BMJ Best Practice

Respiratory syncytial virus infection

Straight to the point of care

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Summary

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis; nearly every child has been infected by 2 years of age.

Typical seasonal outbreaks occur during winter months from October through February in the northern hemisphere, and from May through September in the southern hemisphere.

Characterised by cough, wheeze, respiratory distress, and hypoxia.

Most episodes are mild and self-limiting.

Treatment is mostly supportive: supplemental oxygen, nasal toilet, respiratory support, and nutritional support as needed.

High-risk groups for severe illness include infants with a history of prematurity, chronic lung disease, complex congenital heart disease, and immune deficiency.

Vaccination is available for older adults and pregnant women. Immunoprophylaxis with nirsevimab or palivizumab is available for infants and vulnerable young children.

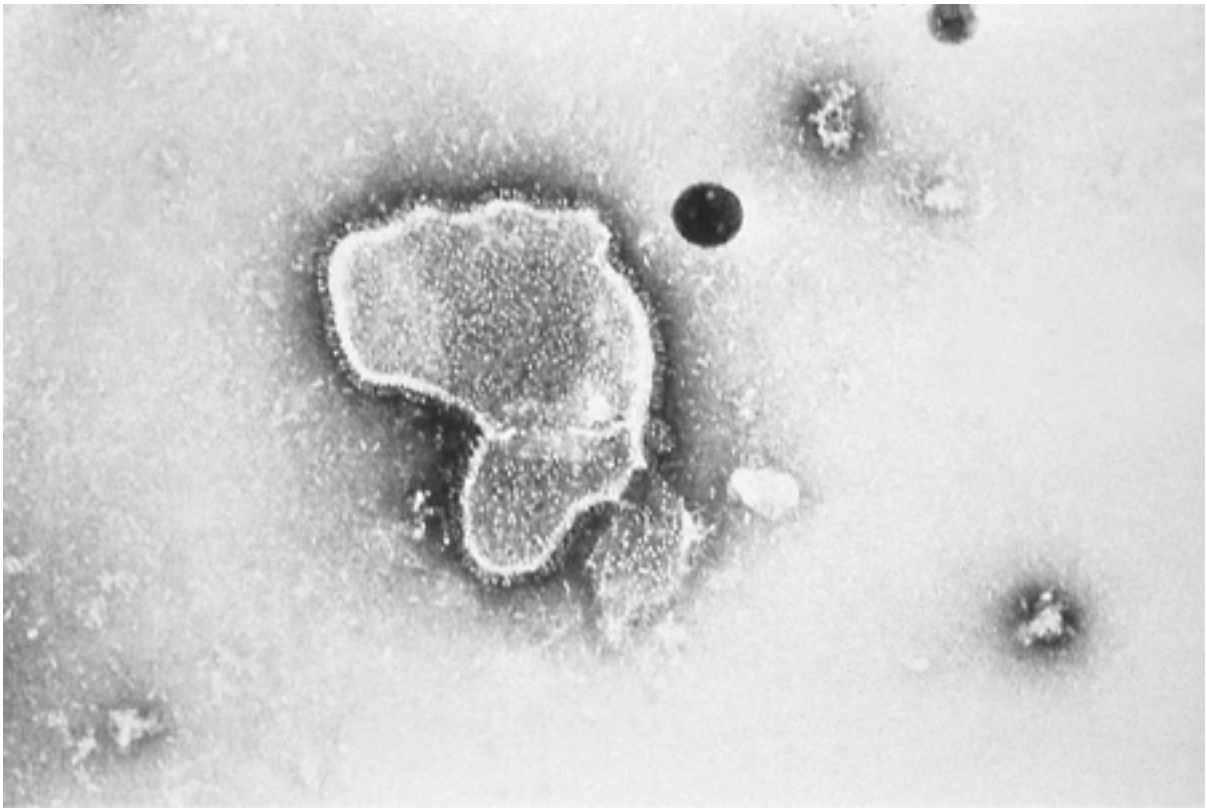
RSV disease in adults is often overlooked but is associated with lower respiratory tract infection, especially in the elderly and those with underlying lung comorbidities.

Definition

RSV is a member of the *Pneumoviridae* family. It is the most common cause of lower respiratory tract infection in infants and young children.[1]

Symptoms of bronchiolitis include rhinorrhoea, cough, wheeze, respiratory distress, and hypoxaemia.[2]

RSV commonly causes symptoms of upper respiratory tract infection in people of all ages as well as bronchiolitis, viral pneumonia, and laryngitis (croup).



Electron micrograph revealing the morphological traits of the RSV

CDC/Palmer EL; used with permission

Epidemiology

Respiratory syncytial virus (RSV) is one of the most important pathogens in early childhood and is the most common cause of bronchiolitis and pneumonia in infancy worldwide.[5] [6] [7]

RSV usually is transmitted by direct or close contact with contaminated secretions, which may occur from exposure to large-particle droplets at short distances or by self-inoculation after touching contaminated surfaces.[8]

One meta-review of 98 studies noted that, prior to the COVID-19 pandemic era, there had been no discernible change in RSV hospitalisations over the past 20 years.[1] Data suggest that social distancing and other lockdown strategies associated with the pandemic significantly reduced the spread of RSV in the community, and led to a large, temporary decrease in diagnosed RSV and hospitalisation.[9] [10] [11] Following the easing of COVID-19 control measures, RSV incidence initially increased during the off-season in many places but has since returned to pre-pandemic epidemic seasonality patterns.[11] [12] [13] [14]

RSV produces significant morbidity and mortality, especially among high-risk infants and those with prematurity, chronic lung disease, complex congenital heart disease, or immune deficiency.[15]

Prematurity (<35 weeks), male sex, age <6 months, birth during the first half of the RSV season, multiple siblings, or daycare exposure have been associated with higher hospitalisation rates.[1][16] [17] [18]

In Scotland, a mean of 1976 children per year for the period 2001 to 2003 were admitted to hospital with the principal diagnosis of bronchiolitis.[19] In the US, RSV accounts for 18% of hospital emergency visits and 20% of admissions to hospital due to acute respiratory infections in children under 5 years of age.[20] Among patients with acute respiratory tract infections in China, RSV accounted for 18.7% (95% CI 17.1% to 20.5%) of infections.[21]

In 2015, a global estimate of 33.1 million (uncertainty range [UR] 21.6-50.3) episodes of RSV-acute lower respiratory infection resulted in about 3.2 million (UR 2.7-3.8) hospital admissions and 59,600 (UR 48,000-74,500) in-hospital deaths in children younger than 5 years. In children younger than 6 months, 1.4 million (UR 1.2-1.7) hospital admissions and 27,300 (UR 20,700-36,200) in-hospital deaths were due to RSV-acute lower respiratory infection.[22]

Seasonal outbreaks occur worldwide during the winter months and continue onto early spring.[8] [23] In the US and throughout the northern hemisphere, epidemics generally begin each November, with a peak in January or February. Cases then decline over the next 2 months with sporadic cases occurring throughout the remainder of the year. Regional variability also occurs but is less predictable.[23] In the southern hemisphere, seasonal outbreaks occur from May through September.[23] Tropical regions often have more prolonged circulation in association with the rainy season.

By 2 years of age, nearly all children have been infected with RSV, and half of those have been infected twice. Long-lasting immunity does not occur and re-infection is common, usually with diminished severity.

Adults and older people

There is increasing recognition of the burden of RSV infection in adults and older people.[24] [25] [26] There is growing literature reporting on the impact of RSV infection and other viral disease in long-term care settings, adult day-care centres, and nursing homes.[27] [28]

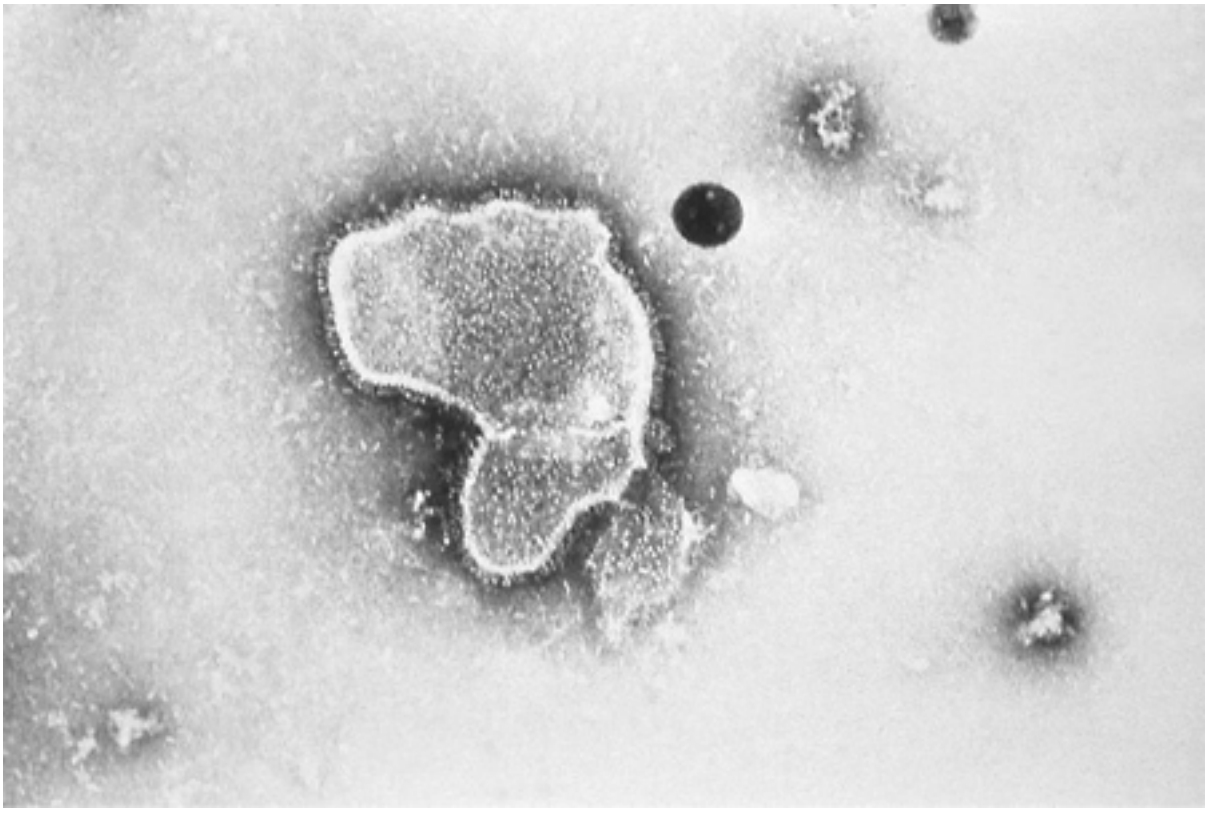
Although less than 1% of adults affected by RSV are estimated to require hospital care, it is the causative agent in up to 12% of acute respiratory illness requiring medical assistance in the US.[25] [29]

Risk factors for progression to viral pneumonia and complications from RSV in adults include immunodeficiency (e.g., patients taking chemotherapy or immunotherapy), underlying lung disease (e.g., asthma, tobacco use, COPD), transplant recipients, heart disease, older age, living in a long term care facility, and frailty.[30]

Aetiology

Respiratory syncytial virus (RSV) is a member of the *Pneumoviridae* family. The viral particle plasma membrane originates from the host cell and surrounds a nucleocapsid. The viral genome within the nucleocapsid consists of a single strand of RNA with 10 genes that encode a total of 11 proteins. Two of these direct viral replication, and the remaining 9 function as structural proteins and surface glycoproteins.[31]

RSV has three surface glycoproteins: fusion protein (F), small hydrophobic protein (SH), and glycosylated attachment protein (G). The F and G proteins are the primary targets for the host's antibodies and therefore play a prominent role in the pathophysiology of RSV. The G protein mediates attachment to the host cell, and the F protein facilitates fusion of the host and viral plasma membranes, enabling transit of the viral RNA into the host cell. The F protein also promotes the aggregation of multi-nucleated cells by fusion of their membranes, resulting in the syncytia for which the virus is named.[31] The role of the SH protein is less clear.



