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Abstract

Lower respiratory tract infections in children are often viral in origin. Unfortunately in this time of significant antimicrobial resistance of infectious organisms, especially bacteria, there is still a tendency for clinicians to manage a child who coughs with antibiotics. In addition, the World Health Organization (WHO) has defined “pneumonia” as a condition that only occurs in children who have “fast breathing or chest wall indrawing”. That would delineate upper respiratory tract infections from those in the lower airway. However, in addition to pneumonia another important entity exists in the lower respiratory tract that is almost always viral in origin. This condition is acute viral bronchiolitis. The concept of “acute lower respiratory tract infection” (ALRTI) has emerged and it is becoming increasingly evident from a number of studies that the infectious base of both acute pneumonia (AP) and acute bronchiolitis in children has a mixed etiology of microorganisms. Therefore, whilst certain clinical phenotypes do not require antibiotics the actual microbial etiology is much less distinct.

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2.1 Introduction

Lower respiratory tract infections in children are often viral in origin. Unfortunately in this time of significant antimicrobial resistance of infectious organisms, especially bacteria, there is still a tendency for clinicians to manage a child who coughs with antibiotics. In addition, the World Health Organization (WHO) has defined “pneumonia” as a condition that only occurs in children who have “fast breathing or chest wall indrawing” [1]. That would delineate upper respiratory tract infections from those in the lower airway. However, in addition to pneumonia another important entity exists in the lower respiratory tract that is almost always viral in origin. This condition is acute viral bronchiolitis. The concept of “acute lower respiratory tract infection” (ALRTI) has emerged and it is becoming increasingly evident from a number of studies that the infectious base of both acute pneumonia (AP) and acute bronchiolitis in children has a mixed etiology of microorganisms. Therefore, whilst certain clinical phenotypes do not require antibiotics the actual microbial etiology is much less distinct.

Both pneumonia and acute viral bronchiolitis are major causes of health care utilization and hospitalization in higher socio-economic regions of the world and pneumonia is the leading cause of death in children, under 5 years of age, in developing countries [2–5]. The HIV epidemic has contributed enormously to more severe AP and thus increased the mortality [3, 5]. ALRTI accounts for between 30 and 40% of hospital admissions, with associated case fatality rates of between 15 and 28% in developing countries but death is less common in the developed world [5, 6]. Despite the provision of effective and affordable vaccines and antibiotics that have reduced pneumonia mortality from four million in 1981 [7] to just over one million in 2013 [8], pneumonia still accounts for nearly one-fifth of childhood deaths worldwide. Risk factors for AP are reflected in Table 2.1.

2.2 Definitions

AP is usually community acquired, although children in hospital and in long-term health and social facilities are at risk of hospital acquired infections. Community acquired pneumonia (CAP) can be defined as an acute infection (of less than 14

Table 2.1 Risk factors for acute pneumonia in children

Young children
Prematurity
Malnutrition
Immunosuppression (including HIV)
Poor social/environmental circumstances (including household crowding)
Passive tobacco smoke exposure
Indoor fuel exposure
Inadequate vaccine administration
Winter season

days' duration), acquired in the community, of the lower respiratory tract leading to cough or difficult breathing, tachypnoea or chest-wall in-drawing [9]. For the purposes of this chapter AP will be assumed to be community acquired.

Bronchiolitis is a viral-induced lower respiratory tract infection (LRTI) that occurs predominantly in children <2 years of age, particularly infants [10].

2.3 Etiology of ALRTI in Children

AP is caused mostly by viruses and bacteria. Not only is it clinically impossible to distinguish viral from bacterial pneumonia, new evidence suggests that most cases of AP in children have a mixture of micro-organisms in the airway and that both bacteria and viruses occur in combination [11]. In addition, finding an organism on the common tests employed (of airway secretions) does not prove that organism is causing the LRTI. In addition, the problem is compounded by the fact that many healthy children harbor both viruses and bacteria in their airways [11]. These findings suggest that the management of a LRTI in children requires choosing therapies based on clinical findings rather than on special investigations. The possible causes of pneumonia in children are listed in Table 2.2.

Bacteria are the important organisms causing pneumonia-related death [1, 3, 4]. *Streptococcus pneumoniae* is the commonest cause of bacterial pneumonia, but with the introduction of vaccination against pneumococcus around the world, this cause of pneumonia is becoming less common. Other bacteria that remain a cause

Table 2.2 Common causes of AP in infants and children

<i>Viruses</i>
Respiratory syncytial virus
Human metapneumovirus
Parainfluenza virus types 1 and 3
Adenovirus
Influenza A and B
Rhinovirus
Other viruses - measles, boca and corona virus
<i>Bacteria</i>
<i>Streptococcus pneumoniae</i>
<i>Haemophilus influenzae</i>
<i>Staphylococcus aureus</i>
<i>Mycobacterium tuberculosis</i>
<i>Moraxella catarrhalis</i>
<i>Bordetella pertussis</i>
<i>Mycobacterium tuberculosis</i>
<i>Atypical bacteria</i>
<i>Mycoplasma pneumoniae</i>
<i>Chlamydia trachomatis</i>
<i>Chlamydophila pneumoniae</i>

of pneumonia include *Staphylococcus aureus* and *Haemophilus influenzae*, both type b (Hib) and non-typeable disease. The routine immunization of children against Hib has decreased the incidence of pneumonia due to this bacterium, although non-typeable strains are still responsible for a significant proportion of pneumonia.

In addition pathogens vary by age and neonates and children younger than 2 months of age Gram-negative bacteria, Group B streptococcus, *S. aureus*, and *C. trachomatis*, are important causes. Atypical bacteria are said to be more common in children older than 5 years of age, but may occur at any age.

Mycobacterium tuberculosis (TB) has been recognized as an important cause of AP in both HIV-infected and HIV-uninfected children [12]. In Uganda 20% of 270 children with severe AP had clinically suspicious TB and 10% had a culture confirmed diagnosis [13].

Respiratory syncytial virus (RSV) is the commonest cause of viral AP, especially in the first year of life. RSV causes significant mortality and morbidity, especially in children born prematurely and who have other risk factors (Table 2.5). HIV-infected children with RSV are more likely to develop pneumonia rather than bronchiolitis compared with HIV-uninfected children. Other important respiratory viruses include human metapneumovirus, parainfluenza virus types 1 and 3, adenovirus, influenza A and B, rhinovirus, bocavirus, coronavirus and measles virus.

The most frequent cause of bronchiolitis is human rhinovirus (RV) and of severe bronchiolitis, respiratory syncytial virus (RSV) infection, with other respiratory viruses (para-influenza virus (PIV), influenza virus, human metapneumovirus (hMPV), measles virus, bocavirus and coronavirus) being less common.

RSV is an RNA virus. The two major RSV subgroups are A (RSV-A) and B (RSV-B), which are further characterized into several genotypes, based on antigenic and genetic variability of the G-protein. A number of genotypes can produce disease at the same time in a single season, and genotypes often vary from year to year.

