Bronchiolitis

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Abstract

Bronchiolitis produces significant morbidity and mortality worldwide every year. Approximately 3–10 % of all infants hospitalized with bronchiolitis develop acute respiratory failure and require admission to a pediatric intensive care unit. The vast majority of cases are caused by Respiratory Syncytial Virus (RSV), though other viruses (human metapneumovirus, parainfluenza, influenza, adenovirus, rhinovirus, coronavirus and bocavirus) may also cause bronchiolitis. Bronchiolitis is not merely a single organ disease (i.e. lung), but impacts on extrapulmonary organ systems. Basic supportive management remains the cornerstone. There is a paucity of established therapeutic options, with supplementary oxygen, continuous positive airway pressure (CPAP), humidified high-flow nasal oxygen, mechanical ventilation being the mainstay of respiratory support.

Keywords

Bronchiolitis • Respiratory syncytial virus (RSV) • Co-morbidity

Introduction

Bronchiolitis is a common acute, potentially life-threatening, viral respiratory illness that affects predominantly infants and young children around the world, usually as a seasonal epidemic. Although "bronchiolitis" is actually a pathological description, bronchiolitis is used as a clinical diagnosis for a disease characterized by coryza, cough, fever, increased respiratory effort, hyperinflation of the chest, wheezing, widespread fine crackles on auscultation, and poor feeding. Around 2–3 % of all infants in resource-rich countries are admitted to the hospital with bronchiolitis. Annually, bronchiolitis is estimated to account for two million children under 5 years of age requiring medical attention and 60,000–90,000 hospitalizations in the USA alone [1]. Approximately 3–10 % of infants hospitalized with bronchiolitis develop respiratory failure and require admission to a pediatric intensive care unit (PICU) [2, 3]. This chapter will concentrate on severe bronchiolitis that requires critical care, and especially respiratory, support.

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Pathogens, Pathogenesis and Pathophysiology

Respiratory syncytial virus (RSV) accounts for 50–70 % of the cases of bronchiolitis, with less common viral pathogens being parainfluenza, influenza, adenovirus, human metapneumovirus, rhinovirus, coronavirus, and bocavirus. Even though outbreaks of pyrexial respiratory illnesses have been

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described for many centuries, probably the first description of an outbreak of RSV was reported in 1941 [4]. Adams described an outbreak of nosocomial chest infections in 32 infants in a neonatal unit that resulted in 9 deaths, with cytoplasmic inclusions identified in the lungs at autopsy. RSV was first identified in 1956 from a colony of chimpanzees with coryza and designated "chimpanzee coryzal agent". Subsequently a year later in 1957 it was isolated from children with lung disease in Baltimore, USA [5]. Since then RSV has been recognized as the single most important virus causing acute respiratory tract infections in infants and young children throughout the world [1, 6, 7]. Although primarily a respiratory pathogen of infants and young children, RSV infects and re-infects adults, and causes significant disease in the elderly and in those patients with chronic lung disease or immunocompromise [6].

RSV is classified in the order *Mononegavirales*, family *Paramyxoviridae* (Greek *para* for "beside" or "beyond" + *myxa* for "mucus") and subfamily *Pneumovirinae*, with the closely-related human metapneumovirus. Other family members include the *Paramyxivirinae*: parainfluenza virus types 1, 2, 3; mumps and the morbillivirus measles. In the same order *Mononegavirales*, the fellow RNA viruses influenza A and influenza B reside in the family *Orthomyxoviridae* (Greek *orthos* for "straight" + *myxa* for "mucus"). RSV is a pleomorphic (spherical or filamentous form) enveloped RNA virus 120–300 nm in size that contains a non-segmented single-strand negative-sense RNA genome. Two large surface glycoproteins, fusion protein (F) and attachment protein (G), are the major antigenic determinants and induce antibody production. There are two major groups of RSV strains, A and B, that are distinguished by antigenic characteristics, mainly in variations in the G (attachment) protein, as there are few differences in the F (fusion) protein between the strains [6, 8, 9].

RSV infects respiratory epithelial cells by attaching itself to the cell surface by means of a capsular glycoprotein, the G (attachment) protein. A second capsular glycoprotein, the F (fusion) protein, mediates fusion with the epithelial cell membrane along with adjacent cells, resulting in the formation of giant multinucleated cells – syncytia – for which the virus is named [10]. It is suggested that another structural capsular/envelope protein, the SH (small hydrophobic) protein, plays a role in both syncytial formation and blocking of cell death/apoptosis. RSV virion assembly occurs at the plasma membrane of infected cells and are released by budding, taking a lipid bilayer membrane derived from the infected host cell with them. Infectious RSV is probably in the filamentous form [10].

RSV (and other paramyxoviruses) transmission is by direct inoculation of contagious secretions from hands and self-inoculation of eyes and nose. Transmission requires close or direct contact with large droplets residing on fomites like skin, cloth or clinical surfaces. Transmission through aerosolization is more a feature of the influenza viruses, adenovirus, rhinovirus and coronavirus. RSV's incubation period can be 2–8 days, usually 2–5 days [6]. The virus replicates in nasopharyngeal epithelium and then spreads to lower respiratory tract 1–3 days later.