Electron micrograph revealing the morphological traits of the RSV

CDC/Palmer EL; used with permission

Pathophysiology

The virus is transmitted by inoculation of the conjunctival or nasopharyngeal mucosa with infected respiratory droplets.[32] [33] RSV can remain viable on hard surfaces for up to 6 hours.[34]

The incubation period ranges from 2 to 8 days; 4 to 6 days is most common. [8]

Immunocompetent patients shed the virus, on average for between 3 and 8 days, although this can continue for up to 4 weeks especially in young infants and immunosuppressed children.[8] [32] [35] Immune deficient patients may shed the virus for 4 to 6 weeks.

Viral replication begins in the nasal epithelium and then progresses downwards through the bronchiolar epithelium and types 1 and 2 alveolar pneumocytes.[36] [37] The viral infection is generally limited to the respiratory tract with extrapulmonary disease rarely reported.[38]

Viral replication results in bronchiolar epithelial necrosis, followed by peribronchiolar T-lymphocytic infiltration and submucosal oedema.[39] There may be a genetic predisposition to severe RSV disease involving mutations to interleukin-4, toll-like receptor 4, and CD14 genes.[40] [41]

Viscous mucous secretions, primarily neutrophilic inflammation, increase in quantity and mix with cellular debris.[42] The loss of ciliated epithelium makes clearance of these secretions difficult. The end result is dense mucous plugging of the narrowed airways, producing wheeze, cough, air trapping, and ventilation/perfusion ratio mismatch.

Respiratory virus co-infections are commonly reported, but their impact on disease severity is unclear. One systematic review and meta-analysis found no association between co-infection with RSV and other viruses and clinical severity, except for co-infection with RSV and RSV-human metapneumovirus, where co-infection was found to be associated with a higher risk of ICU admission.[43]

Classification

Classification of viruses

RSV was historically placed in the Paramyxovirus family. It has been recategorised to the order *Mononegavirales* as a member of the *Pneumoviridae* family.[3] [4] This family includes several respiratory pathogens of animals in addition to the human metapneumovirus.

Case history

Case history #1

A 6-month-old, previously well, female infant presents in midwinter with a 3-day history of rhinorrhoea, cough, and malaise. Several other school-age children in the home also have respiratory symptoms. The infant has a temperature of 38.5°C (101.2°F), respiratory rate of 70 breaths per minute, and oxygen saturation of 85% on room air. She has nasal flaring, head bobbing, and suprasternal and intercostal retractions. Auscultation reveals bilateral wheeze with prolonged expiration. The infant's work of breathing improves mildly with nasal suctioning, and her oxygenation improves with warm, humidified oxygen through nasal cannula, but there is no improvement with nebulised salbutamol.

THEORY

Other presentations

Respiratory syncytial virus (RSV) bronchiolitis or pneumonia may produce severe respiratory distress as well as low-grade fever, persistent cough, and malaise. High-risk infants, such as those with prematurity, chronic lung disease, complex congenital heart disease, or immune deficiency, are more likely to present with severe disease.

Apnoea is a common complication, especially in very young infants, and may be the presenting sign. Laryngotracheobronchitis, commonly called croup, is another possible presentation of RSV and should be managed as any other viral cause of croup would be.

Approach

The suspicion for respiratory syncytial virus (RSV) can generally be entertained based on the season, history, and physical examination. However, numerous viruses cause similar symptoms and have been linked to bronchiolitis.[81] While a definitive diagnosis can be confirmed only by laboratory testing, this is not routinely recommended.[2]

Clinical features

RSV infection almost always produces symptoms. The severity varies depending on the patient's age, history of previous infection, and comorbidities.[44] [82]

Clinicians should determine whether the patient is at high risk for developing severe illness, including the following factors:[1] [15][16][17] [18] [46][83]

- History of prematurity
- Age <6 months at the start of RSV season
- Chronic lung disease
- Complex congenital heart disease
- Immune deficiency

These patients require closer observation and are frequently admitted to the hospital.[2]

Infants and young children

Infants typically present with upper respiratory tract findings such as rhinorrhoea and congestion. The physician may suspect RSV as the diagnosis when, over the next 2-4 days, the lower respiratory tract becomes involved and illness manifests as tachypnoea, cough, wheeze, prolonged expiration, and increased work of breathing.

Signs of moderate illness include hypoxaemia (oxygen saturations <90%), tachypnoea, increased work of breathing (nasal flaring, intercostal retractions, head bobbing), inadequate feeding, and dehydration. More severe cases are associated with hypoxia and respiratory failure.[2] [44]

Physicians should enquire about difficulty with feeding, malaise, and signs of otitis media, as these may also be present. Apnoea may be the sole presenting finding in very young infants (age <1 month) and may be severe enough to result in death.[84] Very young infants may also present with sepsis.

Older children and adults

RSV disease in older children and healthy adults is typically limited to the upper respiratory tract but may progress to tracheobronchitis.[85] Symptoms include nasal congestion, ear and sinus involvement, productive cough, and wheezing.[85]

In young adults who are otherwise well, RSV typically presents as an upper respiratory tract infection with mild to moderate symptoms, and only very rarely causes severe disease.[86] Additionally, healthy children and adults may be asymptomatic facilitating the spread of infection to more vulnerable hosts.[87]

Immune deficiency, increasing age, and comorbidity

Older people, people with immune deficiency, and those with respiratory or cardiac comorbidity, are at risk of developing severe lower respiratory disease.[86] [88]

Among immune deficient patients, the greatest incidence of RSV infection is seen in patients receiving haematopoietic stem cell transplants and lung transplants.[30] Patients with RSV receiving haematopoietic stem cell transplants develop progression from upper to lower respiratory tract infection in 40% to 60% of cases; in these patients, lower respiratory tract infection is associated with mortality rates of up to 80%.[30]

Diagnostic tests

Rapid point-of-care tests for the detection of RSV have a sensitivity and specificity of 75% and 99%, respectively.[89] However, the American Academy of Pediatrics (AAP) recommends that the diagnosis of bronchiolitis should be established based on findings in the history and physical examination.[2] The AAP further recommends that clinicians should not routinely order laboratory or radiographical studies for diagnosis.[2] Likewise, studies in adult populations have not proved to be of benefit.[8] [90]

Nonetheless, confirming the presence of RSV may be advantageous in order to isolate and cohort patients with known infection.[91] Rapid viral testing has been shown to reduce the number of chest radiographs undertaken in the accident and emergency department, and results suggest a beneficial effect in terms of lowering antibiotic usage, although this was not statistically significant.[92]

Testing of nasopharyngeal aspirates for RSV is available through rapid antigen testing (often available for use at the point-of-care) as well as polymerase chain reaction (PCR) testing. PCR testing has a higher sensitivity and equivalent specificity as compared with antigen testing, especially in the adult population where antigen test sensitivity can be as low as 50%.[93] Increasing availability and speed of PCR-based tests have made these more commonly used.[94]

Pulse oximetry

Pulse oximetry is readily available in most clinical settings. It is a rapid and accurate method for assessing hypoxaemia. Measuring oxygen saturation using pulse oximetry should be carried out in every baby and child presenting to secondary care with clinical evidence of bronchiolitis.[2] [53]

Disease severity is characterised by the following:

- Mild illness: no hypoxaemia. May have mildly increased respiratory rate, but retains ability to feed adequately.
- Moderate illness: hypoxaemia (oxygen saturations <90% to 92%), tachypnoea, increased work of breathing (nasal flaring, intercostal retractions, head bobbing), inadequate feeding, and dehydration.
- Severe illness: refractory hypoxaemia, progressive respiratory distress, or frank respiratory failure.

