavoring fumes (e.g. diacetyl) – infection with RSV, adenovirus, or Mycoplasma pneumoniae – and ingestion of busulfan, gold, or penicillamine. Other potential causes could be aspiration, lung and bone marrow transplantation, connective tissue diseases and Stevens–Johnson syndrome [10]. However, the term acute bronchiolitis generally refers to a disease characterized by acute wheezing in infants or children, associated with signs or symptoms of respiratory infection [11–13]. Bronchiolitis is a clinical diagnosis described as "a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort, wheezing and diffuse bilateral crackles in children less than 12 months of age" by the European Respiratory Society (ERS) and in children no less than 24 months by the American Academy of Pediatrics (AAP) [14]. Common viruses, such as rhinoviruses, which are typically limited to the upper respiratory tract, can trigger recurrent wheezing [15]. Approximately 20% of children develop acute bronchiolitis in the first year of life [16–19], mostly in winter, and 2–3% of them are hospitalized as a result [14,20–23]. The most common etiologic agent is RSV (60–80% of cases) [13,24,25] but adenoviruses, rhinoviruses, enteroviruses, influenza and parainfluenza viruses, and human metapneumovirus (HMPV) can also be responsible [14,26–28]; in particular, rhinovirus is the second most common virus inducing acute bronchiolitis, and HMPV seems to account for 3–19% of bronchiolitis cases [29,30]. Other pathogens are mycoplasma and...
Table 1. Classification of bronchiolar disorders Adapted from [1]

- Acute bronchiolitis
- Constrictive bronchiolitis
- Respiratory bronchiolitis
- Diffuse panbronchiolitis
- Follicular bronchiolitis
- Mineral dust airway disease
- Interstitial lung diseases with bronchiolar involvement (RB-ILD/DIP, HP, COP, pulmonary Langerhans’ cell histiocytosis, sarcoidosis, bronchiolocentric interstitial pneumonia)
- Large airway diseases with bronchiolar involvement (chronic bronchitis, bronchiectasis, asthma)
- Other bronchiolar disorders (e.g., diffuse aspiration bronchiolitis, lymphocytic bronchiolitis)

RB-ILD/DIP, respiratory bronchiolitis–associated interstitial lung disease/desquamative interstitial pneumonia; HP, hypersensitivity pneumonitis; COP, cryptogenic organizing pneumonia.

Chlamydia, and other fungal and mycobacterial infections [11,12,31–33]. Dual infections are reported in 20–30% of children, most commonly with RSV and either HMPV or rhinovirus [34], but whether concomitant infection modifies the severity of bronchiolitis is not known [18,34–39]. Pathological changes of the airways of children with bronchiolitis can explain symptoms of the disease and help in finding appropriate treatment [11,40]. The infection starts in the upper airways and spreads to the lower airways within a few days, with subsequent bronchial inflammation and invasion of white blood cells (mostly mononuclear cells), edema of the submucosa and adventitia [18,22]. Airways can be partially or totally obstructed by plugs of necrotic epithelium and fibrin [1,15,40], sometimes with a “ball-valve” mechanism, resulting in trapping of air distal to obstructed areas, atelectasis and mismatch of pulmonary ventilation and perfusion [21,22]. Smooth-muscle constriction seems to be much less important in the pathological process [15,22]. Epithelium damage may be caused directly by viruses [18] or indirectly by several chemokines, including macrophage inflammatory protein-1, interleukin (IL)-8, IL-6, IL-1, and Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES) [41,42]. These cytokines can recruit and activate neutrophils, lymphocytes, macrophages, eosinophils, and natural killer cells [41,42], and can also increase mucus production and airway hyper-reactivity [43].