Respiratory viruses causing bronchiolitis (especially RSV) have a direct cytopathic effect on respiratory epithelial cells. The characteristic infective and inflammatory process of bronchiolitis leads to loss of cilial motility, submucosal edema, increased mucus secretion, infiltration by leukocytes, necrosis and sloughing of the respiratory epithelial cells of the small airways, all of which obstructs airflow through the small/distal airways [10]. During expiration this enhances dynamic small/distal airways narrowing, producing disproportionate turbulence and decreased airflow causing air-trapping. Further air-trapping can be caused by a ball-valve mechanism of airway obstruction due to intraluminal plugging by mucus and cellular debris. Clinically the inflammatory process in the small/distal airways (i.e. bronchiolitis) can result in both pulmonary hyperinflation and areas of atelectasis, along with wheezing due to small/distal airways obstruction.

The extent to which structural/anatomical factors impact on the degree of distal airways obstruction is governed by vector properties (for example Pouiseille's Law dictating that the turbulence in the airflow in a cylinder increases to the power of 4 with each decrease in radius), and the physical size/absolute diameter of the distal airway. Inherent variations in the infected individual's inflammatory and apoptotic response also influence the degree of submucosal edema, increased mucus secretion, and sloughing of epithelial cells. The former factors probably account for the high incidence of respiratory disease in younger smaller individuals with their smaller distal airways (e.g. premature infants) [3, 10]. The latter, individualistic inflammatory response, continues to fuel much research worldwide.

Clinically, air-trapping and atelectasis increase work of breathing due to increased end expiratory lung volume and decreased lung compliance. Respiratory failure is usually the result of worsening lung compliance and respiratory muscle fatigue. Apnea, which is common in infants with bronchiolitis, can be secondary to severe lung disease or central in origin.

The respiratory epithelial cells usually recover within 2–4 days, but histologically the ciliated epithelial cells take 2 weeks to regenerate [6]. Both laboratory and human studies have demonstrated that immune competent hosts clear the virus following natural RSV infection within 3 weeks, whereas immunocompromised hosts with deficiencies of cellular immunity tend to suffer more severe disease and have prolonged viral shedding [6].

Immune Response to RSV Infection

Protection against upper (URTI) and lower respiratory tract infections (LRTI) requires a balance between humoral and cellular immunity. Local secretory IgA is the prominent humoral mediator of resistance in the upper respiratory tract, whereas serum IgG provides additional protection in the lower respiratory tract. The F and G surface glycoproteins are the only RSV proteins to induce protective neutralizing antibodies (mainly of the IgG1 subclass) in children [6]. In neonates and infants, high levels of maternally-derived neutralizing antibodies confer some protection [6, 7].

Cellular immunity plays the predominant role in combating and recovering from RSV infection, with T-lymphocytic stimulation and response playing an integral function. The antiviral and cell-mediated immune reaction to RSV infection is primarily orchestrated by RSV-infected respiratory epithelial cells and by alveolar macrophages. T helper 1-type cytokines – interferon γ (IFNγ), interleukin type 2 (IL-2), IL-12; T helper 2-type cytokines – IL-4, IL-5, IL-6, IL-10; antiviral interferons – IFNα, IFNβ; and chemokines – C, CC, CXC and CX_3C subgroups, attract and activate leukocytes, especially alveolar macrophages, to the RSV-infected respiratory tract. These cytokines and chemokines may enter the systemic circulation and impact on outlying cells in extrapulmonary sites [8, 11, 12] (Fig. 5.1).

Much of our understanding of the immune response to RSV infection comes from animal models or studies in children with severe disease (i.e. intubated and mechanically ventilated children from whom respiratory samples can be obtained) [11, 12]. Therefore the immunopathogenesis of RSV disease in the great majority of children who develop mild respiratory symptoms, and may not see a doctor or attend hospital, is largely inferred [8, 11, 12]. A misdirected immune cascade, characterised by an overexuberant release of inflammatory mediators ("cytokine storm") and infiltration of a range of monocytes and polymorphonuclear cells may predispose to more severe bronchiolitis, which is further manipulated by host genetic and acquired factors. Contrary to prevailing inflammatory avalanche theories, a study in Chilean children (where mechanical ventilation was not available) dying from RSV or influenza bronchiolitis and