The National Institute for Health and Care Excellence recommends assessing a baby or child in a secondary care setting, and admitting them to hospital if they have any of the following:[53]

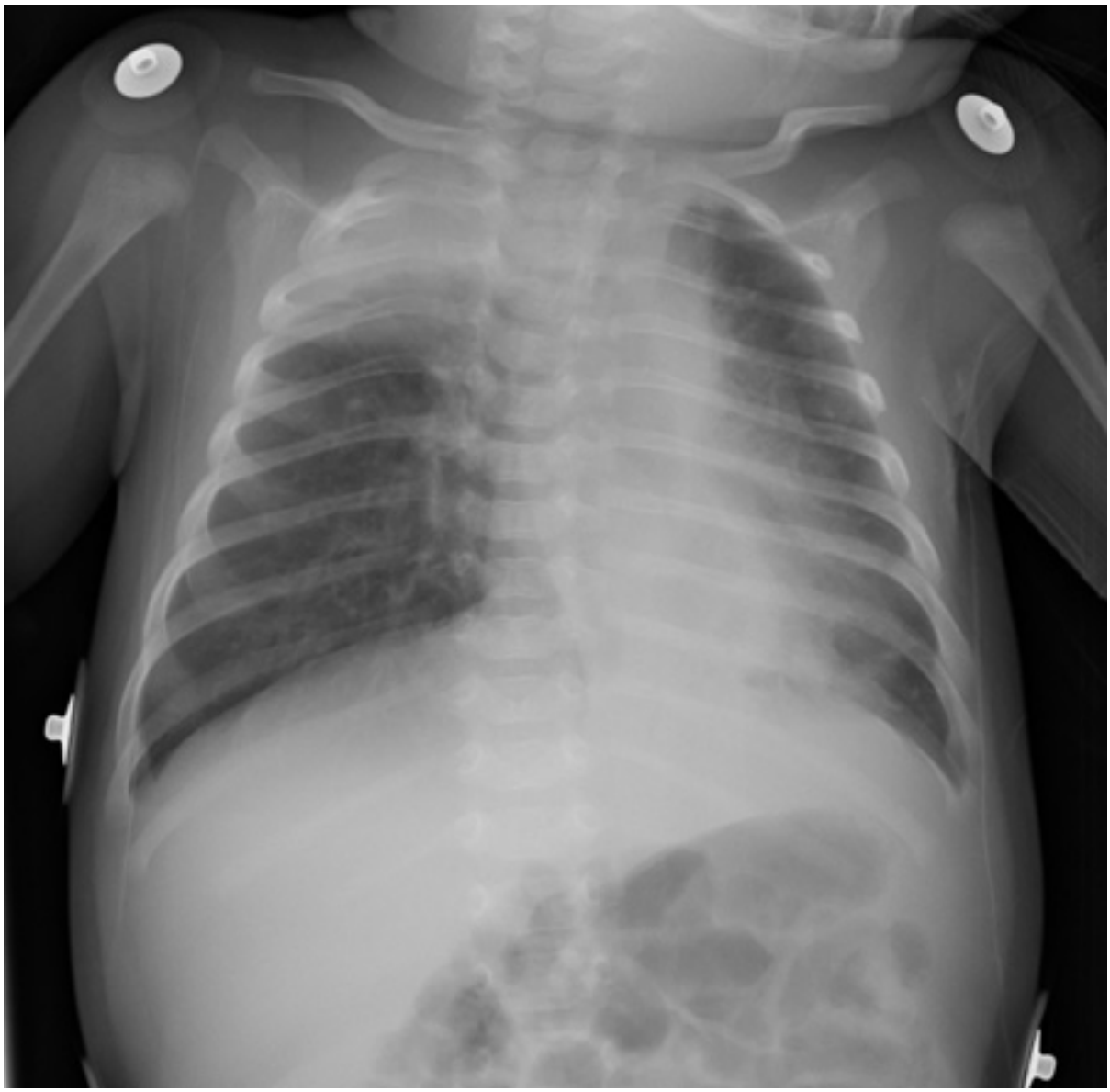
- apnoea (observed or reported)
- persistent oxygen saturation (when breathing air) of:
    - less than 90%, for children aged 6 weeks and over
    - less than 92%, for babies under 6 weeks or children of any age with underlying health conditions
- inadequate oral fluid intake (50% to 75% of usual volume, taking account of risk factors and using clinical judgement)

- persisting severe respiratory distress i.e., grunting, marked chest recession, or a respiratory rate of over 70 breaths/minute.

Other testing

Chest radiograph may reveal atelectasis, hyperexpansion, and peribronchial cuffing.[95] [96] [97] Interstitial infiltrates are less common.

Chest radiography should be reserved for patients with severe disease, and those who do not improve at the expected rate.[2]



Atelectasis

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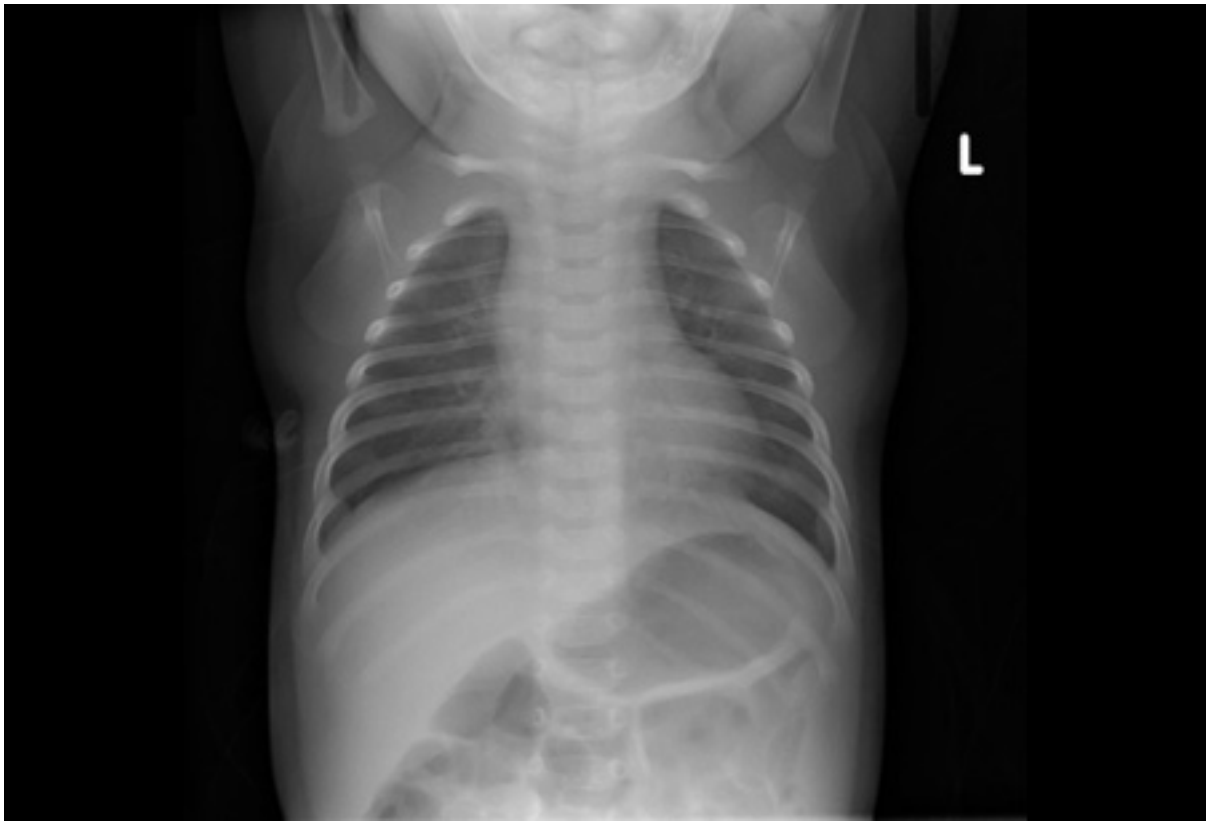

Air trapping and peribronchial cuffing

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The National Institute for Health and Care Excellence recommends only performing a chest x-ray if intensive care is being proposed for a baby or child. A chest x-ray in babies or children with bronchiolitis may mimic pneumonia and should not be used to determine the need for antibiotics.[53]

Full blood count and serum chemistries are not routinely helpful but may be considered in the presence of severe disease. Blood cultures are indicated if bacterial infection is suspected.

Clinically assess the hydration status of babies and children with bronchiolitis to determine the hydration requirements of the patient.[53]

DIAGNOSIS

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include exposure to respiratory syncytial virus (RSV), no recent immunoprophylaxis against RSV, history of prematurity, infants <6 months, chronic lung disease, complex congenital heart disease, immune deficit, winter season, and older age.

exposure to#RSV (common)

- Respiratory syncytial virus (RSV) has a 98% attack rate for first-time infections and a 75% attack rate for subsequent infections.[44] Transmission requires close contact.
- Attendance at day care (nursery), multiple siblings, and birth during the first half of the RSV season are risk factors for more severe RSV disease.[1] [45]

infants at high risk for RSV infection (common)

- Includes infants <6 months and those with a history of prematurity, chronic lung disease, complex congenital heart disease, and immune deficiency, and neuromuscular disorders, particularly infants in this group with no recent immunoprophylaxis against respiratory syncytial virus (RSV).[1] [15][16] [46] [17] [18][83] [98]
- Down's syndrome appears to be an independent risk factor for hospitalisation with RSV disease.[55] [56] [57] [58]

winter season (common)

- Seasonal outbreaks occur worldwide during the winter months.[23]
- In the northern hemisphere, epidemics generally begin each November, with a peak in January or February. Cases then decline over the next 2 months with sporadic cases occurring throughout the remainder of the year.
- Regional variability also occurs but is less predictable.[23]
- In the southern hemisphere, seasonal outbreaks occur from May through September.[23]

older adult age (common)

- Severe respiratory syncytial virus disease risk increases in older patients.[24] [25] [26]

immune deficiency (common)

- There is a higher burden of respiratory syncytial virus (RSV) disease in both adults and children with immune deficiency. Patients who received solid organ or stem cell transplantation as well as those with solid tumours, leukaemia, lymphoma or those receiving chronic immunosuppression are at increased risk of RSV disease.[99]
- Among immune deficient patients, the greatest incidence of RSV infection is seen in patients receiving haematopoietic stem cell transplants and lung transplants.[30] Patients with RSV receiving haematopoietic stem cell transplants develop progression from upper to lower respiratory tract infection in 40% to 60% of cases; in these patients, lower respiratory tract infection is associated with mortality rates of up to 80%.[30]

rhinorrhoea/congestion (common)

- Symptoms of upper respiratory tract illness are common in early respiratory syncytial virus infection.[2] [100]

tachypnoea (common)

- Common in moderate to severe infection.[53]

increased work of breathing (common)

- Head bobbing, grunting, nasal flaring, and intercostal retractions are common with moderate to severe infection.[2] [8] [100]

cough (common)

- May be dry or wet.[2]

wheeze (common)

- Results from the combination of mucous plugging and airway narrowing due to inflammation. May range in severity from mild to pronounced. Wheeze or crackles may be found on chest auscultation.[53]

poor feeding (common)

- Often the presenting complaint in infants and may occur 3-5 days after the start of illness in those with bronchiolitis.[8] [53]

cyanosis (common)

- Common in more severe disease.[53]

rales (common)

- Evidence of lower respiratory tract infection may be present in 20% to 30% of infants.[8]

apnoea (uncommon)

- A well-known complication in infants and has been associated with infant death.[84] Incidence may be as high as 20% in infants <6 months of age but is most common in infants aged <1 month.[84] [101] [102] [103] [104] [105] Respiratory syncytial virus-related apnoea is usually self-limiting and does not recur with subsequent infections.