Clinical picture and diagnosis

The most common clinical signs of bronchiolitis in children are tachypnea, tachycardia, and prolonged expiration [10,11]. Usually, a 2–6 month old infant presents with worsening respiratory symptoms, preceded by a 2–3 days history of rhinorrhea [44,45]. Fever is uncommon and rarely ≥40 degrees centigrade [46,47]. Cyanosis may be observed in severe cases [45], particularly in infants who were premature, with episodes of apnea at presentation [48] as well as feeding problems [18,22]. On examination, there are typically fine inspiratory crackles and/or expiratory wheeze [13], nasal flaring, high respiratory rate and chest retractions [10,11]; an alternative diagnosis should be sought if the infant is drowsy, lethargic, irritable, pale or mottled [45]. Risk factors for bronchiolitis, or a poor outcome, include prematurity, young age, male gender, period of birth, underlying lung disease (such as bronchopulmonary dysplasia), neuromuscular disease, heart disease, exposure to tobacco smoke, young maternal age, short duration/no breastfeeding, maternal asthma and poor socioeconomic factors [18,19,44,48]. Individual clinical findings on physical examination have limited value in predicting outcomes, because of the minute-to-minute variability [15,49]. Recently, specific gene polymorphisms have been identified [50,51], for example, vitamin D receptor gene may reveal neonatal vitamin D levels, associated with wheezing in infants [52,53]. In adults, bronchiolitis should be considered in patients who present with cough and dyspnea, especially when the symptoms do not follow a typical pattern for asthma or chronic obstructive pulmonary disease. The clinical setting may alert the clinician to suspect bronchiolitis; for example, recent toxic fume exposure, symptoms of viral infection, history of organ transplantation, or concomitant connective tissue disease [1]. Acute bronchiolitis usually does not require investigations [11,14,22,54,55]. Viral antigen tests usually have only a small predictive value [56]; the identification of specific agents can be limited to the hospital setting, where it can reduce use of antibiotics, number of investigations and length of hospitalization [18,57–59]. RSV infection should be confirmed by a nasopharyngeal aspirate and can be useful for infection control purposes [14,45]; however, this has been questioned by others [27]. A positive viral test could be useful to exclude bacterial infections in infants with bronchiolitis and fever during the first few months of life; some authors have shown that bacterial infections can accompany RSV infection, mostly in the urinary tract [60]. However, a prospective study of 218 patients excluded serious bacterial infections in young infants with fever [61]. Again, in the majority of cases, the diagnosis of bronchiolitis is clinical. Oxygen saturation should be measured [14,22], while blood gas measurement to detect hypercapnia is indicated only in critical cases [18,62]. Mansbach et al. demonstrated that a pulse oximetry level of 94% could be related to an increased likelihood of hospitalization [63]; Shaw et al. had previously revealed that mild hypoxia could correlate with a more severe
organizing pneumonia. Defined nodules on CT scans may correlate with areas of proliferative bronchiolitis on HRCT. Well or poorly-ground glass density is a characteristic finding of [72]. Subpleural distribution of patchy consolidation or disease, inhalation of toxic fumes, and previous infection in cases related to transplantation, collagen vascular can be seen with constrictive bronchiolitis, particularly [70,71]. Cylindric bronchial dilation or bronchiectasis difficult to distinguish severe asthma from bronchiolitis highly suggestive of bronchiolitis obliterans, it is often seldom necessary to think about a differential diagnosis. Asthma should also be considered in infants older than 12 months of age with recurrent episodes of wheezing [18]. When bronchiolitis is suspected in adults, the most helpful tests are chest imaging, usually a high resolution computerised tomography (HRCT) scan, and pulmonary function testing with diffusing capacity and ambulatory oximetry. The most consistent abnormalities on HRCT are expiratory air trapping (mosaic or diffuse) and bronchial wall thickening (e.g. centriflobular nodules and “v” or “y” shaped branching linear opacities) [66,67]. In addition, a pattern of diffuse ground glass opacity and a mosaic pattern of attenuation are seen in some patients [68,69]. Other than a mosaic pattern of attenuation, which is highly suggestive of bronchiolitis obliterans, it is often difficult to distinguish severe asthma from bronchiolitis [70,71]. Cylindric bronchial dilation or bronchiectasis can be seen with constrictive bronchiolitis, particularly in cases related to transplantation, collagen vascular disease, inhalation of toxic fumes, and previous infection [72]. Subpleural distribution of patchy consolidation or ground glass density is a characteristic finding of proliferative bronchiolitis on HRCT. Well or poorly-defined nodules on CT scans may correlate with areas of organizing pneumonia [73].

Management
A conservative approach to treatment seems adequate in the majority of children, especially for the youngest ones (<3 months) [21,22,72] and treatment is merely supportive. Clinical scoring systems have been proposed [62], but none have been formally accepted [44], although the New Zealand and Scotland guidelines have classified bronchiolitis into mild, moderate and severe (Table 2). Patients with uncomplicated bronchiolitis do not benefit from antibiotics [62]. Patients can deteriorate for 2–3 days after the onset of the disease but then start to improve [46], therefore hospital admission could be arranged after review if there is no improvement [46] and supplemental treatments should then be considered [31,74,75]. An important decision is whether to admit the patient to hospital and what are the indications for admission, candidates being severe disease, very young age, or important comorbidities (Table 3).

Apnea is a very important aspect of the management of young infants with bronchiolitis [15]. A retrospective study of 691 infants revealed that apnea can occur in 2.7% of cases [59], with young age and previous apneic episodes being the major risk factors [59]. Thresholds for oxygen therapy may influence outcomes: low values of oxygen saturation are representative of a higher risk of hospitalization [76] and, in these cases, hospitalization itself can be more prolonged [77]; administration of oxygen is therefore recommended for values of SpO2 <90% [14,77]. It is crucial to monitor oxygen saturation continuously during treatment [78], but monitoring can be slowed down or suspended as the child improves [14]. Recent studies have focused on indications and procedures of home oxygen therapy [79,80]. Adequate hydration is fundamental [1,21] as fever and tachypnoea may cause inadequate feeding and eventually poor hydration [81,82]. Oral feeding may be sustained and breastfeeding should be encouraged [44]. Enteral feeding by gastric tube, as boluses or continuously, should be started if the infant will not suck [78,82–87] as it can improve the nutritional status of infants and can be a direct route for breast milk administration [82,88]. However, it can interfere with breathing in compromised infants and intravenous fluids (IV) are preferred in these cases [21,22,45,82] to reduce the risk of aspiration [89,90].