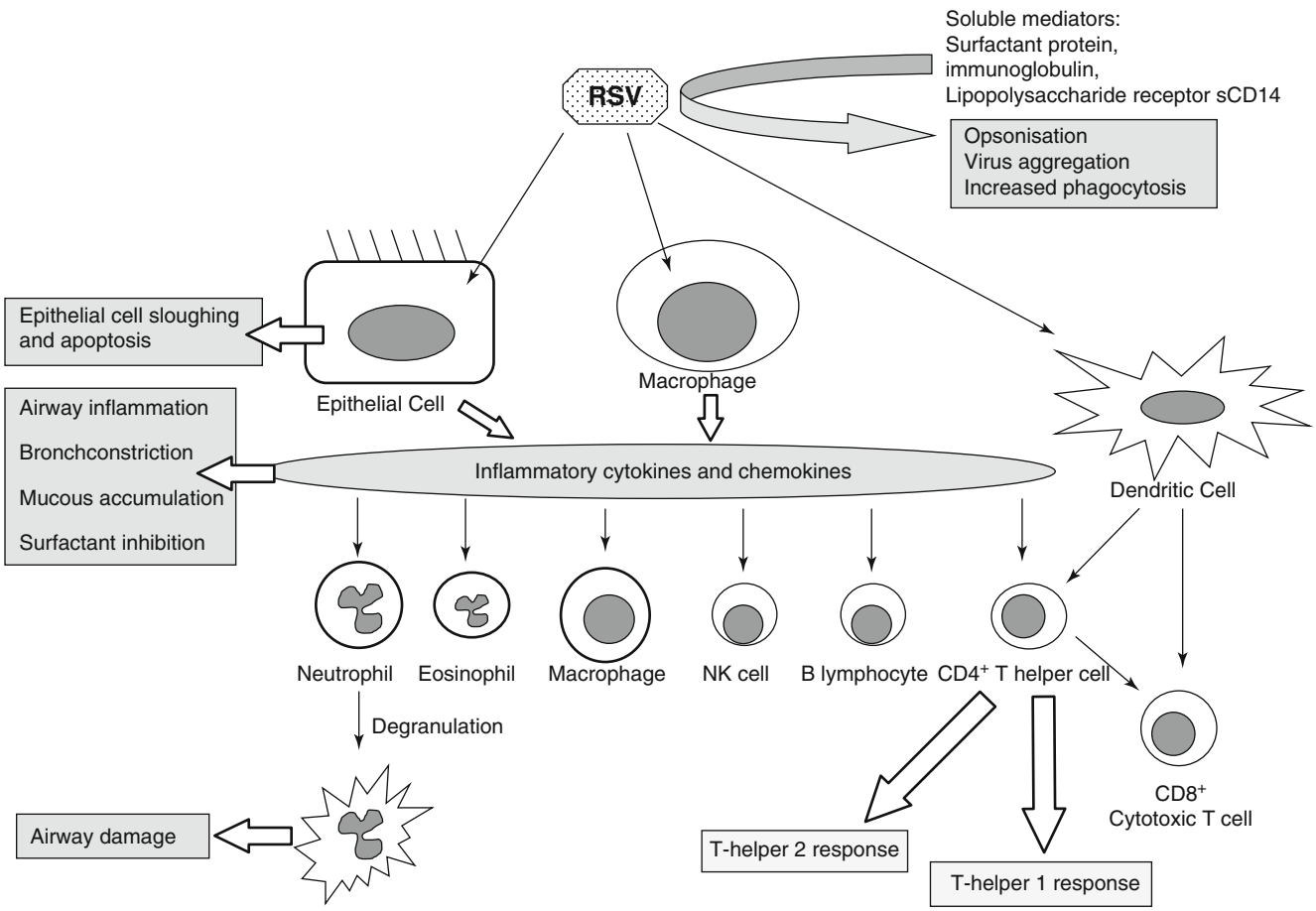

Fig. 5.1 Diagram of the inflammatory pathways and resultant clinical impact triggered by infection with respiratory syncytial virus (RSV)

North American infants surviving RSV or influenza bronchiolitis found a blunted adaptive cell-mediated immune response with a relative absence of cytotoxic T-cells [10]. In the fatal cases, especially with RSV infection, there was excessive viral antigen and overwhelming apoptotic sloughing of infected respiratory epithelial cells [10].

In a trial of a formalin-inactivated vaccine in the late 1960s, immunized children suffered more severe disease than controls when they subsequently contracted natural RSV (re) infection (80 % required hospitalization compared to 5 % of controls). Vaccinated children lacked specific mucosal antibodies; their serum antibodies were deficient in fusion-inhibiting and neutralizing activity; some had increased lymphocytic and/or eosinophilic proliferation [6]. These findings suggested that protection against RSV infection necessitates a balance between humoral and cellular immunity. However, the relative contributions of the humoral and cellular immune components in RSV infection and immunity to subsequent RSV infection is still debated [6, 8, 10]. Effective and appropriately-restrained protection from RSV bronchiolitis most probably requires a viral neutralizing response (humoral/antibody + cellular) without an excessive RSV-specific cytotoxic T-lymphocyte response [8, 11].

Primary infection with RSV does not lead to acquired immunity against future infections. Although naturally acquired immunity is neither durable nor complete, it does appear to provide some protection as subsequent infections are less severe [6, 9]. Despite extensive study of the major surface glycoprotein (G), the fusion protein (F), and even the transcription antiterminator matrix protein, the reasons for this lack of acquired immunity remain unclear [9].

Epidemiology

RSV affects about 60–70 % of infants by the age of 1 year and 90 % of children by the age of 2 years, most commonly as a respiratory tract infection. Peak infection rates occur in infants 6 weeks to 6 months of age. Re-infection occurs frequently (throughout life), but illness tends to be milder [6]. Virtually all children have developed antibodies to RSV by 3 years of age [3].