Other diagnostic factors

fever (common)

- Respiratory syncytial virus infection frequently causes fever (in around 30% of cases), although fever >40°C (>103.9°F) is unusual.[53] [100]

Risk factors

Strong

exposure to RSV

- Respiratory syncytial virus (RSV) has a 98% attack rate for first-time infections and a 75% attack rate for subsequent infections.[44] Transmission requires close contact.
- Attendance at day care (nursery), multiple siblings, and birth during the first half of the RSV season, are risk factors for more severe RSV disease.[1] [45]

haemodynamically significant congenital heart disease

- Infants with haemodynamically significant congenital heart lesions have a significantly increased risk of severe disease.[46]
- The mortality rate may be up to 3.5% in children with respiratory syncytial virus with congenital heart disease.[47] [48]

history of prematurity

- Infants born <35 weeks' gestation have a significant increase in risk of serious disease. This is especially true for those with chronic lung disease such as bronchopulmonary dysplasia.[16] [17] [18]

immune deficiency

- Immune deficiency may be due to chemotherapy for leukemia, immunosuppression after organ transplantation, untreated human immunodeficiency virus, or combined immunodeficiency syndrome. These patients are at increased risk of severe disease, prolonged disease, and prolonged viral shedding.
- Among patients with immune deficiency, the greatest risk of clinically severe respiratory syncytial virus (RSV) infection is seen in patients receiving haematopoietic stem cell transplants and lung transplants. Patients with RSV receiving haematopoietic stem cell transplants develop progression from upper to lower respiratory tract infection in 40% to 60% of cases; in these patients, lower respiratory tract infection is associated with mortality rates of up to 80%.[30]

chronic lung disease

- Bronchopulmonary dysplasia increases risk for severe disease.[49]

indigenous/American-Indians/Alaska native infants and young children

- Aboriginal and Torres Strait Islander infants in Australia have both higher rates of respiratory syncytial virus (RSV)-related hospitalisation and higher rates of RSV mortality than non-indigenous infants.[50] In one US birth cohort study, some of the highest RSV rates were observed in American-Indian/Alaskan native infants.[51]

infants ages <6 months

- Infants <6 months of age at the start of respiratory syncytial virus season are at increased risk of severe disease and admission to hospital.[1] [52]

winter season

- Seasonal outbreaks occur worldwide during the winter months.[23]
- In the US and throughout the northern hemisphere, epidemics generally begin each November, with a peak in January or February. Cases then decline and end in May. Regional variability also occurs but is less predictable.[23] In the southern hemisphere, seasonal outbreaks occur from May through September.[23]

older adult age

- Severe respiratory syncytial virus disease risk increases in older patients.[24] [25] [26]

Weak

smoke exposure

- Tobacco smoke exposure is a risk factor for more severe respiratory syncytial virus disease.[1] [45] [53]

family history of asthma

- The data are conflicting. Family history of asthma may be a risk factor for severe respiratory syncytial virus disease.[54]

Down's syndrome

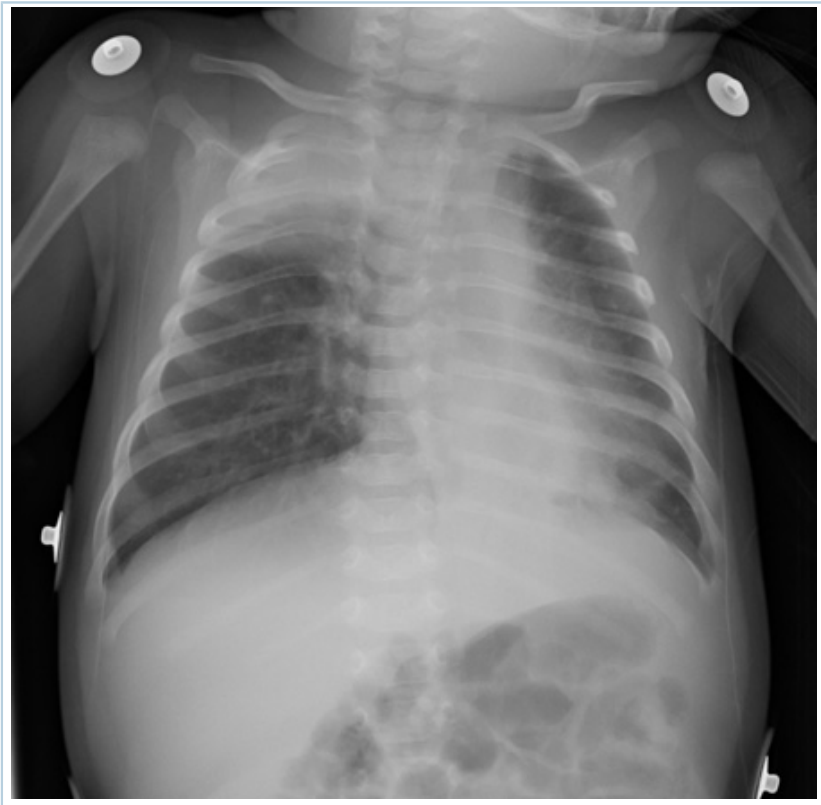
- Down's syndrome appears to be an independent risk factor for hospitalisation with respiratory syncytial virus disease.[55] [56] [57] [58]

Investigations

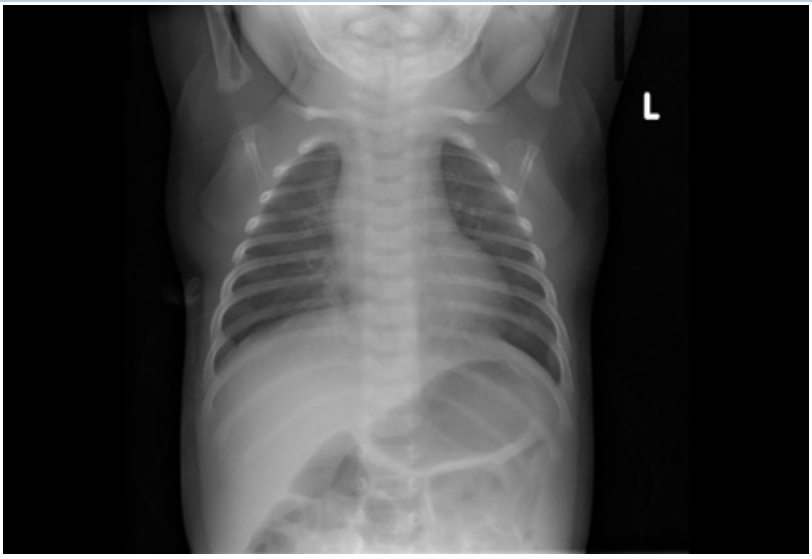
1st test to order

Test	Result
pulse oximetry • A rapid and accurate method for assessing hypoxaemia, its use should be considered in any infant with moderate to severe symptoms.[2] Routine pulse oximetry use has not been shown to improve outcomes.	**hypoxaemia**

Other tests to consider

Test	Result
chest x-ray • Reveals atelectasis, hyperinflation, peribronchial cuffing, and infiltrate. 	**atelectasis, hyperinflation, peribronchial cuffing, infiltrate**

Atelectasis
From the personal collections of Melvin L. Wright, DO and Giovanni Piedimonte, MD; used with permission

Test	Result
 *Air trapping and peribronchial cuffing* *From the personal collections of Melvin L. Wright, DO and Giovanni Piedimonte, MD; used with permission* • Should be reserved for those patients with severe disease, and those who do not improve at the expected rate.[2] [106] • The National Institute for Health and Care Excellence recommends only performing a chest x-ray if intensive care is being proposed for a baby or child. A chest x-ray in babies or children with bronchiolitis may mimic pneumonia and should not be used to determine the need for antibiotics.[53]	
hydration status • Clinically assess the hydration status of babies and children with bronchiolitis to determine the hydration requirements of the patient.[53]	**Hypovolaemic, euvolaemic or hypervolaemic**
rapid antigen detection from respiratory specimen (e.g., nasopharyngeal aspirate) • Commercially available and relatively easy to use. Sensitivity >90%, in young children, but is lower in older children and adults.[107]	**detection of viral antigen**
reverse transcriptase polymerase chain reaction of respiratory specimen (e.g., nasopharyngeal aspirate) • A rapid and sensitive method for detecting respiratory syncytial virus. • The preferred method of viral testing at most large medical centres. • Clinical sensitivity superior to other diagnostic modalities.	**detection of viral ribonucleic acid**
viral culture of respiratory specimen (e.g., nasopharyngeal aspirate) • Not generally useful in the clinical setting given long turnaround time and low sensitivity compared to polymerase chain reaction.	**growth of virus**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Human metapneumovirus	• Produces a clinical syndrome that closely mimics RSV. May be clinically indistinguishable.[108]	• Polymerase chain reaction positive for metapneumovirus.
Influenza virus	• Accounts for 1% to 24% of bronchiolitis.[109] [110] Closely mimics RSV in presentation. Fever frequently >38.9°C (>101.9°F). Coryza frequently present. Greater frequency of pneumonia and bacterial superinfection than RSV.	• CXR may show infiltrates. • Polymerase chain reaction: positive for influenza virus. • Rapid testing by immunoassay or viral neuraminidase detection: positive for influenza virus. • Enzyme-linked immunosorbent assay and viral culture: positive for influenza virus.
Parainfluenza virus	• Accounts for 10% to 30% of bronchiolitis. Parainfluenza type III closely mimics RSV in presentation. Presence of coryza is associated with parainfluenza infection. Parainfluenza type III often occurs in late spring after peak RSV circulation.	• Enzyme-linked immunosorbent assay and polymerase chain reaction testing: positive for parainfluenza virus. • Viral culture: positive for parainfluenza virus (standard test).
Bacterial pneumonia	• Bacterial infections are not associated with wheeze and generally cause higher fevers than RSV.[100] • Fever >40°C (>103.9°F).	• CXR: lobar infiltrate • White blood cell count: elevated with left shift suggests an active bacterial process.
Neonatal sepsis	• Often presents with a history of poor feeding and elevated work of breathing (similarly to RSV infection in infants), decreased level of consciousness, decreased urine output, apnoea, temperature instability, shock.	• Cultures: blood, urine, and cerebrospinal fluid may detect infective organisms or may be normal. • ABG may show respiratory and/or metabolic acidosis, hypoxaemia.
Enterovirus-D68 (EV-D68)	• Produces a clinical syndrome similar to that of the common cold. May cause severe respiratory illness with signs and symptoms of pneumonia. Although EV-D68 causes primarily respiratory illness,	• Many clinical laboratories use real-time polymerase chain reaction assays designed to detect both rhinoviruses and enteroviruses, but these tests do not distinguish between the species.