Human RV is a Picornavirus, a small RNA virus of which there are 100 serotypes. The major group (90% of serotypes) use ICAM-1 as the cellular receptor, the minor groups use, amongst others, the LDL receptor. RV replicates in the nose and LRT.

Influenza and parainfluenza (1–4) are also RNA viruses. PIV 1 and 2 (Respirovirus genus) produce URTI's and laryngo-tracheo-bronchitis in children 2–5 years of age. PIV 3 (Rubulavirus genus) is responsible for bronchiolitis in infants. PIV 4 rarely causes disease. Human coronavirus produces 15% of the common colds and occasional bronchiolitis. HMPV is a common cause of bronchiolitis.

Adenovirus is a large naked DNA virus, which inhibits the expression of host messenger RNA, inducing excessive production of adenoviral proteins. It is responsible for prolonged replication and thus severe disease.

2.4 Epidemiology of ALRTI

Epidemiological studies on pneumonia and bronchiolitis often include all children presenting with a clinical diagnosis of LRTI, and may overestimate the true incidence of each entity (AP or bronchiolitis) alone. In one study of LRTI, in South

Africa (SA), the respiratory viruses were detected in 78% of cases. The viruses that were isolated included RV in 37%, RSV in 26%, adenovirus in 26%, influenza virus in 7% and hMPV in 5% [14]. In 2009 and 2010, this surveillance study evaluated respiratory viruses by a 10-plex real-time reverse-transcription polymerase chain reaction (rRT-PCR) [15]. Respiratory viral co-infections were common and 17.4% of cases had more than two viral coinfections [15].

A number of studies have found that RV is identified in children with bronchiolitis; however, this virus is also commonly identified in healthy children without symptoms and this makes it difficult to definitively link RV to etiology of bronchiolitis. Early studies have suggested that oxygen saturation is generally not as low in children with RV-associated bronchiolitis as in those with RSV-associated bronchiolitis [16]. However, more recent studies suggest that RV may be more sinister [17]. All three types of RV have been identified in LRTI, although RV-A and RV-C are more common than RV-B. RV is associated with symptomatic respiratory illness; however, there is no association between RV type and disease severity [18]. RV-D has subsequently been identified [19].

RSV is the most common cause of moderate to severe bronchiolitis and a leading cause of ALRTI among young children. RSV-associated bronchiolitis occurs most frequently in infancy, being 2–3 times more likely to occur then, than in older children. Within RSV disease, genotypes differ in different studies [20] and these differences could be related to the extent of community immunity to the specific genotype, with more severe disease observed in the presence of lower community immunity to that strain.

Infection with RSV does not result in permanent or long-term immunity, as re-infections, usually of lesser severity, are common and may be experienced throughout life [21]. An estimated 33.8 million new episodes of RSV-associated acute lower respiratory tract infection (ALRTI) occurred worldwide in 2005 in children under-5 (22% of episodes), with at least 3.4 million episodes necessitating hospital admission. An estimated 66,000–199,000 children under-5 died from RSV-associated ALRTI in 2005, with 99% of these deaths occurring in developing countries [22]. In SA, for example, the prevalence of RSV among 4293 LRTI hospitalizations in under-5 children was 27%, including 863 of 1157 (75%) less than 12 months of age, of whom 637 (74%) were less than 6 months old. Nine of 1153 children with RSV-associated ALRTI died (case fatality proportion 1%). Children admitted with RSV-associated ALRTI were younger than those who tested RSV negative [23].

RSV-associated severe ALRTI occurs in all children from both developing and developed countries roughly to the same extent. However, the case fatality rate is higher in developing areas (2.1% vs. 0.3–0.7%) [22]. The case fatality rate for individual risk factors for RSV-associated disease among children with chronic lung disease, congenital heart defects (CHDs), nosocomial infection, intensive care unit admission and prematurity is significantly higher [24, 25]. HIV is associated with a two to three fold greater risk of RSV pneumonia, but seemingly not bronchiolitis [11]. In addition mortality is higher in HIV-infected children (12% vs. 2% in HIV-uninfected children) [23].

2.4.1 Bacterial-Viral Interactions

Bronchiolitis is a disease caused by respiratory viral infections, with little evidence of bacterial coinfection [26]. There may however, be important viral-bacterial co-infections [27]. Bacterial infections may complicate cases of respiratory viral infections but these children usually present with the more classic signs of AP, including alveolar consolidation on chest radiographs, raised C-reactive protein (≥ 40 mg/dL), temperature ≥ 38 degrees centigrade ($^{\circ}\text{C}$) (100.4 $^{\circ}\text{F}$), chest crackles and bronchial breathing on chest auscultation. The role of bacterial co-infections in children with a respiratory virus-associated pneumonia is frequently under emphasized owing to limited tools for diagnosing bacterial pneumonia, with blood culture sensitivity ranging from 3 to 18% for detecting pneumococcal pneumonia [28]. However, epidemiological studies have identified a strong temporal association between some respiratory viruses and invasive pneumococcal disease. Included among these are studies on the temporal association of the influenza virus and RSV epidemics and invasive pneumococcal disease [29]. Further evidence for this association was observed in an randomized controlled trial of an investigational 9-valent pneumococcal conjugate vaccine (PCV), in which children vaccinated with PCV had a 32% lower risk of being hospitalized for a viral-associated pneumonia compared with placebo recipients [30]. This lower risk of respiratory virus-associated hospitalization was evident for influenza virus, hMPV and RSV-associated pneumonia [31]. The biological rationale for the reduction in respiratory virus-associated pneumonia among the PCV-vaccinated children in this study, was attributed to vaccination having prevented the superimposed vaccine-serotype pneumococcal co-infection, which would have led to progression to more severe disease, culminating in hospitalization among the placebo recipients. Notably, there was no reduction in hospitalization for bronchiolitis among the PCV9 vaccinated children, corroborating that pneumococcal co-infection was unlikely to have played a role in the pathogenesis of bronchiolitis.

The pathogenesis of increased susceptibility to pneumococcal infection following RSV infection in mice-model studies has been attributed to RSV G glycoprotein-binding penicillin-binding protein 1a increasing pneumococcal virulence owing to up-regulation of virulence genes, pneumococcal toxin and pneumolysin. This could lead to an increase in the inflammatory response and bacterial adherence to human ciliated epithelial cultures [32, 33]. This again is corroborated by studies in children with alveolar pneumonia associated with RSV or RV infection, among whom higher pneumococcal bacterial load was observed in the nasopharynx than in children with RSV or RV in the absence of alveolar consolidation [34].

Evidence from an epidemiological study in the USA, revealed that RSV AP and pneumococcal pneumonia tended to occur together over similar time periods, with RSV associated with a significant increase in the incidence of pneumococcal pneumonia in children less than 1 year of age (attributable percent 20.3%) and among children aged 1–2 years (attributable percent 10.1%). Similarly, influenza was associated with an increase in pneumococcal pneumonia among children aged 1–2 years. After the introduction of PCV7 into the USA there was an observed decline

in RSV-coded hospitalizations for children <1 year old (attributable percent –18.0% for 2004/2005–2008/2009 vs. 1997/1998–1999/2000) [35]. Although the above mentioned data support an interaction between RSV and pneumococcal superimposed infections, these specifically refer to children who are hospitalized with RSV-associated pneumonia and not to those with bronchiolitis or milder outpatient RSV-associated illness. As such, empiric antibiotic treatment against pneumococcus with RSV-associated pneumonia is only warranted in a child who is hospitalized and whose clinical syndrome is more in keeping with AP rather than uncomplicated bronchiolitis.