RSV infection can occur throughout the year, but RSV epidemics occur at predictable annual intervals during the winter months in moderate climates, and during hot and rainy season in tropical climates [13, 14]. In the northern hemisphere the annual 'RSV season' is usually between November and March, with the typical peak period being December through to February. During their first RSV infection, between 25 % and 40 % of infants have bronchiolitic (or pneumonic) signs and symptoms, and up to 3 % require hospitalization (in developed/resource-rich nations) [1, 15]. In the USA, RSV bronchiolitis accounts for up to 90,000 hospitalizations annually, 20,000 in the UK, and 3,000 in the Netherlands [1, 15]. Generally the reported hospital admission rates for children under 1 year of age in the USA and Europe is around 25–30 per 1,000 infants [3]. Incidence and hospitalization rates for bronchiolitis in resource-limited areas are lacking owing to the paucity of epidemiological studies and cost-saving restrictions in laboratory confirmation of viral infection [4, 7, 16]. Both A and B strains circulate concurrently within a RSV season. There are distinct genotypes within the strains which vary in dominance within a community from year to year [17]. This may account for the frequency of re-infection as any immunity to previous genotypes is evaded [17]. Approximately 3–10 % of infants hospitalized with RSV infection (and about 1 % of all those with bronchiolitis) develop respiratory failure and require admission to PICU [2, 3]. Amongst the children from resource-rich countries admitted to PICU with bronchiolitis, the reported incidence of those requiring mechanical or non-invasive ventilation varies from 50 % to 100 % depending more on the country, than the region or unit [2, 18, 19].

Mortality

The mortality rate for those hospitalized with bronchiolitis is low at 1–3 %, but increases in children with severe bronchiolitis requiring intensive care management [2, 20, 21]. Mortality is higher in those with co-morbidity (especially underlying congenital heart disease, chronic lung disease, immunocompromise, neuromuscular disease), with nosocomial infection [21], and in developing/resource-limited nations. RSV is the most common viral cause of death in children below 5 years of age and especially in infants less than 1 year old [8, 20]. It has been estimated that annually in the USA up to 2,700 deaths are caused by RSV [15, 20], and that world-wide 199 000 deaths in children less than 5 years of age were attributable to RSV-associated lower respiratory tract infection in 2005 [7].

Clinical Diagnosis

The diagnosis of bronchiolitis for the vast majority of children around the world is made on clinical grounds – coryza, cough, fever, increased respiratory effort, hyperinflation of the chest, wheezing, fine crackles on auscultation, poor feeding and dehydration; which may be backed up by non-specific chest radiographic findings of hyperinflation and patchy atelectasis, and/or below normal oxygen saturations on pulse oximetry [3, 22–24]. Chest radiography does not differentiate the different viral causes of bronchiolitis or even viral bronchiolitis from bacterial LRTI [24, 25]. Additionally, clinical severity and chest radiography changes

do not correlate well [25]. Although oxygen saturation measurements may influence clinicians in admitting infants with bronchiolitis, the benefits of pulse oximetry in this group have not been proven [3, 22, 24]. Some authors have suggested that certain clinical features like cyanosis and crackles relate to disease severity in bronchiolitis, but others have questioned the validity and reliability of auscultatory findings due to variations in inter-observer agreement [26].

Laboratory Confirmation of Bronchiolitis

Diagnostic methods for confirming and identifying the viral pathogen in resource-rich countries include viral isolation and culture; direct immunofluorescence and enzyme-linked immunosorbent assays (ELISA) that detect antigen; reverse-transcriptase polymerase chain reaction (RT-PCR) that detect nucleic acid. Serological testing (acute and convalescent antibody viral titres) is usually clinically unhelpful as seroconversion may take weeks and have a poor response. RSV rapid antigen detection tests (immunofluorescence and enzyme-linked immunoassays) generally have overall sensitivity and specificity of 80–90 % (range 60–95 %) [23]. RT-PCR is reported to offer greater sensitivity and multiplex PCR kits that detect several viruses simultaneously are readily available [13]. Most commonly nasopharyngeal aspirates are tested, but in intubated patients an endotracheal aspirate or broncho-alveolar lavage can be utilized. The quality of the sample, largely dependent on the sampler's technique and expertise, govern the accuracy of diagnostic testing rather than the site sampled [23].

Clinical Phenotype

Bronchiolitis is the most common lower respiratory tract manifestation of viral disease and typically results in air-trapping leading to increased end expiratory lung volume and decreased lung compliance, compatible with an obstructive lung disease pattern [3, 6]. However, bronchiolitis is a heterogeneous disease with some patients having a significant degree of lung consolidation and more restrictive, than obstructive, lung disease [27]. Some authors have discriminated restrictive from obstructive RSV lung disease on pulmonary function tests (decrease respiratory compliance) [28] or ventilatory indices (oxygen index, alveolar-arterial oxygen gradient, mean airways pressure) [29], in addition to four-quadrant alveolar consolidation on chest radiograph in mechanically ventilated children. In everyday pediatric practice clinicians cannot strictly dichotomise this heterogeneous lung disease into restrictive and obstructive forms, especially when each potentially occurs within different parts of the same lung [16, 27]. In the USA and some European countries "RSV bronchiolitis" and "RSV pneumonia" are differentiated clinically by the presence of localized crackles and consolidation on chest radiograph [3]. Informed clinicians generally appreciate the pneumonic aspects of severe bronchiolitis whether labelled "RSV bronchiolitis", "RSV pneumonia" or "RSV pneumonitis".