Condition	Differentiating signs / symptoms	Differentiating tests
	systemic disease occurs, especially neurological involvement.	Most clinical laboratories do not routinely perform viral sequence analysis to specifically identify EV-D68.
Coronavirus disease 2019 (COVID-19)	• COVID-19 may present as bronchiolitis in some infants. It may cause fever, coryza, and cough as well as acute gastroenteritis.	• Real-time reverse transcription polymerase chain reaction (RT-PCR): positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA.

Criteria

Disease severity[2]

Mild illness

- No hypoxaemia. May have mildly increased respiratory rate, but retains ability to feed adequately.

Moderate illness

- Hypoxaemia (oxygen saturations <90% to 92%), tachypnoea, increased work of breathing (nasal flaring, intercostal retractions, head bobbing), inadequate feeding, and dehydration.

Severe illness

- Refractory hypoxaemia, progressive respiratory distress, or frank respiratory failure.

Approach

Treatment strategies are largely supportive, with a focus on ensuring adequate oxygenation, ventilation, nutrition, and hydration. No available treatment shortens the course of bronchiolitis or hastens the resolution of symptoms.[8]

High-risk infants include those with a history of prematurity, age <6 months at the start of respiratory syncytial virus (RSV) season, chronic lung disease, complex congenital heart disease, or immune deficiency.[1] [15][16][17] [18] [46][83] These patients require closer observation and are frequently admitted to hospital.

Treatment strategies depend on the severity of the illness.[111]

For adults, management is typically limited to supportive care, with supplemental oxygen, bronchodilators, intravenous fluids, and antipyretics as required and guided by the individual clinical scenario. Antiviral therapy is sometimes considered for patients with RSV following solid organ or haematopoietic stem cell transplantation (HSCT) to prevent progression to lower respiratory tract involvement, although definitive evidence of efficacy is scarce.[30] [112] [113] [114]

Hospitalisation and supportive care

Mild illness

- Patients have no hypoxaemia and can feed adequately.
- For most infants, RSV disease is usually mild and self-limiting and can be treated in the outpatient setting. Outpatient care requires diligent follow-up to ensure that the patient is not deteriorating.
- High-risk infants (e.g., history of prematurity, age <6 months at start of RSV season, chronic lung disease, complex congenital heart disease, or immune deficiency) may require hospital admission.
- Treatment is largely supportive and about providing adequate nutritional support. Infants are obligate nose breathers, and nasal obstruction is a frequent problem. Simple nasal toilet with saline drops and a suction bulb can significantly improve the work of breathing.
- Symptomatic therapy for healthy adults is usually sufficient, as the disease is typically confined to the upper respiratory tract and is self-limiting.

Moderate illness

- Signs of moderate illness in infants include hypoxaemia (oxygen saturations <90% to 92%), tachypnoea, increased work of breathing (nasal flaring, intercostal retractions, head bobbing), inadequate feeding, and dehydration.
- Patients should be admitted for further care and observation.[2]
- Hypoxaemia should be treated with warm, humidified oxygen through a nasal cannula or mask.
- High-flow nasal cannula (HFNC) therapy is safe in a typical ward setting. However, there is no clear evidence that initiating support with HFNC is more effective than standard oxygen therapy with a mask, either in shortening hospital length-of-stay or preventing ICU admissions (although studies have been conflicting).[115] HFNC should be limited to infants who have failed standard oxygen therapy.[115]
- Careful attention should be given to prompt correction of any dehydration and re-establishing adequate nutrition. Infants with poor feeding or significantly elevated work of breathing or respiratory rate should be fed by nasogastric or nasojejunal tube, or receive intravenous fluids.[2]

- Adults who are older, immune deficient, or have comorbidities may have moderate illness and should be managed with supportive care while addressing exacerbations of underlying illnesses.

Severe illness

- Infants with refractory hypoxaemia, progressive respiratory distress, or frank respiratory failure should be transferred to the paediatric intensive care unit.
- These patients often improve with non-invasive mechanical ventilation such as nasal continuous positive airway pressure or non-invasive ventilation, but may require endotracheal intubation with mechanical ventilation.[116] These modalities are associated with significantly decreased RSV-associated mortality.[117]
- Hypoxaemia should be treated with warm, humidified oxygen through a nasal cannula or mask.
- Rehydration and nutrition can be accomplished by enteral or parenteral routes, depending on the degree of disease severity and other clinical considerations. In the UK, the National Institute for Health and Care Excellence recommends giving fluids by nasogastric or orogastric tube in babies and children with bronchiolitis if they cannot take enough fluid by mouth. Alternatively, it recommends intravenous isotonic fluids to babies and children who do not tolerate nasogastric or orogastric fluids or have impending respiratory failure.[53]
- Adults who are older, immune deficient, or have comorbidities may progress to severe illness, requiring intensive care unit admission with respiratory support and intravenous and nutritional support.

Adjunctive therapies

Bronchodilators

- Bronchodilators (e.g., salbutamol and ipratropium) should not be used routinely in the management of bronchiolitis.[2] [53]
- Bronchodilators may be of benefit for patients with asthma, COPD, or severe disease.
- Bronchodilators may transiently improve oxygen saturation and work of breathing, but have not been shown to decrease hospital admissions, length of stay, or length of oxygen therapy.[118] [119] [120] [121]

Nebulised hypertonic saline

- Nebulised hypertonic saline is of potential benefit in reducing symptoms of mild or moderate bronchiolitis in the hospital setting.[122]
- Given the relatively long period of use required to achieve improvement, nebulised hypertonic saline is not recommended for use in the accident and emergency department.[2] [123] [124]

Ribavirin ± intravenous immunoglobulin (IVIG)

- Ribavirin is not recommended for routine use in children with bronchiolitis.[8] [106]
- Ribavirin is a synthetic nucleoside analogue with in vitro activity against RSV. In practice, however, its benefit is less certain.[8]
- Several factors complicate the use of ribavirin: it is expensive; it must be given early in the course of infection for best effect; it may present a risk to those who give it, as it is a potential teratogen when administered by nebulisation.
- Oral ribavirin has been used in immune deficient adults (predominantly transplant recipients and cancer patients with severe RSV disease), although it is not approved for this indication.[125] Its early use in adult bone marrow transplant patients has reduced morbidity and mortality in this patient subset.[126]

- IVIG may be added to inhaled ribavirin for immune deficient patients at high risk for progression to severe lower respiratory tract disease.[125] [126] IVIG with oral ribavirin has also been studied in immune deficient patients.[127]
- Studies with aerosolised ribavirin therapy demonstrated a small increase in oxygen saturation in small clinical trials; however, a decrease in the need for mechanical ventilation or a decrease in the length of stay was not shown. Because of limited evidence for a clinically relevant benefit, potential toxic effects, and high cost, routine use of aerosolised ribavirin is not recommended. [8]

Antibiotics

- Routine administration of empirical antibiotic therapy to infants with RSV bronchiolitis is not recommended, because the risk of concomitant bacterial infection is very low (0.2%).[8]
- Antibiotics should be administered to those with confirmed or strongly suspected bacterial infections.[2] [8]
- For infants with severe RSV bronchiolitis who require intubation, the risk of bacterial pneumonia is significantly higher (26%). These infants may benefit from initiation of antibiotics pending culture results.[2] [106] [128] [129]

Corticosteroids

- Corticosteroids are not effective in the routine management of RSV infection and do not appear to reduce subsequent recurrent wheeze or asthma.[2] [130] [131] [132] [133] In addition, their use in patients with bronchiolitis indicate that they do not reduce hospital admissions and do not reduce length of stay for inpatients.[8]
- The American Academy of Pediatrics guidelines and the Scottish Intercollegiate Guidelines Network guidelines on the management of bronchiolitis recommend against the routine use of corticosteroids for this condition.[2]
- Corticosteroids may be beneficial in patients with atopy, asthma, or chronic lung disease.

Less effective or ineffective therapies

- Chest physiotherapy has not been shown to improve outcomes, and its use is discouraged.[2] [108] In the UK, the National Institute for Health and Care Excellence does not recommend chest physiotherapy on babies and children with bronchiolitis. However, a chest physiotherapy assessment in babies and children who have relevant comorbidities where there may be additional difficulty clearing secretions (e.g., spinal muscular atrophy, severe tracheomalacia) may be warranted.[53]
- Nasal suctioning is widely utilised for infants with bronchiolitis as supportive management, but there is a lack of evidence demonstrating risk or benefit of this intervention.[134] The American Academy of Pediatrics does not make a recommendation about suction due to insufficient data but suggests that the routine use of 'deep' suctioning may not be beneficial.[2] In the UK, the National Institute for Health and Care Excellence does not recommend routinely performing upper airway suctioning in babies or children with bronchiolitis but suggest that it could be considered for those with respiratory distress or feeding difficulties due to upper airway secretions.[53]
- Mucolytic therapy with nebulised recombinant human DNase, acetylcysteine, or carbocisteine has not been effective.[135] [136]
- Surfactant therapy for intubated patients has not been effective.
- Helium-oxygen (heliox) mixtures have shown no benefit in regards to the rate of intubation, rate of accident and emergency department discharge, or length of treatment for respiratory distress in the management of bronchiolitis in infants.[137]

- Montelukast has not been proven effective in the treatment of RSV infection, or in the reduction of post-bronchiolitis wheezing.[138]
- Evidence is lacking for the safety and effectiveness of magnesium sulphate in children ≤2 years with bronchiolitis.[139]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
mild or self-limiting illness		
	1st	outpatient or inpatient supportive care
	adjunct	nebulised hypertonic saline
with atopy, asthma, or chronic lung disease	plus	treatment of underlying disease ± corticosteroid
	adjunct	bronchodilator
at risk of severe disease due to HSCT or other severe immunodeficiency	adjunct	ribavirin ± intravenous immunoglobulin (IVIG)
moderate illness		
	1st	inpatient supportive care
	adjunct	nebulised hypertonic saline
with atopy, asthma, or chronic lung disease	plus	treatment of underlying disease ± corticosteroid
	adjunct	bronchodilator
at risk of severe disease due to HSCT or other severe immunodeficiency	adjunct	ribavirin ± intravenous immunoglobulin (IVIG)
severe illness		
	1st	supportive care in intensive care unit (ICU)
	adjunct	intravenous immunoglobulin (IVIG)
	adjunct	ribavirin
with atopy, asthma, or chronic lung disease	plus	treatment of underlying disease ± corticosteroid
	adjunct	bronchodilator
requiring intubation	adjunct	antibiotics

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

mild or self-limiting illness

1st **outpatient or inpatient supportive care**

» For most infants RSV disease is usually mild and self-limiting, and can be treated in the outpatient setting. Outpatient care requires diligent follow-up to ensure that the patient is not deteriorating.