There are a number of factors that create circumstances in which RSV and subsequent infection, occur. These include geographical locations (latitude and altitude) and climatic factors (temperature, barometric pressure, relative humidity, vapor tension, hours of light, precipitation, dewpoint). In most temperate regions, such as the USA and Europe, RSV outbreaks last an average of 3–4 months, with a peak incidence during winter, although the exact timing of onset of the outbreak is uncertain. In tropical regions, RSV outbreaks are not distinctly related to season, but often occur during the hottest rainy season [36].

RSV disease is not distinctly seasonal in HIV-infected children and often occurs throughout the year because the virus is shed over a longer period (up to 100 days post infection) compared with 5–7 days in HIV-uninfected children [37]. Although HIV-infected children with RSV-associated ALRTI are at increased risk of hospitalization and death, this could be due to greater susceptibility to co-infections. The increased risk of RSV-associated ALRTI hospitalization in HIV-infected children is greatest during infancy, but remains high even into toddlers [23].

2.5 Pathophysiology of Disease

Immunologically children at risk of bronchiolitis often have an abnormal inflammatory response to infection [38]. Conflicting results from different studies of children with bronchiolitis make definitive conclusion about which cellular regulation and cytokines are at play. One study has documented that nasopharyngeal cytokines interleukin (IL)-6, IL-1B and IL-8 are more significantly elevated in more severe RSV-related disease [39], whilst another study revealed that the T helper (Th) 17 related cytokines IL-1B, IL-17A and IL-23 were associated with a reduction in clinical symptoms [40]. Certainly it seems likely that an uncontrolled or abnormal host response to viruses determines clinical outcome. It is also likely that the inflammatory cellular response influences disease severity, with for example, formation of neutrophil extra-cellular traps (NETs) in abundance in more severe disease that occlude small airways [41]. Whilst the role of vitamin D in disease association has been demonstrated for a host of acute and chronic inflammatory conditions at least one study suggest that vitamin D insufficiency is not characteristic of more severe bronchiolitis [42].

The viral infection starts in the upper respiratory tract and spreads to the lower tract within a few days, resulting in inflammation of the bronchiolar epithelium and

edema of the submucosa and adventitia [43]. Plugs of sloughed, necrotic epithelium, fibrin and excessive mucus secretions add to airway obstruction, causing partial or total obstruction to airflow [44]. A “ball-valve” mechanism can result in trapping of air distal to obstructed areas, with subsequent absorption, atelectasis, and a mismatch of pulmonary ventilation and perfusion that may lead to hypoxemia. Smooth-muscle constriction does not contribute significantly to airway obstruction. Although these mechanisms are known for RSV bronchiolitis, it is assumed that other viruses produce similar pathological conditions. In AP the pathology is centered on the alveolus with neutrophil driven inflammation.

2.6 Diagnosis of an ALRTI

The diagnosis of a LRTI should be considered in any child who has an acute onset of respiratory symptoms, particularly cough, fast breathing or difficulty breathing. Diagnosis includes clinical evaluation, radiographic evaluation and etiological investigations to distinguish between pneumonia and bronchiolitis; decide on management based on the severity; and determine the causative organism where possible and necessary (hospitalized children).

2.7 Clinical Diagnosis of ALRTI

A history and clinical examination are the basis for diagnosing AP and evaluating the severity of illness. The physical examination should include assessment of the child’s general appearance, measurement of the respiratory rate, evaluation of the use of accessory muscles and assessment of oxygenation. Auscultation of the chest is an important step.

The principal symptoms of pneumonia are cough, dyspnea or tachypnea (fast breathing). For diagnosis of pneumonia and assessment of the severity of respiratory illness simple clinical signs (respiratory rate and lower chest-wall indrawing) are recommended. WHO guidelines [1] recommend the following:

- That pneumonia be diagnosed when a child older than 2 months has a cough or difficult breathing with tachypnea defined as: (1) more than 50 breaths per minute (bpm) for infants 2–12 months of age; and (2) greater than 40 bpm for children 1–5 years of age.
- That severe/very severe pneumonia be diagnosed when a child has lower chest wall retractions or a general danger sign (Fig. 2.1). The presence of wheezing and clinical chest hyperinflation, without bronchial breathing, on auscultation is suggestive of bronchiolitis as the cause of the lower respiratory tract illness [10].

The presentation of AP can range from mild to severe life threatening illness. It is essential to ensure children with severe disease are hospitalized (Table 2.3) and children with less severe AP are managed as outpatients. Assessment of the general

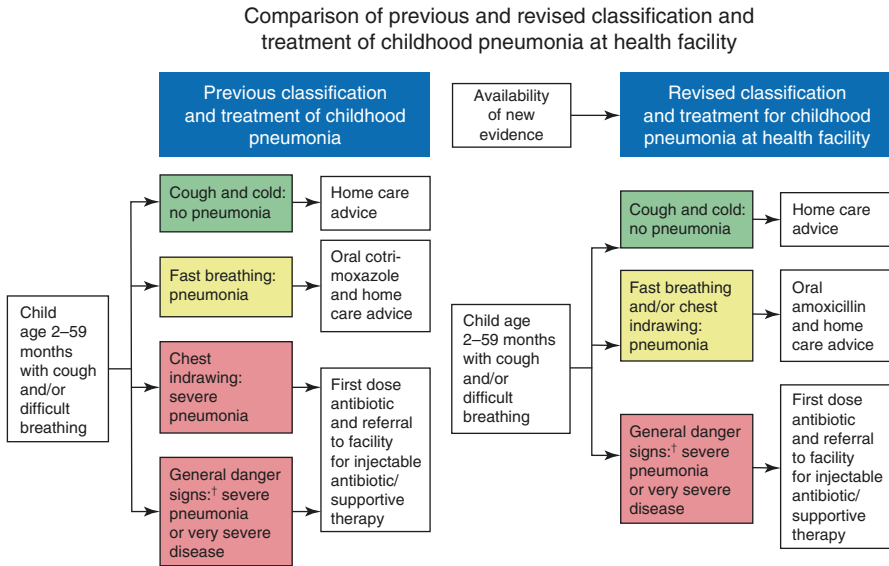


Fig. 2.1 WHO recommendation for management of acute pneumonia. Reprinted with permission from [1]

Table 2.3 Indications for admission to hospital for a child with AP

All children younger than 2 months
Children older than 2 months with:
Impaired level of consciousness
Inability to drink or eat
Cyanosis
Stridor in calm child
Grunting
Severe chest-wall indrawing
Room air SaO ₂ ≤ 92% at sea level or <90% at higher altitudes
Severe malnutrition
Family unable to provide appropriate care
Failure to respond to ambulatory care or clinical deterioration on treatment

appearance of the child is helpful in determining the severity of illness. The WHO guidelines [1] define specific “danger signs” that indicate severe disease requiring referral to hospital including inability to drink, convulsions, abnormal sleepiness, or persistent vomiting. All children with pneumonia under the age of 2 months require admission to hospital (Table 2.3).