| Feeding          | Mild bronchiolitis | Moderate bronchiolitis | Severe bronchiolitis |
|------------------|--------------------|------------------------|----------------------|
| Respiratory rate | <2 months >60/min  | Less than usual >60/min | Not interested >70/min |
| Chest wall recessions | Mild | Moderate Absent Severe |
| Nasal flare or grunting | Absent | Absent Present |
| SpO2            | >92%               | 88-92%                 | <88%                 |
| General behavior | Normal             | Irritable              | Lethargic            |
The current guidelines recommend that the amount of fluids administered to avoid dehydration should be at least 70–80% of the usual daily requirement, especially in infants with more severe disease [14,21,83], but should not exceed 100%, to avoid fluid overload or even electrolyte imbalances [14,81,82,90,91]. Monitoring of body weight, urine and serum osmolarity and electrolytes may therefore be useful in these cases [21,92]. Inhaled normal saline (0.9%) can be administered to increase clearing of mucus [44], although it is not suggested in current guidelines and reviews [14,18,21,22,93]. Hypertonic saline inhalations can determine an osmotic flow of water to the mucus layer [94], modifying the mucociliary clearance, but must include a bronchodilator as it can induce bronchospasm [44,95,96]. However, inhaled hypertonic saline is not recommended, and trials with hypertonic saline without bronchodilators are ongoing [21]. Several studies have focused on the role of bronchodilators in the treatment of bronchiolitis [15,97]. Although bronchodilators can produce an initial transient clinical improvement, especially because of their effect on the bronchial mucosa, a significant clinical benefit has never been demonstrated; therefore epinephrine, for example, does not seem to reduce the duration of hospitalization in patients with moderate or severe bronchiolitis [98] and an “as needed” rather than a continuous administration may be more useful, as it could result in less inhalations per day (12 vs. 17), shorter hospitalization (47.6 vs. 61.3 hours), lower oxygen consumption (38.3 vs. 48.7%) and a reduced need for ventilatory support (4.0 vs. 10.8%) [74]. This effect is mainly observed in children aged less than 3 months, in whom a conservative approach would therefore be preferable. The use of corticosteroids in bronchiolitis is controversial [99]. On one hand, several clinical studies have excluded some benefits of systemic or inhaled steroids [100] in reducing both the rate of hospitalization [101] and the duration of hospitalization [102,103]. On the other hand, van Woensel et al. demonstrated that dexamethasone (0.15 mg/kg every 6 hours for 48 hours) may be useful in mechanically ventilated children or critically ill children in general [104]. The Pediatric Emergency Care Applied Research Network multicenter study found that a single oral dose of dexamethasone was not much more effective than placebo during treatment of the first episode of bronchiolitis in previously healthy children [105]. There are insufficient data to support the use of antibiotics in bronchiolitis in children in general [106], but it can be justified in the case of concomitant bacterial infections in infants with severe disease, especially in those who require mechanical ventilation [107]. Currently, there is no known role for antiviral therapy in bronchiolitis and therefore no indication for ribavirin, either nebulized or intravenous [108,109]. Surfactant also should not be recommended, as suggested in a recent Cochrane review [110]. Continuous positive airway pressure (CPAP) may improve respiratory failure and help avoid intubation of patients in the Intensive Care Unit [111]; CPAP can recruit alveoli, reduce airway resistance and improve lung emptying during expiration, resulting in improved gas exchange and decreased hyperinflation [112,113]. During mechanical ventilation with CPAP, pressure should generally be between 4 and 8 cm H2O, and a pressure of 7 cm H2O seems to be optimal to reduce respiratory distress [114]. The use of heated humidified high-flow nasal cannula (HFNC) can also increase pharyngeal pressure, thereby reducing respiratory efforts [115–117], and is better tolerated by the patient [118–120]. In cases where nasal CPAP is not sufficient, proper mechanical ventilation can be applied [120,121], both volume and pressure cycled, with different values of respiratory rate (10–60 per minute), maximum pressure (20–50 cm H2O) and tidal volume (6–20 ml/kg) [113]. The use of positive end expiratory pressure (PEEP) can also be considered in some cases (0–15 cm H2O) [113]. Finally, children with severe bronchiolitis (especially those with bronchopulmonary dysplasia), who do not improve despite mechanical ventilation, can benefit from extracorporeal membrane oxygenation [122,123]. Cochrane reviews do not recommend RSV immunoglobulin [124,125] or chest physiotherapy [126]. Gentle nasal suction to keep the air passages clear could be

Table 3. Indications for hospital referral for acute bronchiolitis Adapted from [39]

| Absolute indications                                      | Relative indications                                      | Indications for intensive care                        |
|-----------------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------|
| - Cyanosis or very severe respiratory distress (RR >70 breaths/min, nasal flaring and/or grunting, severe chest wall recession) | - Congenital heart disease                                | - Failure to maintain saturations >90% with increasing oxygen requirement |
| - Marked lethargy                                          | - Any survivor of extreme prematurity                     | - Deteriorating respiratory status and impending exhaustion |
| - Respiratory distress preventing feeding                  | - Any pre-existing lung disease or immunodeficiency       | - Worsening episodes of apnea                           |
| - Apneic episodes                                          | - Down’s syndrome                                         |                                                        |
| - Diagnostic uncertainty (toxic infant, temperature ≥40 degrees centigrade) | - Social factors: isolated family                          |                                                        |