Severity of Disease and Risk Factors

The vast majority of children with bronchiolitis will be treated in the community, with only up to 3 % requiring admission to hospital [15, 24, 30] – most studies therefore define severe disease by the need for hospitalization [3, 15, 30]. Approximately 3–10 % of infants hospitalized with bronchiolitis require admission to PICU [2, 3] – most pediatric intensivists would regard PICU admission as representing severe disease. Although a number of clinical scoring systems have been proposed (and frequently utilized in bronchiolitis studies), none have proved better than clinical judgement [30–32]. Even national guidelines on indications for hospital referral, for example those produced by the American Academy of Pediatrics or the Scottish Intercollegiate Guidelines Network, still rely on clinical judgement in interpreting clinical features and recognition of risk factors that predispose to severe disease [24, 30, 33].

Risk factors that are associated with increased severity of disease can be divided into host and environmental risk factors. Host factors include chronological age less than 6 weeks, prematurity, chronic lung disease, congenital heart disease, neurological disease, and immunodeficiency [1, 3, 6, 14, 15, 21]. Additionally there are some indicators to suggest a host genetic predisposition (for example surfactant protein D gene polymorphism) to severe RSV infection [4, 34]. Dual respiratory infections (RSV in addition to other respiratory viruses or concomitant bacteria) have also been shown to increase disease severity as indicated by the need for PICU admission and mechanical ventilation [1, 19, 35, 36]. Environmental factors include poverty, overcrowding, malnutrition, and exposure to postnatal tobacco smoke, older siblings, nursery attendance [1, 3].

The viral strain (A or B) appears not to be an important factor as studies have failed to show significant differences in virulence and severity of disease between A and B strains [6]. The viral load and/or uncontrolled viral replication may well influence disease severity. Higher viral loads in tracheal aspirates of ventilated infants with "severe RSV LRTI" compared to "mild disease" (differentiated on mean airways pressure and oxygenation indices) have been found [37]. A higher nasal viral load in ventilated compared to non-ventilated bronchiolitic children was demonstrated in an initial study, however, a subsequent larger study (from the same research team) failed to find a significant difference [38].

Viral load and/or uncontrolled viral replication being a factor is supported by the finding of excessive viral antigen and overwhelming apoptotic sloughing of infected respiratory epithelial cells in the fatal cases of Chilean children dying from RSV (especially) or influenza bronchiolitis [10]. However, viral strain and viral load alone cannot fully account for variations in disease severity, so it remains likely that variations in pre-existing structural elements of the distal respiratory tree and the inherent immune response also play key roles [10, 14].

Extrapulmonary Manifestations/Effects

Clinical consequences peripheral to the lung parenchyma are well described in RSV infection [39], despite most RSV research having concentrated on the lungs and the mechanics of pulmonary immunopathology. Extrapulmonary effects beg the question as to whether these are direct RSV effects (i.e. RSV infection of that tissue) or indirect, being secondary to parenchymal lung disease and its causative respiratory compromise or consequential of prowling inflammatory mediators?

RSV, like the other *Paramyxiviridae*, can infect non-epithelial cells if it can gain access to the receptors on their surface, as demonstrated by the use of monkey kidney cells for RSV culture in vitro. However the transit of RSV to distant organs would have to be hematogenous. RSV-RNA has been detected by RT-PCR in whole blood, but not plasma of infants and neonates, but this alone merely indicates cell-associated RSV genome. RSV-RNA is not necessarily viable RSV and is more likely to be virus phagocytosed by neutrophils or monocytes. To escape their white cell captors, RSV would need to replicate and break out, which has not yet been demonstrated. Viable RSV floating freely in plasma would hold the potential for distant RSV infection.

Evidence of deposition in distant organs comes from detection of the virus in the myocardium, liver, and cerebrospinal fluid [39]. However, strong convincing evidence of RSV-related inflammation or infection at these sites is less forthcoming. Elevated cardiac troponin levels in infants with severe RSV infection are well described. Unfortunately this is not necessarily indicative of RSV-directed myocardial injury, but more likely the result of (right) heart strain secondary to severe lung parenchymal disease [40, 41]. Likewise, it is highly suggestive that raised hepatic transaminases in this patient group are consequential to hepatic congestion or ischemia due to right heart failure, itself secondary to parenchymal lung disease and/or pulmonary hypertension [41, 42]. Proof of a RSV hepatitis would take histological verification (i.e. liver biopsy), which for ethical reasons is only ever going to occur postmortem. Apneas and seizures undoubtedly occur in RSV infection, but presently there is more support for RSV encephalopathy than RSV encephalitis [39]. The reported frequency of bronchiolitis-induced apnea varies from 1 % to 24 % of those children admitted to hospital, and up to 20 % of those admitted to PICU [43, 44]. Unfortunately many of the reports fail to adequately adjust for the confounding consequence that hypoxic episodes and hypercapnea may have on the patient's neurological status. When not related to hypoxic or electrolyte imbalance triggers, RSV's central influence/effect is probably related to released neurotoxic inflammatory chemokines and cytokines [12, 13]. Endocrine impact/consequences appear to be the sequelae of severe RSV pulmonary disease and/or its treatment. It is likely that occurrences of hyponatremia and hyponatremic seizures are largely related to the use of hypotonic/electrolyte-poor intravenous solutions [39]. Further research is required to scrutinize whether the reported neuroendocrine stress response in RSV bronchiolitis is no more than an epiphenomenon reflecting severity of RSV disease. Extrapulmonary effects are not uncommon and are more likely to be the end result of release of inflammatory mediators than direct effects.