Assessment of oxygenation is important in the evaluation of a child with pneumonia and pulse oximetry should be performed on all children seen at a hospital. To ensure an accurate reading, a pediatric wrap around probe should be used. Children

with a saturation of less than 92% at sea level or less than 90% at higher altitudes should be considered for hospital admission and supplemental oxygen [9].

Clinically AP presents in a similar way in HIV-infected and HIV-uninfected children [45]. However, pneumonia resulting from opportunistic pathogens should also be considered in HIV-infected children. Of these, *Pneumocystis jiroveci* and cytomegalovirus (CMV) are the most common and serious infection among infants, occurring commonly at 6 weeks–4 months of age. These infections are frequently the initial presenting feature of AIDS in HIV-infected children not taking cotrimoxazole prophylaxis [46, 47]. Clinical features include cough, dyspnea and relatively few crackles on chest auscultation. Hypoxia is prominent and often severe. These infants often require ventilator support for the severity of pneumonia and multiple antibiotic strategies [46].

Bronchiolitis may be diagnosed on the basis of clinical signs and symptoms. In a young child, the diagnosis can be made on the clinical pattern of wheezing and hyperinflation. Bronchiolitis follows an upper respiratory tract infection with low-grade fever and cough and 1–2 days later the infant develops fast breathing, hyperinflation and wheeze as a consequence of lower airway inflammation and air trapping [10]. The illness is generally self limiting, but may progressively become more severe and include signs such as grunting, nasal flaring and hypoxemia [21]. The most reliable clinical feature of bronchiolitis is hyperinflation of the chest, evident by loss of cardiac dullness on percussion, an upper border of the liver pushed down to below the 6th intercostal space, and the presence of a Hoover sign (subcostal recession, which occurs when a flattened diaphragm pulls laterally against the lower chest wall) (Fig. 2.2).

Measurement of peripheral arterial oxygen saturation is important to indicate the need for oxygen therapy. As with AP, hypoxia indicates that the child requires hospital admission for oxygen therapy.

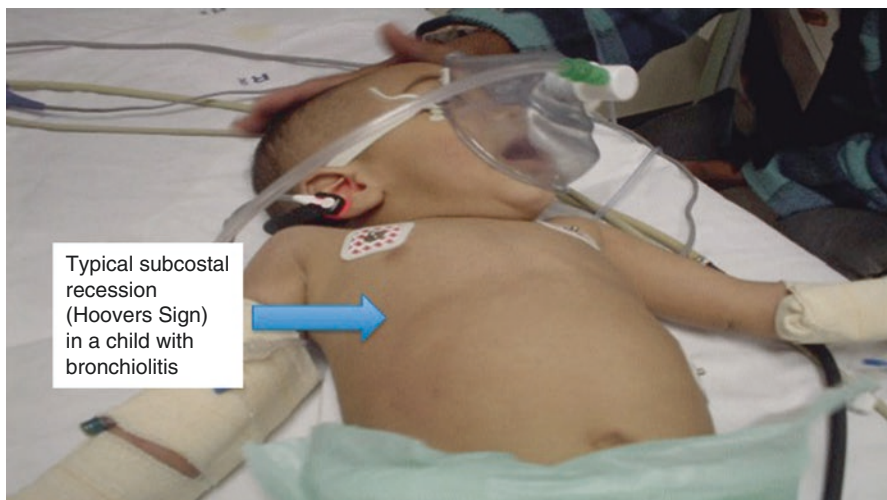


Fig. 2.2 A child with clinical hyperinflation of the chest and a “Hoovers Sign”

2.8 Radiological Diagnosis of ALRTI

A chest radiograph (CXR) may be useful for confirming the presence of pneumonia and detecting complications such as a lung abscess or empyema. CXRs are not useful for distinguishing between viral and bacterial etiologies [48]. Studies have demonstrated that a CXR does not result in improved outcome or change of treatment in an ambulatory setting [49]. The cost, radiation exposure, need for infrastructure, staffing and wide observer variation in interpretation all suggest that routine use of CXRs is not required. There is also no evidence that a routine lateral CXR improves the diagnostic yield in children with AP, except if tuberculosis (TB) is suspected [50].

Definite indications for a CXR include:

- Clinical pneumonia not responding to initial antibiotic therapy
- Unusual clinical presentation or resolution
- When TB is suspected
- Suspected foreign body aspiration
- Hospitalized children to detect complications.

CXRs may also be considered in children presenting with high fever, leukocytosis and no obvious focus of infections, since roughly a quarter of pyrexial children without obvious clinical source may have pneumonia [51].

The interpretation of CXR changes is even more difficult in HIV-infected children as chronic radiological lung changes are common, especially with increasing age [52].

CXRs are generally unhelpful when bronchiolitis is the clinical diagnosis in a child and not required if the clinical diagnosis is obvious. Risk of pneumonia is low in children with saturation greater than 92% and with only mild respiratory distress [53]. Pneumonia is more likely with associated fever [54].

CXRs in bronchiolitis show signs of hyperinflation (Fig. 2.3). The additional features of airway inflammation (peribronchial thickening or sub-segmental

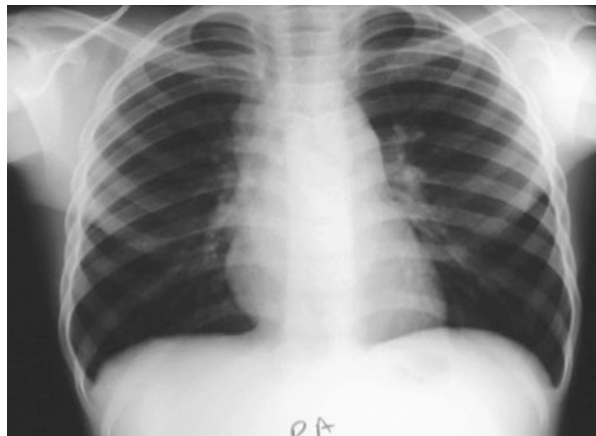


Fig. 2.3 CXR demonstrating marked hyperinflation in acute bronchiolitis

atelectasis) are often misinterpreted as pneumonia. A CXR should only be performed in the following instances [53–55]:

- If complications are suspected, e.g. pleural effusion or pneumothorax
- Severe cases
- Temperature ≥ 38 °C (100.4 °F)
- Uncertain diagnosis
- If the child fails to improve or if their condition deteriorates.

A new modality that is emerging as a diagnostic tool for AP is clinical lung ultrasound and especially point-of-care lung ultrasonography (POCLUS). In one study this form of testing revealed a sensitivity of 87.1% and specificity of 94.8% against CXR interpretation of experienced radiologists [56]. The value of this modality is the lack of ionizing radiation exposure and potential use even in developing nations.