» Treatment is largely supportive regardless of setting, with a focus on improving oxygenation and ventilation and providing adequate nutritional support. No available treatment shortens the course of bronchiolitis or hastens the resolution of symptoms.[8] Infants are obligate nose breathers, and nasal obstruction is a frequent problem. Simple nasal toilet with saline drops and a suction bulb can significantly improve the work of breathing.

» High-risk infants include those with history of prematurity, age under 6 months at start of RSV season, chronic lung disease, complex congenital heart disease, or immune deficiency. These patients require closer observation and, frequently, admission to hospital.

» Symptomatic therapy for healthy adults is usually sufficient, as the disease is usually confined to the upper respiratory tract and is self-limiting.

» For adults with mild RSV illness, therapy is also largely supportive and targeted at relieving symptoms.

adjunct **nebulised hypertonic saline**

Treatment recommended for SOME patients in selected patient group

» Nebulised hypertonic saline is of potential benefit in reducing symptoms of mild or moderate bronchiolitis in the hospital setting.[122] Given the relatively long period of use required to achieve improvement, nebulised hypertonic saline is not recommended for use in the accident and emergency department.[2] [123] [124]

with atopy, asthma, or chronic lung disease **plus** **treatment of underlying disease ± corticosteroid**

Acute

Treatment recommended for ALL patients in selected patient group

Primary options

» prednisolone: children: 1-2 mg/kg/day (maximum 60 mg/day) orally given in 2 divided doses for 3-10 days; adults: 40-80 mg/day orally given in 1-2 divided doses for 3-10 days

» Routine management of co-existent asthma or COPD should continue in accordance with a stepwise approach to therapy.

» Corticosteroids are not effective in routine management of RSV infection. The American Academy of Pediatrics guidelines and the Scottish Intercollegiate Guidelines Network guidelines on the management of bronchiolitis recommend against the routine use of corticosteroids for this condition.[2]

» Corticosteroids may be beneficial in patients with atopy, asthma, or chronic lung disease.

» For adults with mild RSV illness, especially for patients with COPD or asthma, corticosteroids are tried, but no studies have shown a benefit.

adjunct **bronchodilator**

Treatment recommended for SOME patients in selected patient group

» Bronchodilators (e.g., salbutamol, ipratropium) should not be used routinely in the management of bronchiolitis.[2] [53]

» Bronchodilators may be of benefit for patients with asthma, COPD, or severe disease.

» Bronchodilators may transiently improve oxygen saturation and work of breathing, but have not been shown to decrease hospital admissions, length of stay, or length of oxygen therapy.[118] [119] [120] [121]

at risk of severe disease due to HSCT or other severe immunodeficiency

adjunct **ribavirin ± intravenous immunoglobulin (IVIG)**

Treatment recommended for SOME patients in selected patient group

Primary options

» ribavirin: consult specialist for guidance on dose

Secondary options

MANAGEMENT

Acute

» ribavirin: consult specialist for guidance on dose
-and-
» normal immunoglobulin human: consult specialist for guidance on dose

» Oral ribavirin has been used in immune deficient adults (predominantly transplant recipients and cancer patients with severe RSV disease), although it is not approved for this indication.[125] Its early use in adult bone marrow transplant patients has reduced morbidity and mortality in this patient subset.[126]

» Adults with RSV infection who are older, immune deficient, or have comorbidities may also benefit.

» IVIG may be added to ribavirin for immune deficient patients at high risk for progression to severe lower respiratory tract disease.[125] [126] [127]

» Ribavirin is not recommended for routine use in children with bronchiolitis.[8] [106]

» Ribavirin is available as an inhalation solution for the treatment of RSV in some countries. Studies with aerosolised ribavirin therapy demonstrated a small increase in oxygen saturation in small clinical trials; however, a decrease in the need for mechanical ventilation or a decrease in the length of stay was not shown. Because of limited evidence for a clinically relevant benefit, potential toxic effects, and high cost, routine use of aerosolised ribavirin is not recommended.[8]

moderate illness

1st **inpatient supportive care**

» Signs of moderate illness in infants include hypoxaemia (oxygen saturations <90% to 92%), tachypnoea, increased work of breathing (nasal flaring, intercostal retractions, head bobbing), inadequate feeding, and dehydration. Patients should be admitted for further care and observation.[2] Hypoxaemia should be treated with warm, humidified oxygen through nasal cannula or mask.

» High-flow nasal cannula (HFNC) support is safe in a typical ward setting. There is no clear evidence that initiating support with HFNC is more effective than standard oxygen therapy with a mask, either in shortening hospital length-of-stay or preventing ICU admissions, although

Acute

studies have been conflicting. Given the current state of uncertainty and the higher resources needed for HFNC therapy, its use outside of clinical trials should be limited to infants who have failed standard oxygen therapy.[115]

» Careful attention should be given to intravascular fluid and nutritional support. Infants with poor feeding or significantly elevated work of breathing or respiratory rate should be fed by nasogastric or nasojejunal tube or receive intravenous fluids.[2]

» High-risk infants include those with a history of prematurity, age under 6 months at start of RSV season, chronic lung disease, complex congenital heart disease, or immune deficit. These patients require closer observation and, frequent admission to hospital.

» Adults who are older, immune deficiency, or have comorbidities may have moderate illness and should be managed with supportive care while exacerbations of underlying illnesses are addressed.

adjunct **nebulised hypertonic saline**

Treatment recommended for SOME patients in selected patient group

» Nebulised hypertonic saline is of potential benefit in reducing symptoms of mild or moderate bronchiolitis in the hospital setting.[122] Given the relatively long period of use required to achieve improvement, nebulised hypertonic saline is not recommended for use in the accident and emergency department.[2] [123] [124]

with atopy, asthma, or chronic lung disease

plus **treatment of underlying disease ± corticosteroid**

Treatment recommended for ALL patients in selected patient group

Primary options

» prednisolone: children: 1-2 mg/kg/day (maximum 60 mg/day) orally given in 2 divided doses for 3-10 days; adults: 40-80 mg/day orally given in 1-2 divided doses for 3-10 days

» Routine management of co-existent asthma or COPD should continue in accordance with a stepwise approach to therapy.

» Corticosteroids are not effective in routine management of RSV infection.

Acute

» The American Academy of Pediatrics guidelines and the Scottish Intercollegiate Guidelines Network guidelines on the management of bronchiolitis recommend against the routine use of corticosteroids for this condition.[2]

» Corticosteroids may be beneficial in patients with atopy, asthma, or chronic lung disease.

» In adults who are older, immune deficient, or have comorbidities, corticosteroids may be beneficial.

adjunct **bronchodilator**

Treatment recommended for SOME patients in selected patient group

» Bronchodilators (e.g., salbutamol, ipratropium) should not be used routinely in the management of bronchiolitis.[2] [53]

» Bronchodilators may be of benefit for patients with asthma, COPD, or severe disease.

» Bronchodilators may transiently improve oxygen saturation and work of breathing, but have not been shown to decrease hospital admissions, length of stay, or length of oxygen therapy.[118] [119] [120] [121]

at risk of severe disease due to HSCT or other severe immunodeficiency

adjunct **ribavirin ± intravenous immunoglobulin (IVIG)**

Treatment recommended for SOME patients in selected patient group

Primary options

» ribavirin: consult specialist for guidance on dose

Secondary options

» ribavirin: consult specialist for guidance on dose
-and-
» normal immunoglobulin human: consult specialist for guidance on dose

» Oral ribavirin has been used in immune deficient adults (predominantly transplant recipients and cancer patients with severe RSV disease), although it is not approved for this indication.[125] Its early use in adult bone marrow transplant patients has reduced morbidity and mortality in this patient subset.[126]

Acute

» Adults with RSV infection who are older, immune deficient, or have comorbidities may also benefit.

» IVIG may be added to ribavirin for immune deficient patients at high risk for progression to severe lower respiratory tract disease.[125] [127] [127]

» Ribavirin is not recommended for routine use in children with bronchiolitis.[8] [106]

» Ribavirin is available as an inhalation solution for the treatment of RSV in some countries. Studies with aerosolised ribavirin therapy demonstrated a small increase in oxygen saturation in small clinical trials; however, a decrease in the need for mechanical ventilation or a decrease in the length of stay was not shown. Because of limited evidence for a clinically relevant benefit, potential toxic effects, and high cost, routine use of aerosolised ribavirin is not recommended.[8]

severe illness

1st **supportive care in intensive care unit (ICU)**

» Infants with refractory hypoxaemia, progressive respiratory distress, or frank respiratory failure should be transferred to the paediatric ICU. Patients often improve with non-invasive mechanical ventilation such as nasal continuous positive airway pressure but may require endotracheal intubation with mechanical ventilation.[116]

» Hypoxaemia should be treated with warm, humidified oxygen through a nasal cannula or mask, with noninvasive ventilation or mechanical ventilation as required.

» Rehydration and nutrition can be accomplished by enteral or parenteral routes, depending on the degree of disease severity and other clinical considerations. In the UK, the National Institute for Health and Care Excellence recommends giving fluids by nasogastric or orogastric tube in babies and children with bronchiolitis if they cannot take enough fluid by mouth. Alternatively, it recommends intravenous isotonic fluids to babies and children who do not tolerate nasogastric or orogastric fluids or have impending respiratory failure.[53]

» High-risk infants include those with a history of prematurity, age under 6 months at start of RSV season, chronic lung disease, complex congenital heart disease, or immune deficiency.

Acute

» Adults who are older, immune deficient, or have comorbidities may progress to severe illness requiring ICU admission, with respiratory support and intravenous and nutritional support.

adjunct **intravenous immunoglobulin (IVIG)**

Treatment recommended for SOME patients in selected patient group

Primary options

» normal immunoglobulin human: consult specialist for guidance on dose

» IVIG can be considered in immune deficient patients (e.g., people with cancer or haematopoietic stem cell transplant recipients) with disseminated viral disease.[125] [126]

» Use of IVIG or RSV-IG treatment alone did not significantly shorten the duration of hospitalisation of infants with RSV bronchiolitis and/or pneumonia.[140] [141] However, IVIG has been employed as a final resort in deteriorating, critically ill patients with disseminated disease with multiple viruses (e.g. varicella, cytomegalovirus).

adjunct **ribavirin**

Treatment recommended for SOME patients in selected patient group

Primary options

» ribavirin: consult specialist for guidance on dose

» Oral ribavirin has been used in immune deficient adults (predominantly transplant recipients and cancer patients with severe RSV disease), although it is not approved for this indication.[125] Its early use in adult bone marrow transplant patients has reduced morbidity and mortality in this patient subset.[126]

» Adults with RSV infection who are older, immune deficient, or have comorbidities may also benefit.