Therapeutic Options in PICU

> Oxygen is vitally important in bronchiolitis and there is little evidence that any other treatment is useful – Reynolds and Cook 1963 [45].

It is 50 years since this statement by Reynolds and Cook and the clinical situation essentially remains the same. Maintaining adequate oxygenation and hydration is the mainstay of largely supportive treatment in bronchiolitis [23, 33, 46].

Oxygen

There are no randomized controlled trials or systematic reviews investigating the use of oxygen in LRTI, let alone bronchiolitis. Evidence for the use of oxygen supplementation is extrapolated from case–control studies that show hypoxemia as a risk factor for near-fatal asthma. It is generally recommended that oxygen saturation levels are maintained above 90 % (USA) and above 92 % (UK) [24, 30, 33].

Bronchodilators

Bronchodilators, generally $ß_2$ agonists (or the anticholinergic, ipratropium bromide), are commonly prescribed in children with bronchiolitis in North America and Europe [32]. Heterogenicity in study design and the bronchodilator used complicate comparisons between studies. On systematic

review, no improvement in oxygenation, hospital admission rate or duration of hospitalization has been demonstrated [47]. There are few studies investigating the benefit of bronchodilators in children with bronchiolitis requiring mechanical ventilation [48]. Any transient improvement in measured lung functions did not translate to significant and sustained clinical benefit or decrease in length of ventilation [16]. Their routine use in ventilated patients, as with non-ventilated patients, remains unsupported [16, 24, 47].

Adrenergics: Epinephrine (Adrenaline)

Nebulized epinephrine with its ß-adrenergic bronchodilator effect, along with the α-adrenergic effect of pulmonary vasoconstriction and reduction in edema, has been considered useful and used in the treatment of bronchiolitis. Although studies on nebulized epinephrine in bronchiolitis show it to have a good safety profile, short-term improvement in clinical scores when compared to both placebo and salbutamol failed to translate into clinically significant improvement in oxygenation or hospital admission rates as confirmed by a Cochrane review [49]. Routine use is generally not recommended [24, 30]. More recently, combination therapy with dexamethasone has shown promise in decreasing hospital admission [50].

Corticosteroids

The rationale for the use of corticosteroids (inhaled, oral or intravenous) comes from their acknowledged benefit in other obstructive airways disease, such as asthma, and their ability to inhibit the immune response which contributes to the pathogenesis of bronchiolitis [8, 37]. Heterogenicity in study design and the corticosteroid administered make comparisons between studies difficult. Systematic reviews have failed to demonstrate benefit in outcome (requirement for hospital (re)admission, requirement for respiratory support, or length of stay in hospital) from systemic corticosteroids or from inhaled corticosteroids [51]. Recently a prematurely-terminated international multicenter randomized controlled trial (the Steroid Treatment in Artificially ventilated children with RSV infection [STAR] trial) investigating the potential benefit of dexamethasone in ventilated children with RSV bronchiolitis failed to demonstrate a difference (duration of ventilation or supplemental oxygen; length of PICU or hospital stay) between the dexamethasone and placebo groups in both the mild and severe oxygen abnormalities subgroups [52]. Likewise a previous meta-analysis combining three trials investigated the role of corticosteroids in ventilated children with RSV bronchiolitis showed no overall effect on duration of mechanical ventilation or hospitalisation [53].

Methylxanthines

Data from uncontrolled trials suggest that there may be some benefit in using methylxanthines, such as theophylline and caffeine, in infants with bronchiolitis-associated apneas [54]. A randomized, double blind, placebo controlled trial to determine whether treatment with caffeine citrate reduces length of PICU stay (primary measure) and frequency of apneic episodes (secondary measure) in infants with viral bronchiolitis associated with apnea is in progress in Qatar (proposed completion date April 2013) [55]. At present there is no convincing evidence base.

Chest Physiotherapy, Nebulised Hypertonic Saline

Three trials have failed to demonstrate compelling evidence of the benefit of chest physiotherapy in bronchiolitis, as borne out by a systematic review [56]. Hypertonic saline by improving mucus viscosity and elasticity, enhancing mucus transport, and decreasing epithelial edema may counter some of the bronchiolitis pathophysiological complications [57]. A meta-analysis of four trials investigating the effect of nebulization with hypertonic 3 % saline solutions vs. 0.9 % saline solutions suggested that nebulized 3 % saline solutions may hold some benefit – reduced length of hospital stay and a decreased clinical severity score. However, none of the studies included mechanically ventilated children [58].