2.9 Investigations for ALRTI

The clinical and radiographic features of AP cannot reliably determine the etiology of pneumonia. However, additional tests to help identify a causative agent should be sought in hospitalized children as identification of a pathogen may allow for more directed therapy, provide important epidemiological data and allow for the implementation of infection control measures to reduce the risk of nosocomial transmission of specific pathogens (Table 2.4). However, identifying a specific etiological agent is difficult and may not be possible in most children. Diagnostic testing should not lead to delay in initiation of therapy as this may adversely affect outcome. Empirical treatment should be commenced based on the most likely pathogen and modified according to microbiological results. The following points should be considered when investigating the etiology:

- General tests of infection including acute phase reactants (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)), white cell count (WBC), neutrophil count and procalcitonin will not differentiate between bacterial and viral pneumonia [57–59]
- Blood culture may be useful to identify bacterial pathogens and their antimicrobial sensitivity, but only about 5% of blood cultures are positive in HIV-uninfected children with bacterial CAP. The sensitivity of blood cultures is greater in HIV-infected children, in whom approximately 18% of cultures are positive [28]

Table 2.4 Investigations in children hospitalized for acute pneumonia

Pulse oximetry/arterial blood gas
Chest radiograph
Blood culture (recognizing the limited value)
Induced sputum for TB testing (where appropriate)
Tuberculin skin testing (where appropriate)
NPA for viral detection
Aspiration of pleural fluid

- Pleural fluid, if present, should be aspirated and sent for culture and sensitivity testing
- Specimens for culture from the lower respiratory tract can be obtained using sputum induction [60], endotracheal aspiration in intubated children and bronchoalveolar lavage (BAL). The isolation of bacteria from these samples (either on culture or using new PCR techniques) may, however, represent contamination with bacteria that normally colonize the nasopharynx
- Tuberculin skin testing (Mantoux method) and induced sputum or gastric lavage are indicated when TB is suspected [61].

Blood tests are not needed routinely for children with definitive clinically diagnosed bronchiolitis. Risk factors in patients with severe bronchiolitis that require hospitalization and may even cause death, include prematurity, congenital heart disease and congenital lung malformations.

Hematological testing (including complete blood counts and C-reactive protein) does not provide additional information in managing bronchiolitis [14, 62]. If the infant appears severely ill, consider alternative diagnoses (bacterial co-infection and other causes of airway obstruction). Clinical signs of concern include pallor, lethargy, severe tachycardia, high temperature, hypotonia or seizures. In cases of serious sepsis investigations may include a CXR, blood culture, and urinary and cerebrospinal fluid analysis [17].

Nasopharyngeal aspirates (NPAs) are not usually taken and viral testing does not assist in the management of bronchiolitis. However, NPAs may be helpful for purposes of disease surveillance, and also in the following cases [17, 43]:

- Neonates
- Where apnea is a prominent feature
- Isolation of patients.

The correct procedure for a NPA should be followed in order to achieve best results. NPAs should be placed in viral transport medium at 4–8 °C (39.2–46.4 °F) and transported to an appropriate laboratory within 72 hours of collection. Specimens should be tested by multiplex real-time reverse-transcription polymerase chain reaction (rRT-PCR) assay for respiratory viruses. Comparative studies have shown that rRT-PCR assays are more sensitive than viral culture and immunofluorescence assays [63]. Multiplex PCR testing has been documented to allow testing for a number of viruses in one assay and is thus more cost-effective [63].

2.10 Severe and Chronic Disease

In infants certain factors predispose to more serious lower respiratory tract illnesses, bronchiolitis and pneumonia. Infants less than 1 year of age are at greatest risk of bronchiolitis, and more severe when additional risk factors are present (Table 2.5) [64–69]. Debate about the importance of RSV infection as a cause of hospitalization in late preterm infants has raged because of the cost of prophylactic therapy. Recent

Table 2.5 Risk factors for more severe bronchiolitis

Age under 1 year
Male sex
Day care attendance
Prematurity
Congenital heart disease
Chronic lung disease
Immunodeficiency
Household smoker

reports have suggested that these infants are at equal risk and require prophylaxis [70, 71]. Studies have revealed that the mean duration of symptoms following bronchiolitis was 12 days. After 21 and 28 days, 18% and 9%, respectively, were still ill. Many infants require additional follow-up visits to a doctor [72].

Many studies have concluded that the respiratory viruses, especially RSV and RV, may predispose to recurrent wheezing in early life and possibly asthma [73–76]. There is now increasing evidence that the asthma phenotype expression is strongly influenced by respiratory viral infection. Whilst allergy may contribute to asthma initiation, viruses and recurrent viral infections are now understood to be equally important. The effect on asthma, however, is strongest when both factors (allergy and infection) operate in synergy [77]. New evidence suggests that susceptibility to recurrent viral infections, failure to generate protective immune tolerance to aero-allergens, and the interaction of these factors with airway inflammation may result from innate immune defects of respiratory epithelial (including mucosal dendritic) cells [77–80]. The resultant viral interaction with airway cells produces up-regulation of high-affinity IgE receptors on myeloid precursor cells, amplifying local airway inflammation. The genetic profile and polymorphisms of these associations are now being discovered [81]. Toll-like receptor 1 single nucleotide polymorphisms (TLR1 SNPs) has been associated with both atopy and multiple viral presence in host airways [81].

2.11 Differential Diagnosis of Viral LRTI

The differential diagnosis of acute and chronic respiratory symptoms is a long one, however, some of the conditions listed in Table 2.6 should be considered.

2.12 Management of ALRTI

AP is always treated with an antibiotic, even though many are viral, or mixed infection, in etiology [9]. The actual antibiotic/s used depend on the local microbial epidemiology drug resistance patterns, confounding factors such as comorbid disease and availability of antibiotics in the region. In most regions of the world the common causative organisms are sensitive to amoxicillin, and hence most

Table 2.6 Differential diagnosis of LRTI

Acute symptoms
Bronchopneumonia or bronchiolitis—other etiology
Pertussis
Foreign body
Myocarditis
Recurrent wheeze or cough
Cystic fibrosis
Cardiac disease
Gastro-esophageal reflux
HIV/tuberculosis

studies and local guidelines recommend amoxicillin as the antibiotic of choice [82–84]. In addition the dosing recommendation is now **40 mg/kg/dose twice daily (80 mg/kg/day) for three to 5 days [1]. Three days of therapy is recommended for AP without chest in-drawing and 5 days for AP with chest in-drawing [1]**. It must be noted that the etiology of pneumonia in children differs with age. Children younger than 2 months of age are more likely to harbor a Gram-negative infection and they usually require Gram-negative cover with an aminoglycoside or a cephalosporin. It is always claimed that children older than 5 years of age are more likely to have pneumonia caused by *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, and may therefore require a macrolide [85, 86]. It is also true that such infections may occur at any age and any child who does not respond to first line antibiotics or who has an atypical presentation should be considered for a macrolide [85].