» The use of ribavirin in conjunction with intravenous immunoglobulin (IVIG) for the treatment of patients with RSV disease has been studied.[127] A meta-review reported that recipients of dual therapy (aerosolised ribavirin with either IVIG or palivizumab) had less progression to lower respiratory tract infection than those patients who received aerosolised ribavirin alone.[125]

Acute

» Ribavirin is not recommended for routine use in children with bronchiolitis.[8] [106]

» Ribavirin is available as an inhalation solution for the treatment of RSV in some countries. Studies with aerosolised ribavirin therapy demonstrated a small increase in oxygen saturation in small clinical trials; however, a decrease in the need for mechanical ventilation or a decrease in the length of stay was not shown. Because of limited evidence for a clinically relevant benefit, potential toxic effects, and high cost, routine use of aerosolised ribavirin is not recommended.[8]

with atopy, asthma, or chronic lung disease — **plus** — **treatment of underlying disease ± corticosteroid**

Treatment recommended for ALL patients in selected patient group

Primary options

» prednisolone: children: 1-2 mg/kg/day (maximum 60 mg/day) orally given in 2 divided doses for 3-10 days; adults: 40-80 mg/day orally given in 1-2 divided doses for 3-10 days

» Routine management of co-existent asthma or COPD should continue in accordance with a stepwise approach to therapy.

» Corticosteroids are not effective in routine management of RSV infection.

» The American Academy of Pediatrics guidelines and the Scottish Intercollegiate Guidelines Network guidelines on the management of bronchiolitis recommend against the routine use of corticosteroids for this condition.[2]

» Corticosteroids may be beneficial in patients with atopy, asthma, or chronic lung disease.

» In adults who are older, immune deficient, or have comorbidities, corticosteroids may be beneficial.

adjunct — **bronchodilator**

Treatment recommended for SOME patients in selected patient group

» Bronchodilators (e.g., salbutamol, ipratropium) should not be used routinely in the management of bronchiolitis.[2] [53]

» Bronchodilators may be of benefit for patients with asthma, COPD, or severe disease.

Acute

» Bronchodilators may transiently improve oxygen saturation and work of breathing, but have not been shown to decrease hospital admissions, length of stay, or length of oxygen therapy.[118] [119] [120] [121]

requiring intubation **adjunct** **antibiotics**

Treatment recommended for SOME patients in selected patient group

» Infants who have severe RSV bronchiolitis and require intubation have a 26% risk of bacterial pneumonia. These infants may benefit from initiation of antibiotics pending culture results.[2] [106] [128] [129] Routine administration of empiric antibiotic therapy to infants with RSV bronchiolitis is not recommended, because the risk of concomitant bacterial infection is very low (0.2%). [8]

Emerging

Novel antiviral compounds

Given the scarce evidence for efficacy of ribavirin (the only approved therapy for RSV), a therapy with clear efficacy would be a welcome breakthrough. Several antiviral compounds are in clinical development.[142] These include therapies blocking RSV fusion protein (RSV-F) , inhibiting viral polymerase (RSV-L), or other central viral proteins (RSV-N , RSV-M2). These therapies are at various stages of clinical development.[30] [86] [143] [144]

Primary prevention

Vaccines

Until 2022 there was no vaccine available against respiratory syncytial virus (RSV). Difficulties encountered in RSV vaccine development include: ineffective protective immunity arising from natural infection; difficulty establishing end point metrics for measuring vaccine response; and the need for rigorous safety analysis due to enhanced disease severity caused by a formalin-inactivated RSV vaccine candidate in the 1960s.[59]

In 2023, the first two vaccines for the prevention of RSV were approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). The first vaccine (commercially known as Arexvy®) is a recombinant RSV-specific antigen glycoprotein F stabilised in the prefusion conformation (RSVPreF3), combined with the AS01E adjuvant system. The second vaccine (commercially known as Abrysvo®) is a bivalent RSV prefusion F (RSVpreF) protein-based vaccine.

Both Abrysvo® and Arexvy® are approved for the active immunisation of adults aged ≥60 years for the prevention of lower respiratory tract disease caused by RSV. Arexvy® is also approved by the FDA and EMA for the prevention of RSV lower respiratory tract disease in adults aged 50-59 years who are at increased risk.

Abrysvo® is recommended for use in pregnant women between 32 and 36 weeks' gestation using seasonal administration (i.e., during September through the end of January in most of the continental US) to provide passive protection against lower respiratory tract disease caused by RSV in infants from birth through to 6 months of age.[60] [61]

In large, randomised, controlled trials in adults aged ≥60 years, the vaccines provided up to 70% efficacy in preventing RSV infection and up to 90% efficacy against severe disease, when dosed intramuscularly once prior to RSV season, with good safety profiles.[62] [63] Further data about the possible need for annual repeat dosing are not yet available.

When pregnant women between 24 and 36 weeks' gestation were administered one dose of RSVpreF, the efficacy for prevention of RSV infection in their infants up to 6 months of age was 50%, and for prevention of severe RSV disease in infants up to 6 months of age was almost 70% compared to infants of mothers who received the placebo. Somewhat higher rates of protection against both infection and severe disease were seen in the first 3 months of life in the infants of vaccinated mothers.[64] A 2024 systematic review including six RCTs (25 study reports) comparing RSV vaccination with placebo in 17,991 pregnant women concluded that RSV vaccination during pregnancy reduces RSV-related hospitalisations in infants and has little or no effect on the risk of birth defects.[65]

In 2024, the FDA and EMA also approved an mRNA vaccine (commercially known as Mresvia®) to protect adults aged ≥60 years from lower respiratory tract disease caused by RSV infection. The vaccine contains an mRNA sequence that encodes RSV glycoprotein F stabilised in the prefusion conformation. This glycoprotein, crucial for viral entry into host cells, is expressed on the surface of the virus. The prefusion conformation of the F protein is a significant target of potent neutralising antibodies and is highly conserved across both RSV-A and RSV-B subtypes.

Data from the phase 3 ConquerRSV clinical trial, involving 35,541 adults aged ≥60 years in 22 countries, showed a vaccine efficacy for the mRNA vaccine of 83.7% against RSV-associated lower respiratory tract disease with at least two signs or symptoms and 82.4% against the disease with at least three signs or symptoms over a median follow-up of 3.7 months.[66]

Immunoprophylaxis

Palivizumab and nirsevimab are monoclonal antibodies that are directed at targets on the RSV F protein and are approved for RSV immunoprophylaxis in infants and children. Nirsevimab is a monoclonal antibody engineered to bind to the prefusion RSV F protein and with an Fc region engineered to prolong its half-life. The changes improve the drug's efficacy (with early studies showing that the risk of hospitalisation for RSV is decreased by up to 80% as compared to about a 50% decrease in risk of hospitalisation with palivizumab use) and give it the advantage of only requiring a single intramuscular dose (compared to 5 doses with palivizumab).[67] [68]

Palivizumab

Palivizumab was the first monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by RSV in high-risk infants and children. It is still approved in the US and Europe.

Immunoprophylaxis with palivizumab for infants at high risk reduced hospital admissions by 45% to 55% and was associated with a reduction in all-cause mortality.[69] [70] The need for frequent injections and its expense limited its use on a large scale.[71]

Current indications for use of palivizumab are based on shortages of nirsevimab. There is no known indication for using palivizumab when nirsevimab is available, given the lower cost, easier administration, and likely greater efficacy of nirsevimab. Neither palivizumab nor nirsevimab is indicated for treating active RSV infection.[72]

Nirsevimab

Nirsevimab is a long-acting RSV F protein-directed fusion inhibitor monoclonal antibody indicated for the prevention of RSV lower respiratory tract disease in paediatric patients. It is approved in the US and Europe. In the US, it is approved for children up to the age of 19 months. In Europe, it is approved for children up to the age of 24 months. Nirsevimab has an extended half-life, and is intended to protect infants for an entire RSV season with a single intramuscular dose.[73]

The American Academy of Pediatrics (AAP) recommends that all infants, especially those at high risk, receive a single dose of nirsevimab. Specifically the AAP and the Center for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommend a single dose of nirsevimab for:[74] [75] [76]

- All infants <8 months of age born during or entering their first RSV season
- Infants and children 8-19 months of age who are at increased risk of severe disease and entering their second RSV season

These recommendations were amended for the 2022-2023 season due to supply chain issues, but remain the ACIP recommendations when the needed supply of nirsevimab is available.

In healthy preterm infants, nirsevimab resulted in fewer hospitalisations for RSV-associated lower respiratory tract infections compared with placebo.[67] One phase 3 trial found that a single dose of nirsevimab provided protection against medically attended RSV-associated lower respiratory tract infection when given to healthy late-preterm and term infants before an RSV season.[68] The safety and efficacy of nirsevimab were supported by three clinical trials which found that nirsevimab reduced the risk of RSV lower respiratory tract infection by approximately 70% to 75% relative to placebo.[68] [77] [78] [79] Initial results of a population-based longitudinal study conducted in Spain show that nirsevimab substantially reduced infant hospitalisations for RSV-associated LRTI, severe RSV-associated LRTI requiring oxygen, and all-cause LRTI when given in real-world conditions.[80]

Secondary prevention

Hand washing in the clinical and non-clinical settings is important.[2] Hand washing and washing of shared toys is important for all family members and close contacts to limit spread of respiratory syncytial virus (RSV) infection.

Patients requiring hospitalisation should be placed in isolation with contact precautions.[8] Proper use of barriers such as gowns, gloves, and masks is effective if large respiratory droplets are present and should be worn when providing care to these patients.[151] [152] [153] [154] An N95 respiratory mask is not required, and is not more effective than a simple surgical mask.[35] [91] [155] Screening for RSV in suspected patients allows for cohorting and isolation of patients with confirmed infection, limiting further spread of the virus.[91]

Patient discussions

Carers should be aware of the signs of worsening respiratory status (signs include grunting, nasal flaring, and intercostal and/or subcostal retractions), poor feeding, poor fluid intake, cyanosis or apnoea, and lethargy/exhaustion.[2] [53] They should be instructed to return for follow-up if the patient's clinical status deteriorates or does not improve. Ensure that carers are advised not to smoke in the baby or child's home as it increases the risk of severe symptoms in bronchiolitis.[1] [45][53]

Monitoring

Monitoring

Respiratory syncytial virus disease is generally mild and self-limiting. Diligent follow-up is required for infants treated as outpatients to ensure that a decline in respiratory status or nutrition is not overlooked.