Cyanosis or very severe respiratory distress, respiratory distress preventing feeding, Cyanosis or very severe respiratory distress, and Apneic episodes mean that hospitalization may be useful in these cases [21,92]. Inhaled normal saline (0.9%) can be administered to increase clearing of mucus [44], although it is not suggested in current guidelines and reviews [14,18,21,22,93]. Hypertonic saline inhalations can determine an osmotic flow of water to the mucus layer [94], modifying the mucociliary clearance, but must include a bronchodilator as it can induce bronchospasm [44,95,96]. However, inhaled hypertonic saline is not recommended, and trials with hypertonic saline without bronchodilators are ongoing [21]. Several studies have focused on the role of bronchodilators in the treatment of bronchiolitis [15,97]. Although bronchodilators can produce an initial transient clinical improvement, especially because of their effect on the bronchial mucosa, a significant clinical benefit has never been demonstrated; therefore epinephrine, for example, does not seem to reduce the duration of hospitalization in patients with moderate or severe bronchiolitis [98] and an “as needed” rather than a continuous administration may be more useful, as it could result in less inhalations per day (12 vs. 17), shorter hospitalization (47.6 vs. 61.3 hours), lower oxygen consumption (38.3 vs. 48.7%) and a reduced need for ventilatory support (4.0 vs. 10.8%) [74]. This effect is mainly observed in children aged less than 3 months, in whom a conservative approach would therefore be preferable. The use of corticosteroids in bronchiolitis is controversial [99]. On one hand, several clinical studies have excluded some benefits of systemic or inhaled steroids [100] in reducing both the rate of hospitalization [101] and the duration of hospitalization [102,103]. On the other hand, van Woensel et al. demonstrated that dexamethasone (0.15 mg/kg every 6 hours for 48 hours)
beneficial in infants with copious secretion [45]. In adults, treatment of the various forms of bronchiolitis depends upon the underlying cause or associated disorder. Inhaled bronchodilators and cough suppressants are often employed to control the cough that is frequently present. Macrolide antibiotics are being increasingly used in the management of bronchiolitis because of their success in improving symptoms, lung function, and mortality [127–130], mostly in bronchiolitis associated with mycoplasma infections. Glucocorticoids are commonly employed and are quite effective, particularly when bronchiolitis is associated with organizing pneumonia (e.g. cryptogenic organizing pneumonia) [131]; a dose of prednisone 0.5 to 1 mg/kg lean body weight per day to a maximum of 60 mg per day is usually recommended in the acute phase, then gradually tapered over three to six months. In bronchiolitis due to toxic inhalation injury, glucocorticoids are occasionally effective in the management of both the acute-phase illness (pulmonary edema) and the late-phase illness (bronchiolitis obliterans). Bronchiolitis in the setting of rheumatoid arthritis is sometimes related to medication (e.g. penicillamine, or gold), so any potential culprit medications should be discontinued. High dose systemic glucocorticoids have been used with variable success [132]. In patients with bronchiolitis obliterans following organ transplantation, intensification of immunosuppression is sometimes successful; gastroesophageal reflux disease (GERD) is prevalent in lung transplantation recipients, and non-acid reflux has been associated with the development of bronchiolitis obliterans syndrome. Aggressive therapy for GERD, possibly including surgery, has been proposed to prevent the progression of bronchiolitis obliterans syndrome, although additional studies are needed. Overall, the mortality rate of acute bronchiolitis is less than 1% [31,75] and varies from 2.9 (UK) to 5.3 (US) deaths per 100,000 for RSV bronchiolitis occurring in children aged less than 12 months [133,134]. The majority of deaths are observed in infants younger than 6 months and risk factors are premature birth, concomitant cardiopulmonary disease, immunodeficiency [14,133] or difficult socio-economic conditions [44]. Wainwright evaluated children with bronchiolitis treated in outpatient clinics and described the resolution of symptoms in 40% of cases after 14 days and the persistence of symptoms in 10% after 4 weeks [18].

Many children complain of coughing and wheezing for several weeks after an episode of bronchiolitis (post-bronchiolitis syndrome) and intermittent symptoms may persist for several years [62]. Children hospitalized for bronchiolitis during infancy may have an increased risk of developing asthma or bronchial hyper-reactivity in the future [135,136]. The increased risk of bronchial asthma is more frequent in RSV-negative bronchiolitis or rhinovirus-bronchiolitis [137,138], whereas the association between RSV-bronchiolitis and respiratory disease seems to decrease with age [139,140]. In a small subgroup of patients, recovery from an episode of acute bronchiolitis can lead to chronic obstruction of the small airways resulting in expiratory airflow limitation, or so-called constrictive bronchiolitis [31,75]. This phenomenon is observed more frequently in adenovirus infections, measles, pertussis, mycoplasma, and influenza A [32]; unilateral hyperlucent lung and/or a combination of geographic hyperlucency, central bronchiectasis, and vascular attenuation (Swyer-James syndrome) has been observed [21,75].

**Conclusion**

Acute bronchiolitis in children is characterized by viral upper respiratory prodromes followed by increased respiratory effort, wheezing and diffuse bilateral crackles; the most common etiologic agent is RSV. The diagnosis of bronchiolitis is mostly clinical and usually does not require investigation. A conservative approach to treatment seems adequate in the majority of children, especially for the youngest ones, and the current management primarily consists of supportive care, including hydration, supplemental oxygen and mechanical ventilation when required.

**Abbreviations**

CPAP, continuous positive airway pressure; GERD, gastroesophageal reflux disease; HFNC, high-flow nasal cannula; HMPV, human metapneumovirus; HRCT, high resolution computerised tomography; RSV, respiratory syncytial virus.

**Disclosures**

The authors declare that they have no disclosures.

**References**

1. Ryu JH, Myers JL, Swensen SJ: Bronchiolar disorders. Am J Respir Crit Care Med 2003, 168:1277-92.
2. King TE Jr: Overview of bronchiolitis. Clin Chest Med 1993, 14:607.
3. King TE Jr: Bronchiolitis. In Interstitial Lung Disease. 4th edition. Edited by King TE Jr. Schwarz MI. Ontario: BC Decker; 2003:787.
4. Hendrick DJ: “Popcorn worker’s lung” in Britain in a man making potato crisp flavouring. Thorax 2008, 63:262.
5. van Rooy FG, Rooyackers JM, Prokop M, Houbia R, Smit LA, Heederik Dij: Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavourings. Am J Respir Crit Care Med 2007, 176:498.
6. Hsieh TR, Guo YL, Chen KW, Chen CW, Lee CH, Chang HY: Dose-response relationship and irreversible obstructive ventilatory defect in patients with consumption of Saurupus androgynus. Chest 1998, 113:71.
7. Lockey JE, Hilbert TJ, Levin LP, Ryan PH, White KL, Borton EK, Rice CH, McKay RT, LeMasters GK: Airway obstruction related
to diacetyl exposure at microwave popcorn production facilities. Eur Respir J 2009, 34:63.

8. Harber P, Levine J, Bansal S: How frequently should workplace spirometry screening be performed?: optimization via analytic models. Chest 2009, 36:1086.

9. Centers for Disease Control and Prevention (CDC): Obliterative bronchiolitis in workers in a coffee-processing facility - Texas, 2008-2012. MMWR Morb Mortal Wkly Rep 2013, 62:305-7.

10. Kim CK, Kim SW, Kim JS, Koh YY, Cohen AH, Deterding RR, White CW: Bronchiolitis obliterans in the 1990s in Korea and the United States. Chest 2001, 120:110-6.