HIV-infected children, with more severe pneumonia or who are malnourished should have the possibility of a Gram-negative organism covered with appropriate antibiotics [87, 88]. In addition in HIV-infected young infants PCP should be considered and co-trimoxazole added [1].

When *S. aureus* is suspected, cloxacillin is the drug of choice. This should be considered if there is clinical evidence of skin lesions and abscesses and radiological evidence of pneumatocele, empyema or abscess formation or if the child remains pyrexial 48 hours after starting amoxicillin. In HIV-infected children, approximately 60% of community acquired *S. aureus* may be resistant to cloxacillin and require treatment with vancomycin [89].

World-wide there is an increase in the incidence of *S. pneumoniae* resistance to the beta-lactam antibiotics, as well as other classes of antibiotics [1, 84]. However, the benefits of amoxicillin when used in the treatment of pneumonia still makes it the preferred antibiotic [1, 84]. In children with pneumonia, the increasing resistance of pneumococcus to penicillin can be overcome by giving a higher dose of amoxicillin. The use of high-dose amoxicillin (40–45 mg/kg/dose twice a day) is advocated. Antibiotic recommendations are summarized in Table 2.7.

Intravenous and intramuscular administration of antibiotics is traumatic to children, expensive and does not improve outcome in uncomplicated pneumonia. Oral amoxicillin has similar efficacy to parenteral penicillin in treatment of severe

Table 2.7 Empirical antimicrobial therapy for pediatric pneumonia [1]

0–2 months of age	– Recommend admission to hospital
	– Ampicillin/penicillin + gentamicin/aminoglycoside iv
3 months–5 years	– Oral amoxicillin po high dose for ambulant children
	– Ampicillin/penicillin iv + aminoglycoside iv for hospitalized children
	– Add: cloxacillin if suspect <i>Staphylococcus aureus</i>
Older than 5 years	– Amoxicillin po high dose or
	– Macrolide po (erythromycin/clarithromycin/azithromycin) if suspect <i>Mycoplasma pneumoniae</i> or <i>Chlamydomphila</i> spp.
	– Ampicillin or 3rd generation cephalosporin (Cefuroxime, Cefotaxime, Ceftriaxone) iv for hospitalized children
	– Add: cloxacillin if suspect <i>Staphylococcus aureus</i>

po oral, iv intravenous

pneumonia [84]. Parenteral administration should only be given to those children who are severely ill and those with gastrointestinal disturbances (vomiting and diarrhea) in whom absorption may be problematic.

It is generally recommended that 3–5 days of therapy is sufficient for uncomplicated pneumonia. A Pakistan study of HIV-uninfected children with uncomplicated pneumonia reported that the clinical efficacy of 3 days of oral amoxicillin was similar to 5 days for outpatient therapy [90]. Children with *S. aureus* pneumonia should be treated for 14–21 days and children infected with *M. pneumoniae* or *C. pneumoniae* require erythromycin for 10 days or a newer macrolides such as azithromycin for 3–5 days.

In addition to antibiotics, supportive management is essential for children with AP.

Hypoxemia must be accurately assessed with a pulse oximeter. Oxygen therapy should be used to treat hypoxia. When pulse oximetry is available oxygen therapy should be administered when transcutaneous saturation is less than 90–92% in room air. When pulse oximetry is not available, oxygen should be administered when there is central cyanosis, lower chest indrawing, grunting, restlessness, inability to drink or feed or respiratory rate more than 70 breaths per minute [9]. Nasal prongs are recommended for most children who require oxygen. Humidified low-flow oxygen (0.5–3.0 L/min) applied by nasal prongs is effective for hypoxic children. Nasal prongs give a maximum inspired oxygen of 28–35% except in small infants, when higher oxygen concentrations may be obtained. Oxygen should be weaned when the child improves clinically and as hypoxia resolves. Oxygen should be stopped when the transcutaneous saturation is above 90% in room air.

A fever is a useful response of the host in immunological response to infection and does not necessarily require antipyretics [91]. However, pain associated with pneumonia may be due to pleurisy or to pathology involving the upper airways. Pain or discomfort should be treated as it may severely compromise respiratory function and adequate clearance of secretions. The most appropriate agent is paracetamol at

a dose of 15 mg/kg/dose given four to six hourly. Aspirin is contraindicated in most children because of the association with Reye's syndrome.

Children with uncomplicated pneumonia should receive normal maintenance fluids and usually orally. Appropriate rehydration is required in children who are dehydrated.

Children with pneumonia should be encouraged to feed orally and breastfeeding is best in infants, unless they are:

- Too distressed to drink or swallow safely
- Having frequent severe coughing episodes that may be associated with vomiting and possible aspiration of gastric contents
- Dehydrated or shocked.

If children are too distressed to take fluid and feeds orally, continuous enteral feeds via a nasogastric tube may be provided. Ensuring adequate caloric intake is essential as there is an excessive demand on the energy reserves in children with pneumonia, in whom the work of breathing is increased. Children in hospital or pediatric intensive care units (PICU) should not be starved for more than 24 hours.

Intravenous fluids must be used with great care and only if there is adequate monitoring available.

Vitamin A should be given to children with measles to prevent pneumonia [92, 93]. For measles, 200,000 IU vitamin A given daily for 2 days substantially reduced overall and pneumonia-specific mortality [92]. There is no evidence that vitamin A improves outcome in non-measles pneumonia [93].

In children with AP, and especially who are malnourished, adjuvant treatment with 20 mg zinc per day until discharge was found to accelerate recovery from severe pneumonia, reducing the duration of hypoxia [94–96].

A very small proportion of children will require ventilator support for severe ALRTIs. Indications for ventilator support include children who cannot maintain normal oxygen saturations on nasal prong oxygen who are in respiratory failure or who are tiring from excessive work of breathing.

There are a number of therapies that have no proven benefit in the management of children with AP:

- Chest physiotherapy
- Mucolytic agents
- Postural drainage
- Nebulized bronchodilators or saline
- Oral or inhaled corticosteroids.

Because acute bronchiolitis is viral in etiology, most therapies used for other forms of airway inflammation, such as asthma, have no proven value [97]. There is currently no proven effective therapy, other than oxygen, for hypoxic children [98, 99].

Rapid, short-acting inhaled or nebulized bronchodilator therapy such as albuterol or salbutamol has not been documented to be of benefit in the treatment of bronchiolitis [100]. A Cochrane review of 30 trials, including all severities of disease, reported no change in any end points, from nebulized bronchodilators [100]. In addition, bronchodilators cause adverse events in infants and therefore, bronchodilators should not be recommended for the routine treatment of bronchiolitis. Adrenalin too, has not been documented to provide clinical benefit. A Cochrane review suggested a short-term benefit from adrenaline, especially in the first 24 hours of the illness [101], however, no differences were found for length of hospital stay. There was some evidence that adrenaline combined with steroids was effective for reducing the number of hospital admissions [101]. However, despite some benefit, most guidelines state that “there is currently insufficient evidence to support the use of adrenalin for the treatment of bronchiolitis among children admitted to hospital”. Inhaled ipratropium bromide has also not been shown to be effective [102].