Ribavirin

Ribavirin is a purine nucleoside analogue that is believed to interfere with viral nucleic acid function. Ribavirin has activity against RSV and influenza. Ribavirin is expensive, difficult to deliver as the nebulized droplets adhere to the ventilatory circuit, and teratogenic (therefore potentially toxic to both the patient and the treating team). Systematic reviews have failed to show any convincing effect in the acute [59] or ventilated setting [53]. Because of high cost, safety concerns, challenges in delivery, and weakness with trial data, ribavirin is usually only considered in immunocompromised children in the PICU setting in Europe [33], and the American Association of Pediatrics recommends against its routine use [24].

Antibiotics

Because bronchiolitis has a viral etiology and the reported incidence of extrapulmonary concurrent or secondary bacterial infections is low, many advocate against the routine use

of antibiotics in bronchiolitis [3, 6, 24, 30]. However, in the critical care environment this approach is challenged as bacterial co-infection/concomitant bacterial pneumonia can be found in up to 40 % children requiring mechanical ventilation for severe RSV bronchiolitis [19, 60, 61]. Co-morbidity does not seem to convey additional risk for concomitant bacterial pneumonia [19, 60]. Pediatric intensivists should consider tracheobronchial sampling on intubation or PICU admission, empirical antibiotic cover, and antibiotic review/rationalization with subsequent microbiological results.

Exogenous Surfactant

Endogenous surfactant lowers the surface tension within the alveoli at the alveolar-capillary membrane level. The rationale for exogenous surfactant comes from the findings of low levels of surfactant phospholipids and proteins, along with reduced surfactant function, in children with severe bronchiolitis [18, 62]. Due to its endotracheal route of administration exogenous surfactant can only be considered in intubated children. A systematic review of the three published randomized controlled trials (79 patients) highlighted the inadequacy of available data – variations in surfactant used, study designs, and between-study lengths of ventilation of the control groups confound effective interpretation [62]. Any future large randomized controlled trial will be hampered by the need for multiple centers to obtain adequate numbers and the expense of exogenous surfactant.

Helium – Oxygen (Heliox) Mixture

The pathophysiological rationale for heliox is that with a density one-seventh that of air it would result in decreased resistance to airflow. A number of randomized controlled (some even double-blind) studies using inhaled heliox have been performed in infants with bronchiolitis. None have demonstrated significant beneficial effect in real clinical terms (i.e. need for intubation, duration of ventilation or of PICU stay) [63].

Inhaled Nitric Oxide (iNO)

Inhaled nitric oxide (iNO) by nature of its route of administration produces vasodilation in the bronchial tree, thereby enhancing the blood flow and the ventilation-perfusion quotient. There is a single study examining the effect of inhaled nitric oxide on respiratory mechanics in 12 ventilated infants with RSV bronchiolitis [64]. It concluded that iNO had no apparent bronchodilator effect in the majority of acutely ill infants with bronchiolitis and did not appear to provide any additional benefit over the use of salbutamol. A Cochrane review of randomized controlled trials (535 ventilated children and adults) analysed the effect of iNO in acute hypoxemic respiratory failure [65]. It found that iNO did not demonstrate any statistically significant effect on mortality or ventilator-free days, and only transiently improved oxygenation in patients with hypoxemic respiratory failure.

Recombinant Human DNAse (rhDNAse)

Intraluminal mucus plugs in the distal airways are an important pathophysiologic feature in RSV bronchiolitis. DNA released by degenerating leukocytes is present in these mucus plugs and contributes to their increased viscosity and adhesiveness [66]. By cleaving this released DNA, rhDNAse can help liquefy the mucus. Anecdotal data suggested that rhDNAse was effective in infants with severe RSV bronchiolitis [66]. A multicenter, randomized, double-blind placebo-controlled study in 224 infants with RSV bronchiolitis found that administration of rhDNAse did not reduce the length of hospital stay, duration of supplemental oxygen, and number requiring intensive care or mechanical ventilation [67].

Respiratory Support

If despite oxygen supplementation children develop respiratory failure artificial respiratory support (non-invasive or mechanical ventilation) may become necessary. The application of continuous positive airway pressure (CPAP) keeps the airways open and thereby facilitates expiratory flow, improves compliance, reduces work of breathing and enhances gas exchange. There is supportive evidence that delivery of CPAP via a mask or nasal prongs may reverse impending respiratory failure and avoid intubation [68–70]. On this front, humidified high-flow nasal oxygen is demonstrating great promise in providing effective respiratory support – preventing progression of respiratory failure to needing mechanical ventilation and shortening admissions [71]. Intubation and mechanical ventilation (positive pressure ventilatory support) is the mainstay of supportive therapy for children with viral bronchiolitis-induced respiratory failure due to worsening lung compliance, imminent respiratory collapse secondary to exhaustion, or apnoea and respiratory arrest. Already in the 1980s, retrospective studies confirmed the effectiveness of mechanical ventilation in bronchiolitis-associated respiratory failure [72]. Unfortunately there are no randomized controlled trials on the level of positive end-expiratory pressure (PEEP) or ventilatory strategies (for example, volume-controlled versus pressure controlled, or high frequency versus conventional ventilation) for ventilated children with bronchiolitis-induced respiratory failure [18]. Perhaps this is because bronchiolitis is a heterogeneous lung disease with varying obstructive and restrictive

elements, rather than a homogenous clinical entity [18, 27]. When maximum conventional mechanical ventilation or high frequency oscillatory ventilation (HFOV) fail to stabilize or reverse deteriorating oxygenation (and ventilation), extracorporeal life support (ECLS)/extracorporeal membrane oxygenation (ECMO) is the last port of call for these refractory cases. Survival rates of ECLS/ECMO for RSV bronchiolitis are better than other indications for ECLS/ECMO and range from 71 % [73] to as high as 96 % [74], with a low reported rate of neurological sequelae [75].