11. Hall CB: Respiratory syncytial virus and parainfluenza virus. N Engl J Med 2001, 344:1917-28.

12. Andersen P: Pathogenesis of lower respiratory tract infections due to Chlamydia, Mycoplasma, Legionella and viruses. Thorax 1998, 53:302-7.

13. Lelahman M, Armon K, Bordley C, MacFaul R, Smith S, Vyas H: An evidence based guideline for the management of children presenting with acute breathing difficulty. University of Nottingham, 2002. [www.nottingham.ac.uk/paediatric-guideline/breathingguideline.pdf]

14. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis: Diagnosis and management of bronchiolitis. Pediatrics 2006, 118:174-93.

15. Zorc JJ, Hall CB: Bronchiolitis: Recent Evidence on Diagnosis and Management. Pediatrics 2010, 125:342.

16. Birkhaug JP, Inchley CS, Aamodt G, Anestad G, Nystad W, Nakstad B: Infectious burden of respiratory syncytial virus in relation to time of birth modifies the risk of lower respiratory tract infection in infancy: the Norwegian mother and child cohort. Pediatr Infect Dis J 2013, 32:e235-41.

17. Midulla F, Scagnolari C, Cangiano G, Bonci E, Salvadori S, Scagnolari C, Moretti C: Respiratory syncytial virus, human bocavirus and rhinovirus bronchiolitis in infants. Arch Dis Child 2010, 95:35-41.

18. Wainwright C: Acute viral bronchiolitis in children- a very common condition with few therapeutic options. Paediatr Respir Rev 2010, 11:39-45. quiz 45.

19. Carroll KN, Gebretsadik T, Griffin MR, Wu P, Dupont WD, Mitchell EP, Enriquez R, Hartert TV: Increasing burden and risk factors for bronchiolitis-related medical visits in infants enrolled in a state health care insurance plan. Pediatrics 2008, 122:58-64.

20. Yorita KL, Holman RC, Sejvar JJ, Steiner CA, Schonberger LB: Infectious disease hospitalizations among infants in the United States. Pediatrics 2008, 121:244-52.

21. Nagakumar P, Doull I: Current therapy for bronchiolitis. Arch Dis Child 2012, 97:827-30.

22. Zorc JJ, Hall CB: Bronchiolitis: recent evidence on diagnosis and management. Pediatrics 2010, 125:342-9.

23. 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.

24. Deshpande SA, Northen 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, 88:1065-9.

25. Wright AL, Tausig LM, Ray CG, Harrison HR, Holberg CJ: The Tucson Children’s Respiratory Study. II. Lower respiratory tract illness in the first year of life. Am J Epidemiol 1989, 129:1232-46.

26. Wolf DG, Greenberg D, Kalkstein D, Shemer-Avni Y, Givon-Lavi N, Saleh N, Goldberg MD, Dagan R: Comparison of human metapneumovirus, respiratory syncytial virus and influenza A virus lower respiratory tract infections in hospitalized young children. Pediatr Infect Dis J 2006, 25:320-4.

27. Mansbach JM, McAdam AJ, Clark S, Hain PD, Flood RG, Acholonu U, Camargo CA Jr: Prospective multicenter study of the viral etiology of bronchiolitis in the emergency department. Acad Emerg Med 2008, 15:111-8.

28. Boivin G, De Serres G, Côté S, Gilca R, Abed Y, Rochette L, Bergeron MG, Dery P: Human metapneumovirus infections in hospitalized children. Emerg Infect Dis 2003, 9:634-40.

29. Kahn JS: Epidemiology of human metapneumovirus. Clin Microbiol Rev 2006, 19:546-57.

30. van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Foucheur RA, Osterhaus AD: A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001, 7:719-24.

31. Schlesinger C, Koss MN: Bronchiolitis: update 2001. Curr Opin Pulm Med 2002, 8:112-6.

32. Penn CC, Liu C: Bronchiolitis following infection in adults and children. Clin Chest Med 1993, 14:465-54.

33. Francquet T, Stern EJ: Bronchial inflammatory diseases: high-resolution CT findings with histologic correlation. Eur Radiol 1999, 9:1290-303.

34. Paranhos-Bacalá G, Komurian-Pradel F, Richard N, Vernet G, Lina B, Floret D: Mixed respiratory virus infections. J Clin Virol 2008, 43:407-10.

35. Jartti T, Lehtinen P, Vuorinen T, Ruuskanen O: Bronchiolitis: age and previous wheezing episodes are linked to viral etiology and atopic characteristics. Pediatr Infect Dis J 2009, 28:311-7.

36. Midulla F, Pierangeli A, Cangiano G, Bonci E, Salvadori S, Scagnolari C, Moretti C, Antonelli G, Ferro V, Papoff P: Rhinovirus bronchiolitis and recurrent wheezing: 1-year follow-up. Eur Respir J 2012, 39:396-402.

37. Brand HK, de Groot R, Galama JM, Brouwer ML, Teuwen K, Hermans PW, Melchers WJ, Warris A: Infection with multiple viruses is not associated with increased disease severity in children with bronchiolitis. Pediatr Pulmonol 2012, 47:393-400.

38. Semple MG, Cowell A, Dove W, Greensill J, McNamara PS, Halfhide C, Shears P, Smyth RL, Hart CA: Dual infection of infants by human metapneumovirus and human respiratory syncytial virus is strongly associated with severe bronchiolitis. J Infect Dis 2005, 191:382-6.

39. Caraciolo S, Miniini C, Colombrita D, Rossi D, Miglioti N, Vettore E, Caruso A, Fiorentini S: Human metapneumovirus infection in young children hospitalized with acute respiratory tract disease: virologic and clinical features. Pediatr Infect Dis J 2008, 27:406-12.