There is inconsistent data regarding the efficacy of hypertonic saline nebulization (3 or 5%) in the treatment of acute bronchiolitis. A 2013 Cochrane review reported a reduction in duration of hospital stay and improvement in clinical scores in children who were inpatients, but no short-term effects in children in four trials conducted in an emergency unit setting [103]. However, recently the largest reported randomized controlled study of nebulized hypertonic saline in acute bronchiolitis in hypoxic children, found no difference in outcomes between children who received hypertonic saline compared with those who received standard care [104]. Other recently published randomized trials have also added to the evidence against the use of hypertonic saline in bronchiolitis, showing no difference in length of hospital stay, clinical scores or improvement in oxygenation compared with children receiving normal saline nebulization or salbutamol [105–108]. Because current evidence does not demonstrate important benefits with the use of hypertonic saline, it is therefore not recommended.

Systemic or inhaled corticosteroids have been shown not to be effective in reducing hospital admission or improving clinical scores in ambulatory patients [97, 109]. However, among inpatients, corticosteroids improved clinical scores within the first 12 hours, but did not have any effect on length of stay. Therefore, corticosteroids should not be routinely recommended [109].

Five randomized controlled trials have shown no evidence of benefit for inhaled corticosteroids started in the acute phase of bronchiolitis for prevention of post-bronchiolitic wheezing [110]. Routine use of systemic or inhaled steroids in the management of bronchiolitis is therefore not indicated.

Montelukast is not effective in the management of bronchiolitis. A study of montelukast (4 mg daily until discharge) found that it demonstrated no improvement in the clinical course of the disease [111]. In a study of post-bronchiolitis wheeze, montelukast did not improve respiratory symptoms of post-RSV bronchiolitis in children [112]. In addition, aerosolized ribavirin has been reported not to have any significant consistent beneficial effect in the management of bronchiolitis [97, 113].

Chest physiotherapy (using vibration and percussion techniques) does not contribute to resolution or reduction in severity of disease in infants with acute bronchiolitis [114].

In acute bronchiolitis antibiotics are seldom required. A Cochrane review of antibiotics compared with placebo for bronchiolitis, including two studies of azithromycin compared with placebo, found no difference in duration of illness [115]. Antibiotics should therefore not be used routinely in bronchiolitis, except in children with severe disease in whom bacterial lower respiratory tract infection is suspected [116].

An example of an algorithm to manage acute viral bronchiolitis is provided in Fig. 2.4 [117].

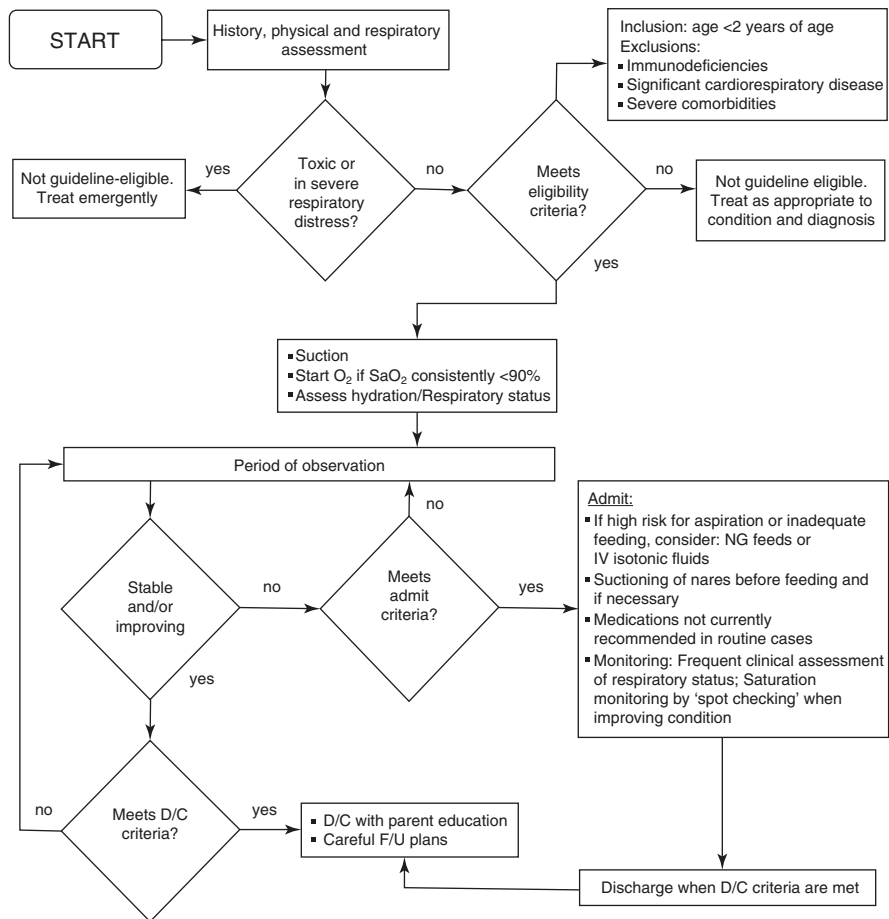


Fig. 2.4 Canadian acute viral bronchiolitis management algorithm. Source: Adapted with permission from [117]

2.13 Prevention of Childhood ALRTI's

Attention to adequate nutrition and growth monitoring should be encouraged as malnutrition frequently predisposes children to pneumonia. Breastfeeding has been documented to decrease the risk of pneumonia in young children by up to 32% [118]. Breastfeeding should be encouraged for the first 6 months of life.

HIV-infected or malnourished children should receive micronutrient supplementation (Vitamin A and zinc) [119, 120], as part of routine care.

Exposure to passive environmental tobacco smoke, indoor cooking fumes and smoke should be avoided.

Vaccines should be considered the most effective form of prevention of AP and every child should receive primary and booster immunizations to BCG, diphtheria-pertussis-tetanus (DPT), Hib conjugate vaccines, pneumococcal conjugate vaccines and measles. Pneumococcal vaccination is specifically relevant, reducing pneumococcal pneumonia by up to 80%, even with the 7-valent vaccine [121]. Additional vaccines may be available in some regions of the world.

Influenza vaccine may be considered appropriate for all children, however, most guidelines advocate mandatory vaccines for children with chronic diseases (pulmonary, cardiovascular or immunosuppressive) and those on long-term aspirin therapy. Children should be vaccinated annually, with influenza vaccine, before the start of the influenza season. Evidence suggests that influenza vaccination is safe in HIV-infected children, especially those with restored CD4 counts on therapy.

Co-trimoxazole prophylaxis for *Pneumocystis jiroveci* is indicated for HIV-infected infants as per local guidelines (see Vol. 1, Chap. 5).

All children under 5 years of age exposed to a household TB contact should be given INH prophylaxis (10 mg/kg) daily for 6 months once active TB disease has been excluded. HIV-infected children exposed to a household contact should be given prophylaxis for 6 months irrespective of their age. Prophylaxis should also be given to HIV-infected tuberculin skin test-positive children even in the absence of a known household contact.