Preventive Therapies and Treatments

RSV Immunotherapy

Hyperimmune RSV immunoglobulin (RSVIG) and monoclonal RSV immunoglobulin augment neutralizing antibodies and are used for immunoprophylaxis in high risk patients [3, 6, 24]. They have been shown to reduce hospital admissions from RSV bronchiolitis [76, 77]. Both are expensive, offer partial protection, and require monthly intravenous (RSVIG) or intramuscular (monoclonal RSV immunoglobulin) injections [77]. Their prohibitive expense has lead to many cost-effectiveness analyses and the restriction of use to targeted high risk groups [24, 77, 78]. The use of hyperimmune RSV (polyclonal) immunoglobulin has fallen out of favour due to its intravenous route, the intravenous volume required, an increased risk of adverse outcomes in infants with cyanotic heart disease, and possible inactivation of live vaccines (for example measles-mumps-rubella) [78]. RSVIG is not licensed for treatment in the UK.

Palivizumab, the first humanized monoclonal antibody against the surface F glycoprotein in RSV, is the immunoprophylactic agent generally favored and has been studied extensively [77]. Palivizumab has been shown to reduce RSV-related hospital admission by 55 % in preterm infants born at less than 32 weeks gestation [76] and by 45 % in infants born with significant congenital heart disease [79]. Despite this reduction in hospital admission for serious RSV disease, the cost-benefit balance for infants born at more than 32 weeks gestation or with congenital heart disease is still debated intensely [24, 77]. Although the RSV-IMpact trial examining the efficacy of palivizumab in preterm infants demonstrated an overall reduction in hospitalization of 55 % compared to controls, it did not impact on the number requiring PICU admission (1.3 % vs. 3 %) or the number requiring mechanical ventilation (0.2 % vs. 0.7 %) [76]. Similarly, despite an overall reduction in hospitalization of 45 % compared to controls in the trial examining the efficacy of palivizumab in children with congenital heart disease, the number requiring PICU admission (2 % vs. 3.7 %) or the number requiring mechanical ventilation (1.3 % vs. 2.2 %) was not significantly different [79]. Post palivizumab licensure studies comparing the number of children requiring PICU admission and mechanical ventilation in the RSV seasons prior to palivizumab to those in the RSV seasons following its prophylactic use have found no significant reductions following the introduction of palivizumab [80]. Currently a second generation recombinant humanized monoclonal IgG1 antibody, motavizumab, with enhanced anti-RSV neutralizing activity is being tested.

Internationally guideline recommendations for RSV immunoprophylaxis with palivizumab generally reflect widely accepted high risk subgroups [30, 33, 78]:

1. Children under 2 years of age with chronic lung disease (oxygen dependency for at least 28 days from birth) on home oxygen or who have had prolonged use of oxygen, or receiving medical therapies for chronic lung disease
2. Children under 2 years of age (USA) or infants less than 6 months of age (UK) who have hemodynamically significant congenital heart disease (cyanotic or acyanotic) and/or pulmonary hypertension
3. Children under 2 years of age with severe congenital immuno-deficiency (UK)
4. Children under 2 years of age with "significant congenital abnormalities of the airway or a neuromuscular condition that compromises handling of respiratory tract secretions" (USA).

Vaccination

The first RSV vaccine produced in the 1960s was a formalin-inactivated vaccine. Even though it produced high serum antibody levels it resulted in worse bronchiolitis following RSV infection in the vaccinated group than the control non-vaccinated children [3, 6, 15]. Development of an effective RSV vaccine is being actively explored and is a high research priority [3, 6]. A RSV vaccine needs to offer better protection than that from natural infection and be effective in the first weeks of life when maternally-acquired anti-RSV antibodies are still present. Live attenuated vaccines have the potential advantages of being delivered intranasally and inducing both a local mucosal and a systemic immune response. However, they tend to be unstable, too virulent and revert back to wild-type virus [3, 6, 15]. Vaccines produced from purified viruses, recombinant vectors, and plasmids containing complementary DNA of the viral genome that generally target the F (fusion) and G (attachment) transmembrane glycoproteins are being trialled [3, 6, 32].

New Anti-RSV Agents

Novel small molecule antivirals (for example, small inhibitory RNAs) are currently being developed that inhibit RSV replication by interfering with specific mRNA causing

mRNA degradation and targeted down-regulation [81]. They may hold the potential for a direct and directed anti-RSV therapy.

Conclusion

Bronchiolitis produces significant morbidity and mortality worldwide every year. Not all children are equal when it comes to bronchiolitis – those with underlying chronic conditions/comorbidity carry an additional risk of severe disease and death. Although a basic supportive management approach remains the cornerstone, our understanding of bronchiolitis, its pathogenesis and pathophysiology, its impact on multiple organ systems and its treatment options, has progressed over time.

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