40. Johnson BA, Iacono AT, Zeevi A, McCurry KR, Duncan SR: Statin use is associated with improved function and survival of lung allografts. Am J Respir Crit Care Med 2003, 167:1271-8.

41. McNamara PS, Syth RL: The pathogenesis of respiratory syncytial virus disease in childhood. Br Med Bull 2002, 61:13-28.

42. Harrison AP, Bonville CA, Rosenberg HF, Domachowske JB: Respiratory Syncytial virus-induced chemokine expression in the lower airways. Am J Respir Crit Care Med 1999, 159:1918-24.

43. Miller AL, Strieted RM, Gruber AD, Ho SB, Lukacs NW: CXCR2 regulates respiratory syncytial virus-induced airway hyper-reactivity and mucus production. J Immunol 2003, 170:3348-56.

44. Knut Øymar, Håvard Ove Skjerven, Ingvild Bruun Mikalsen: Acute bronchiolitis in infants, a review. Scand J Trauma Resusc Emerg Med 2014, 22:23.

45. Andrew Bush, Anne H Thomson: Acute bronchiolitis. BMJ 2007, 335:1037-41.

46. Fitzgerald DA, Kilham HA: Bronchiolitis: assessment and evidence-based management. Med J Aust 2004, 180:399-404.

47. Putto A, Ruuskanen O, Meurman O: Fever in respiratory virus infections. Am J Dis Child 1986, 140:1159-63.

48. Paediatric Society of New Zealand: Wheeze and chest infection in infants under 1 year. PSNZ, 2005, [http://www.paediatrics.org.nz/files/guidelines/wheezen dorsed.pdf]

49. Murray J, Bottle A, Sharland M, Modi N, Aylin P, Majeed A, Saxena S: Medicines for Neonates Investigator G: Risk factors for hospital admission with RSV bronchiolitis in England: a population-based birth cohort study. PLoS One 2014, 9:e89186.
50. Siezen CL, Bont L, Hodemakers HM, Ermers MJ, Doornbos G, Van’t Slot R, Wijmenga C, Houwelingen HC, Kimpen JL, Kimman TG, Hoebbe B, Janssen R: Genetic susceptibility to respiratory syncytial virus bronchiolitis in preterm children is associated with airway remodeling genes and innate immune genes. Pediatr Infect Dis J 2009, 28:333-5.

51. Janssen R, Bont L, Siezen CL, Hodemakers HM, Ermers MJ, Doornbos G, van’t Slot R, Wijmenga C, Goeman JJ, Kimpen JL, van Houwelingen HC, Kimman TG, Hoebbe B. Genetic susceptibility to respiratory syncytial virus bronchiolitis is predominantly associated with innate immune genes. J Infect Dis 2007, 196:826-34.

52. Devereux G, Litonjua AA, Turner SW, Craig LC, McNell G, Martindale S, Helms PJ, Sexton A, Weiss ST: Maternal vitamin D intake during pregnancy and early childhood wheezing. Am J Clin Nutr 2007, 85:853-7.

53. Mansbach JM, Camargo CA Jr: Bronchiolitis: lingering questions about its definition and the potential role of vitamin D. Pediatrics 2008, 122:177-9.

54. Choi J, Lee GL: Common pediatric respiratory emergencies. Emerg Med Clin North Am 2012, 30:529-63.

55. Bodeker WC, Viswanathan M, King VJ, Sutton SF, Jackman AM, Sterling L, Lohr KN: Diagnosis and testing in bronchiolitis: a systematic review. Arch Pediatr Adolesc Med 2004, 158:119-26.

56. Henrickson KJ, Hall CB: Diagnostic assays for respiratory syncytial virus disease. Pediatr Infect Dis J 2007, 26:536-40.

57. Ferronato AE, Gilo AE, Ferraro AA, Paulis M, Vieira ES: Etiological diagnosis reduces the use of antibiotics in infants with bronchiolitis. Clinics (Sao Paulo) 2012, 67:1001-6.

58. Ralston S, Hill V: Incidence of apnea in infants hospitalized with respiratory syncytial virus bronchiolitis: a systematic review. J Pediatr 2009, 155:728-33.

59. Willworth 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.

60. Levine DA, Platt SL, Dayan PS, Macias CG, Zorc JJ, Krief W, Schor J, Bank D, Fefferman N, Shaw KN, Kuppermann N: Multicenter RSV-SBI Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. Pediatrics 2004, 113:1728-34.

61. Lugnbuhl LM, Newman TB, Pantell RH, Finch SA, Wasserman RC: Office-based treatment and outcomes for febrile infants with clinically diagnosed bronchiolitis. Pediatrics 2008, 122:947-54.

62. SIGN clinical guideline: Bronchiolitis in children. Scottish Intercollegiate Guidelines Network; 2006. [http://www.sign.ac.uk/pdf/sign91.pdf]

63. Mansbach JM, Clark S, Christopher NC, LoVecchio F, Kunz S, Acholonu U, Camargo CA Jr: Prospective multicenter study of bronchiolitis: predicting safe discharges from the emergency department. Pediatrics 2008, 121:680-8.

64. Shaw KN, Bell LM, Sherman NH: Outpatient assessment of infants with bronchiolitis. Am J Dis Child 1991, 145:151-5.

65. Schu S, Lalan A, Allen U, Manson D, Babyn P, Stephens D, MacPhee S, Makansi M, Khalkin S, Dick P: Evaluation of the utility of radiography in acute bronchiolitis. J Pediatr 2007, 150:429-33.

66. Zompettori M, Poletti V, Rimondi MR, Ballaglia M, Carrelli P, Maraldi F: Imaging of small airways diseases, with emphasis on high resolution computed tomography. Monaldi Arch Chest Dis 1997, 52:242-8.