The use of HAART to reconstitute immunity is very effective for decreasing the incidence of pneumonia and opportunistic infections in HIV-infected children (see Vol. 1, Chap. 4).

2.14 Prevention of RSV Disease in High-Risk Children

A specific RSV monoclonal antibody, palivizumab, is available for children at risk of severe ALRTI. RSV-associated risk of hospitalization is 5.2/1000 cases [122]. However, hospitalization becomes more likely with prematurity. Hospitalization for RSV-related disease is more common in young infants and infants with chronic lung disease [122].

Palivizumab has been effective in reducing RSV-related hospitalization and especially more severe disease resulting in the need for PICU admission among premature infants and those with chronic lung disease [123]. Meta-analysis has confirmed

this across all populations of preterm infants [124]. Palivizumab is also effective in reducing duration of hospitalization and severity of disease in infants with congenital heart defects [125]. In most countries of the world health regulators and managed health care organisations have restricted the use of palivizumab to high risk groups because of the cost of the product [126].

For the prevention of RSV-associated ALRTI, most guidelines for the use of palivizumab recommend that it should be restricted for use in the first 6 months of life in high risk children, defined as premature infants [123, 124]. Furthermore, infants with chronic lung disease of prematurity or those with congenital heart defects with significant haemodynamic instability (complex lesions with pulmonary hypertension) should be covered during the first 24 months of life and during the RSV season. RSV prophylaxis may be considered in children with profound immunocompromise or pulmonary neuromuscular disease. The value of palivizumab is uncertain in children with Down syndrome, cystic fibrosis, recurrent wheeze and in nosocomial outbreaks. Some national bronchiolitis guidelines advocate the use of Palivizumab against a set of scored points to adjudicate risk [126], whilst some controversially recommend Palivizumab prophylaxis only in very young premature infants [21].

Palivizumab treatment should commence before start of the RSV season in infants identified to be most at risk. The standard dose of 15 mg/kg is given monthly and in most guidelines advocated for 5 months of use. Where the premature infant is still in the hospital environment at the time of dosing requirement, Palivizumab should be initiated there.

2.15 New RSV Vaccines and Maternal Vaccination

RSV was first identified in 1956 as causing human LRTI. Since the 1960s many efforts have been made to develop an effective and safe vaccine. One of the first attempts (a formalin-inactivated vaccine) led to significant mortality and further research efforts were put on hold for many years. In the early 1980s alternative vaccine candidates were explored. However, attempts at attenuation of the RS virus, resulted in vaccine candidates that were either too reactogenic or inadequately effective.

The F-protein on the surface of RSV was utilized as a target to develop palivizumab, a humanized monoclonal antibody that has been shown—since the mid-1990s—to prevent RSV lower respiratory tract infection in young children with underlying risk factors. This monoclonal antibody, however, requires monthly intramuscular injections for 4–5 months of the year and is substantially costly. For these reasons it is currently advocated only for premature infants and those with chronic conditions who are at substantive risk. The majority of children, in whom disease is common and severe, are thus not protected.

In the last few years a number of advances have been made. This includes the successful development of a re-engineered F-protein monoclonal antibody that has an extended half-life, which would allow for a single dose to provide protection

Table 2.8 Key elements of an educational message for parents of children with ALRTI

The condition may start as an upper respiratory tract infection with low-grade fever
Symptoms are cough and fast breathing and/or wheeze
When a child has fast breathing, additional medical help should be sought
Bronchiolitis is caused by a virus; antibiotics are not needed
Bronchiolitis is usually self-limiting, although symptoms may occur for up to 4 weeks in some children
AP requires antibiotic treatment but the dose and duration are important

against RSV illness for the duration of the RSV season (4–5 months). There are a number of other candidate vaccines in development [127]. These include live attenuated RSV vaccines, vector-based vaccines, F-protein-based subunit vaccines, including the use of nanoparticle technology or targeting the prefusion epitopes of the F-protein [128, 129].

Since RSV disease begins in very early life the ultimate value of vaccination may lie in targeting pregnant mothers. Accordingly, the first studies of the nanoparticle RSV F-protein vaccine candidate in pregnant women were recently completed, and a multicenter safety and efficacy trial is currently underway in pregnant women. Other vaccines, also targeted at the F-protein, are in development.

Vaccine targets for RSV are critical for all children. This includes affordable vaccines in developing countries.

2.16 Parent and Caregiver Education

As doctors it behoves us a clinicians to ensure that parents of sick children are knowledgeable about the condition, its symptoms, management and expected outcome. This is critical for children who are not admitted to hospital, and for those who leave hospital. The important messages that should be conveyed are listed in Table 2.8.

2.17 Severe Respiratory Syndromes

2.17.1 Severe Acute Respiratory Syndrome (SARS)

SARS is a more severe respiratory tract infection caused by infection with the SARS-associated coronavirus. During 2003 there was a global outbreak with significant mortality, however, children were less affected and the disease, in children, was significantly milder [130]. Fever is a prominent feature of the condition and 60% of children had a cough. All had clinical and radiographic features of pneumonia. No deaths were reported among children with SARS, and at 6 months after illness only mild residual changes were reported in exercise tolerance and pulmonary function [130].

2.17.2 Middle East Respiratory Syndrome (MERS)

MERS is a similar severe acute respiratory tract condition caused by a MERS coronavirus. There have been very few pediatric cases reported, most from the Kingdom of Saudi Arabia [131]. Once again the condition is less severe in children.

2.17.3 Hantavirus Pulmonary Syndrome (HPS)

HPS is a severe respiratory illness transmitted by rodents. The highest number of cases are reported in central and south America and in the southwestern USA [132, 133]. The overall case-fatality rate was 35%, however this was mostly in adults [132].

Most persons had chest radiographs showing unexplained bilateral infiltrates (often labeled as interstitial pneumonia) and required supplemental oxygen. Fever, thrombocytopenia and renal dysfunction are common [132].

2.17.4 Enterovirus D68 (EV-D68) Acute Respiratory Illness

In 2014 there were reports of respiratory infections caused by EV-D68 in the USA. Most individuals affected were children [134]. Many children were hospitalized with severe lower respiratory symptoms and asthma. Investigators noted an association between EV-D68 infection, polio-like acute flaccid paralysis, and cranial neuropathy in children [135].

2.17.5 Avian Influenza

Avian influenza viruses A (H5N1) is significantly more common in children than A (H7N9) [136]. Lower severity and greater transmission is found in the H7N9 childhood cases than in the H5N1 childhood cases [136]. Respiratory disease is an invariable finding.

2.18 Other Respiratory Virus Associations

New evidence is emerging that respiratory viruses may play an important role in hospital-acquired infections, including in the PICU. They often cause pneumonia or even sepsis-like clinical disease. Nosocomial transmission of viruses is an important source of such infections. Viruses play an important role in severe infections in transplant recipients and here CMV is an important organism. Finally, viruses are now being understood to cause important acute exacerbations of chronic illnesses, including cystic fibrosis and other chronic lung diseases.

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