67. Poletti V, Casoni GL, Zompettori M, Carloni A, Chilosi M: Obliterative Bronchiolitis: Classification, Causes and Overview. In: Interstitial Pulmonary and Bronchial Disorders. Edited by Joseph P Lynch. New York: Informa Healthcare; 2008:525-42.

68. Mahaebe-Gittens EM, Bachman DT, Shapiro ED, Dowd MD: Chest radiographs in the pediatric emergency department for children < or = 18 months of age with wheezing. Clin Pediatr (Phila) 1999, 38:395-9.

69. Devakonda A, Raoof S, Sung A, Travis WD, Naidich D: Bronchiolitis disorders: a clinical-radiological diagnostic algorithm. Chest 2010, 137:938.

70. Pipavath S, Lynch DA, Cool C, Brown KK, Newell JD: Radiologic and pathologic features of bronchiolitis. Am J Roentgenol 2005, 185:354.

71. Jensen SP, Lynch DA, Brown KK, Wenzel SE, Newell JD: High-resolution CT features of severe asthma and bronchiolitis obliterans. Clin Radiol 2002, 57:1078.

72. Lynch DA: Imaging of small airways disease and chronic obstructive pulmonary disease. Clin Med Chest 2008, 29:165.

73. Garg K, Lynch DA, Newell JD, King TE Jr: Proliferative and constrictive bronchiolitis: classification and radiologic features. Am J Roentgenol 1994, 162:803.

74. Skjerven HO, Hunderi QJ, Brugmann-Pieper SK, Brun AC, Engen H, Eskedal L, Haavaldsen M, Kvenshagen B, Lunde J, Rolfsjord LB, Haavaldsen M, Kvenshagen B, Lunde J, Rolfsjord LB, Siva C, Vikin T, Mowinckel P, Carlsen KH, Ledrup Carlsen KC: Racemic adrenaline and inhalation strategies in acute bronchiolitis. N Engl J Med 2013, 368:2286-93.

75. Panitch HB: Bronchiolitis in infants. Curr Opin Pediatr 2001, 13:256-60.

76. Mallory MD, Shay DK, Garrett J, Bordley WC: Bronchiolitis management preferences and the influence of pulse oximetry and respiratory rate on the decision to admit. Pediatrics 2003, 111:e45-51.

77. Schroeder AR, Marmor AK, Pantell RH, Newman TB: Impact of pulse oximetry and oxygen therapy on length of stay in bronchiolitis hospitalizations. Arch Pediatr Adolesc Med 2004, 158:527-30.

78. Unger S, Cunningham S: Effect of oxygen supplementation on length of stay for infants hospitalized with acute viral bronchiolitis. Pediatrics 2008, 121:470-5.

79. Bajaj L, Turner CG, Bothner J: A randomized trial of home oxygen therapy from the emergency department for acute bronchiolitis. Pediatrics 2006, 117:633-40.

80. Tie SW, Hall GL, Peter S, Vine J, Verheugen M, Pascoe EM, Wilson AC, Chaney G, Stick SM, Martin AC: Home oxygen for children with acute bronchiolitis. Arch Dis Child 2009, 94:641-3.

81. Kugelman A, Raibin K, Dabbah H, Chistyakov I, Srugo I, Even L, Bazinisky N: Riskin A: Intravenous fluids versus gastric-tube feeding in hospitalized infants with viral bronchiolitis: a randomized, prospective pilot study. J Pediatr 2013, 162:640-2. e641.

82. Oakley E, Babi FE, Acworth J, Borland M, Kreiser D, Neutze J, Theophilos T, Donath S, South M, Davidson A: A prospective randomised trial comparing nasogastric with intravenous hydration in children with bronchiolitis (protocol): the comparative rehydration in bronchiolitis study (CRIB). BMC Pediatr 2010, 10:37.

83. Nagakumar P, Doull I: Current therapy for bronchiolitis. Arch Dis Child 2012, 97:827-30.
84. Oakley E, Borland M, Neutze J, Acworth J, Krieser D, Dalziel S, Davidson A, Donath S, Jachno K, South M, Theophilos T, Babi FE, Paediatric Research in Emergency Departments International Collaborative (PREDICT): Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial. Lancet Respir Med 2013, 1:13-20.

85. Brand PL, Vaessen-Verberne AA: Differences in management of bronchiolitis between hospitals in The Netherlands. Dutch Paediatric Respiratory Society. Eur J Pediatr 2000, 159:343-7.

86. Babi FE, Sherriff N, Neutze J, Borland M, Oakley E: Bronchiolitis management in pediatric emergency departments in Australia and New Zealand: a PREDICT study. Pediatr Emerg Care 2008, 24:656-8.

87. Norwegian Society of Pediatricians Guidelines; Bronchiolitis. [http://www.helsebiblioteket.no/retningslinjer/akuttveileder-i-pediatri/lunge-og-luftveislykdommer/akutt-bronkiolitt]

88. Azizi A, Atzori L, Moretti C, Barbeneri L, Noto A, Octonello G, Pusceddu E, Fanos V: Metabolomics in paediatric respiratory diseases and bronchiolitis. J Matern Fetal Neonatal Med 2011, 24(Suppl 2):59-62.

89. Hernandez E, Khoshsou V, Toppil D, Edell D, Ross G: Aspiration: a factor in rapidly deteriorating bronchiolitis in previously healthy infants? Pediatr Pulmonol 2002, 33:30-1.

90. Kennedy N, Flanagan N: Is nasogastric fluid therapy a safe alternative to the intravenous route in infants with bronchiolitis? Arch Dis Child 2005, 90:320-1.

91. van Steensel-Holl HA, Huzelzet JA, van der Voort E, Neijens HJ, Hackeng WH: Excessive secretion of antidiuretic hormone in infections with respiratory syncytial virus. Arch Dis Child 1990, 65:1237-9.

92. Gozal D, Colin AA, Jaffe M, Hochberg Z: Water, electrolyte, and endocrine homeostasis in infants with bronchiolitis. Pediatr Res 1990, 27:204-9.

93. Miller ST: How I treat acute chest syndrome in children with sickle cell disease. Blood 2011, 117:5297-305.

94. Mandelberg A, Amirav I: Hypertonic saline or high volume normal saline for viral bronchiolitis: mechanisms and rationale. Pediatr Pulmonol 2010, 45:36-40.

95. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP: Nebulised hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev 2013, 7:CD006458.

96. Chen YJ, Lee WL, Wang CM, Chou HH: Nebulized hypertonic saline treatment reduces both rate and duration of hospitalization for acute bronchiolitis in infants: an updated meta-analysis. Pediatr Neonatal 2014, S1875-9572:00229-5.

97. Gadomski AM, Bhasale AL: Bronchodilators for bronchiolitis. Cochrane Database Syst Rev 2006, 3:CD001266.

98. Hartling L, Wiebe N, Russell K, Patel H, Klassen TP: Epinephrine for bronchiolitis. Cochrane Database Syst Rev 2004, 1:CD003123.

99. Hartling L, Fernandes RM, Bialy L, Milne A, Johnson D, Plint A, Klassen TP, Vandermeer B: Steroids and bronchodilators for acute bronchiolitis in the first two years of life: updated systematic review and meta-analysis. BMJ 2011, 342:d1714.

100. Patel H, Platt R, Lozano JM, Wang EEL: Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database Syst Rev 2004, 3:CD004878.

101. Fernandes RM, Bialy LM, Vandermeer B, Tjiosvold L, Plint AC, Patel H, Johnson DW, Klassen TP, Hartling L: Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database Syst Rev 2013, 6:CD004878.
116. Manley BJ, Dold SK, Davis PG, Roehr CC: High-flow nasal cannulae for respiratory support of preterm infants: a review of the evidence. Neonatology 2012, 102:300-8.

117. Milese C, Baleine J, Matecki S, Durand S, Combes C, Novais AR, Combonie G: Is treatment with a high flow nasal cannula effective in acute viral bronchiolitis? A physiologic study. Intensive Care Med 2013, 39:1088-94.

118. Thorburn K, Ritson P: Heated, humidified high-flow nasal cannula therapy in viral bronchiolitis-Panacea, passing phase, or progress? Pediatr Crit Care Med 2012, 13:700-1.

119. Abboud PA, Roth PJ, Skiles CL, Stoll B, Rowin MJ: Predictors of failure in infants with viral bronchiolitis treated with high-flow, high-humidity nasal cannula therapy. Pediatr Crit Care Med 2012, 13:e343-9.

120. Klingenberg C, Pettersen M, Hansen EA, Gustavsen LJ, Dahl IA, Leknesund A, Kaaresen PI, Nordhov M: Patient comfort during treatment with heated humidified high flow nasal cannulae versus nasal continuous positive airway pressure: a randomised cross-over trial. Arch Dis Child Fetal Neonatal Ed 2014, 99:F134-7.

121. Beggs S, Wong ZH, Kaul S, Ogden KJ, Walters JA: High-flow nasal cannula therapy for infants with bronchiolitis. Cochrane Database Syst Rev 2014, 1:CD009609.

122. Flamant C, Hallafel F, Nolent P, Chevalier JY, Renolleau S: Severe respiratory syncytial virus bronchiolitis in children: from short mechanical ventilation to extracorporeal membrane oxygenation. Eur J Pediatr 2005, 164:93-8.

123. Mansbach JM, Piedra PA, Stevenson MD, Sullivan AF, Forgey TF, Clark S, Espinola JA, Camargo CA Jr, Investigators M: Prospective multicenter study of children with bronchiolitis requiring mechanical ventilation. Pediatrics 2012, 130:492-500.

124. Lederc F, Scalfaro P, Noizet O, Thumerelle C, Dorkenoo A, Fourier C: Mechanical ventilatory support in infants with respiratory syncytial virus infection. Pediatr Crit Care Med 2001, 2:197-204.

125. Fuller H, del Mar C: Immunoglobulin treatment for respiratory syncytial virus infection. Cochrane Database Syst Rev 2006, 4:CD004883.

126. Perrote C, Ortiz Z, Roque M: Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. Cochrane Database Syst Rev 2005, 2:CD004873.

127. Nagai H, Shishido H, Yoneda R, Yamaguchi E, Tamura A, Kurashima A: Long-term low-dose administration of erythromycin to patients with diffuse panbronchiolitis. Respiraion 1991, 58:145.

128. Azuma A, Kudoh S: Securing the safety and efficacy of macrolide therapy for chronic small airway diseases. Intern Med 2005, 44:167.

129. Khalid M, Saghri A, Saleemi S, Al Dammas S, Zeitouni M, Al Mobieereek A, Claudhny N, Sahovic E: Azithromycin in bronchiolitis obliterans complicating bone marrow transplantation: a preliminary study. Eur Respir J 2005, 25:490.

130. Yang M, Dong BR, Lu J, Lin X, Wu HM: Macrolides for diffuse panbronchiolitis. Cochrane Database Syst Rev 2010, 12:CD007716.

131. King TE Jr, Mortensen RL: Cryptogenic organizing pneumonia. The North American experience. Chest 1992, 102:85-135.

132. Cortot AB, Cottin V, Miossec P, Fauchon E, Thivolet-Béjui F, Cordier JF: Improvement of refractory rheumatoid vasculitis-associated constrictive bronchiolitis with etanercept. Respir Med 2005, 99:511.

133. Fleming DM, Pannell RS, Cross KW: Mortality in children from influenza and respiratory syncytial virus. J Epidemiol Community Health 2005, 59:586-90.

134. Thompson WV, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, Fukuda K: Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003, 289:179-86.