Complications

Complications	Timeframe	Likelihood
asthma	**long term**	**low**
Debate continues as to whether severe respiratory syncytial virus (RSV) infection is a risk factor for asthma or simply an indicator of predisposition.[147] Several studies support an association or causal link.[148] [149] [150] However, severe RSV disease is associated with the development of chronic respiratory complications such as recurrent wheezing and asthma.[83] Infants who have severe lower respiratory tract disease (eg, bronchiolitis or pneumonia) from RSV have an increased risk of developing asthma later in life.[8]		
bronchiolitis	**variable**	**high**
Respiratory syncytial virus bronchiolitis may produce severe respiratory distress. High-risk infants, such as those with prematurity, chronic lung disease, complex congenital heart disease, or immune deficiency, are more likely to present with severe disease. Apnoea is a common complication, especially in very young infants, and may be the presenting sign.		
pneumonia	**variable**	**high**
Respiratory syncytial virus (RSV) can cause pneumonia in children and, rarely, in immunocompetent adults. RSV pneumonia usually presents with low-grade fever, persistent cough, and malaise.		

Prognosis

Respiratory syncytial virus (RSV) infection is generally self-limiting and resolves in 10-14 days.

Previously healthy infants who develop RSV bronchiolitis do not typically require hospitalisation, and most who are hospitalised improve with supportive care and are discharged after 2 or 3 days. However, approximately 1% to 3% of all children in the first 12 months of life will be hospitalised because of severe RSV lower respiratory tract disease, with the highest rate of RSV hospitalisations occurring in the first 6 months of life.[8] Worldwide, 1 out of every 200 infants is admitted to the hospital for RSV each year.[22][145]

In the US, 2% to 5% of infants admitted to hospital with bronchiolitis require mechanical ventilation but mortality is low (estimated to be <0.1%).[146] In developing countries, with limited access to advanced respiratory support, in-hospital case fatality rates are estimated to be approximately 1% with the total number of infant deaths exceeding 20,000 infants per year.

Diagnostic guidelines

United Kingdom

Bronchiolitis in children: diagnosis and management (https://www.nice.org.uk/guidance/ng9)

Published by: National Institute for Health and Care Excellence **Last published:** 2021

Europe

RSV in preterm and ill infants (https://www.efcni.org/activities/projects-2/position-paper-rsv)

Published by: The European Foundation for the Care of Newborn Infants **Last published:** 2020

North America

The diagnosis, management, and prevention of bronchiolitis (https://publications.aap.org/pediatrics/pages/policy)

Published by: American Academy of Pediatrics **Last published:** 2014

Treatment guidelines

United Kingdom

Bronchiolitis in children: diagnosis and management (https://www.nice.org.uk/guidance/ng9)

Published by: National Institute for Health and Care Excellence **Last published:** 2021

North America

The diagnosis, management, and prevention of bronchiolitis (https://publications.aap.org/pediatrics/pages/policy)

Published by: American Academy of Pediatrics **Last published:** 2014

Oceania

Australasian bronchiolitis guideline (https://www.predict.org.au/bronchiolitis-guideline/)

Published by: Paediatric Research in Emergency Departments International Collaborative (PREDICT)

Last published: 2024

South Australian paediatric clinical practice guidelines bronchiolitis in children (https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+programs+and+practice+guidelines?az=az-b)

Published by: Department for Health and Wellbeing, Government of South Australia.

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Images

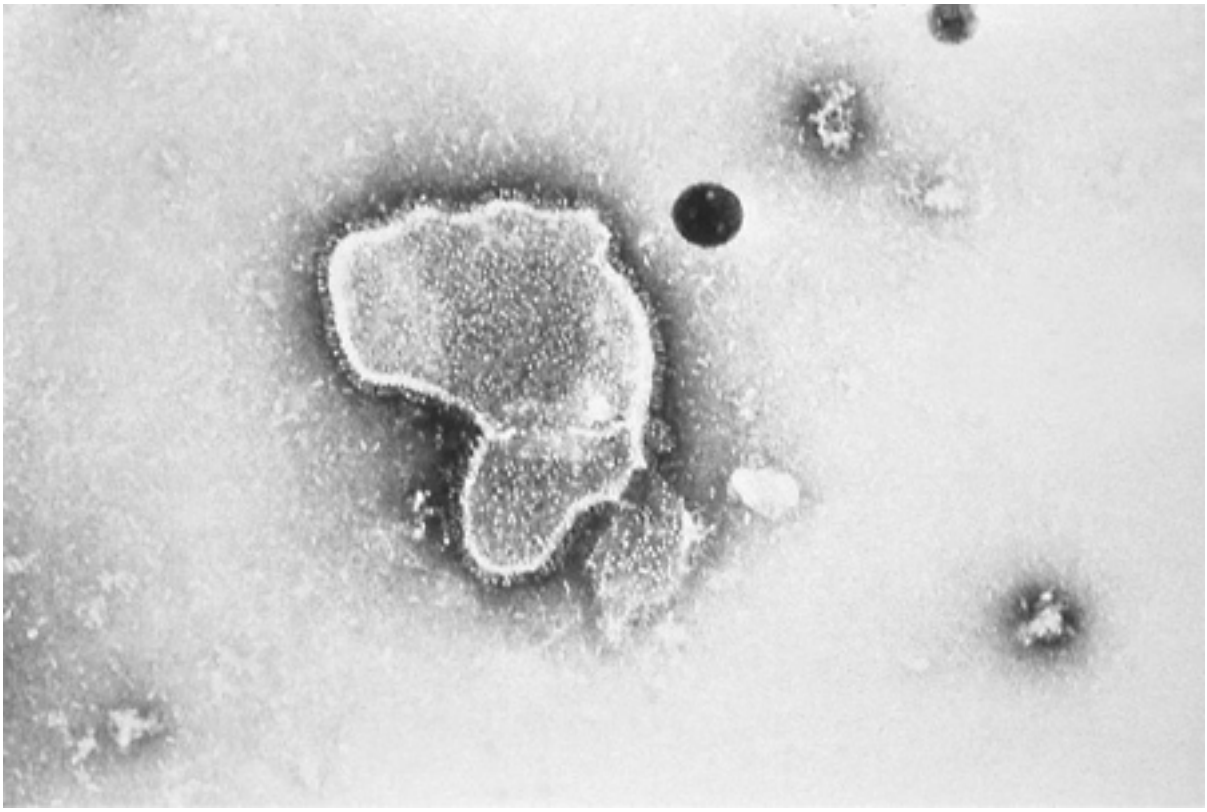

Figure 1: Electron micrograph revealing the morphological traits of the RSV

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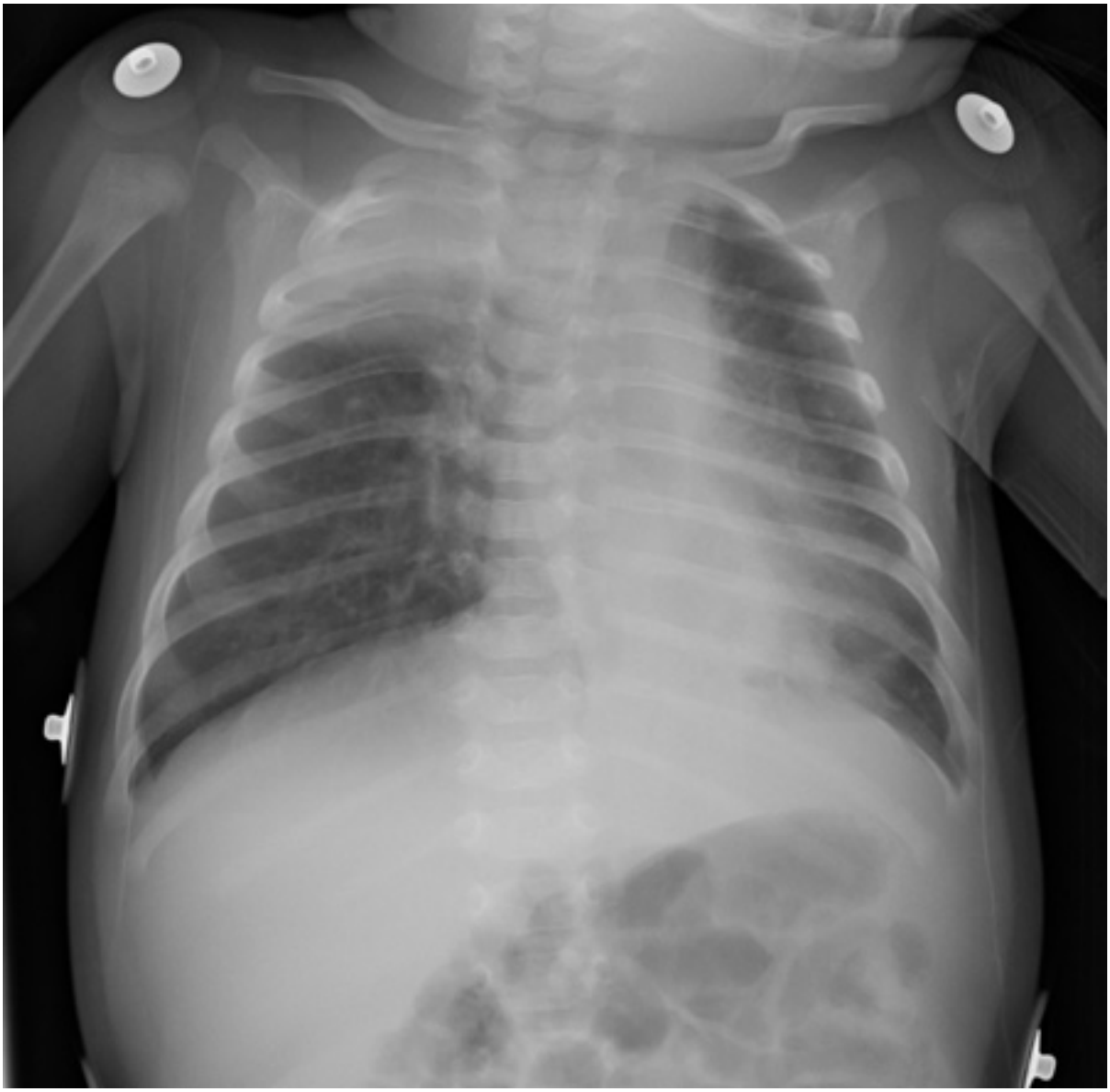

Figure 2: Atelectasis

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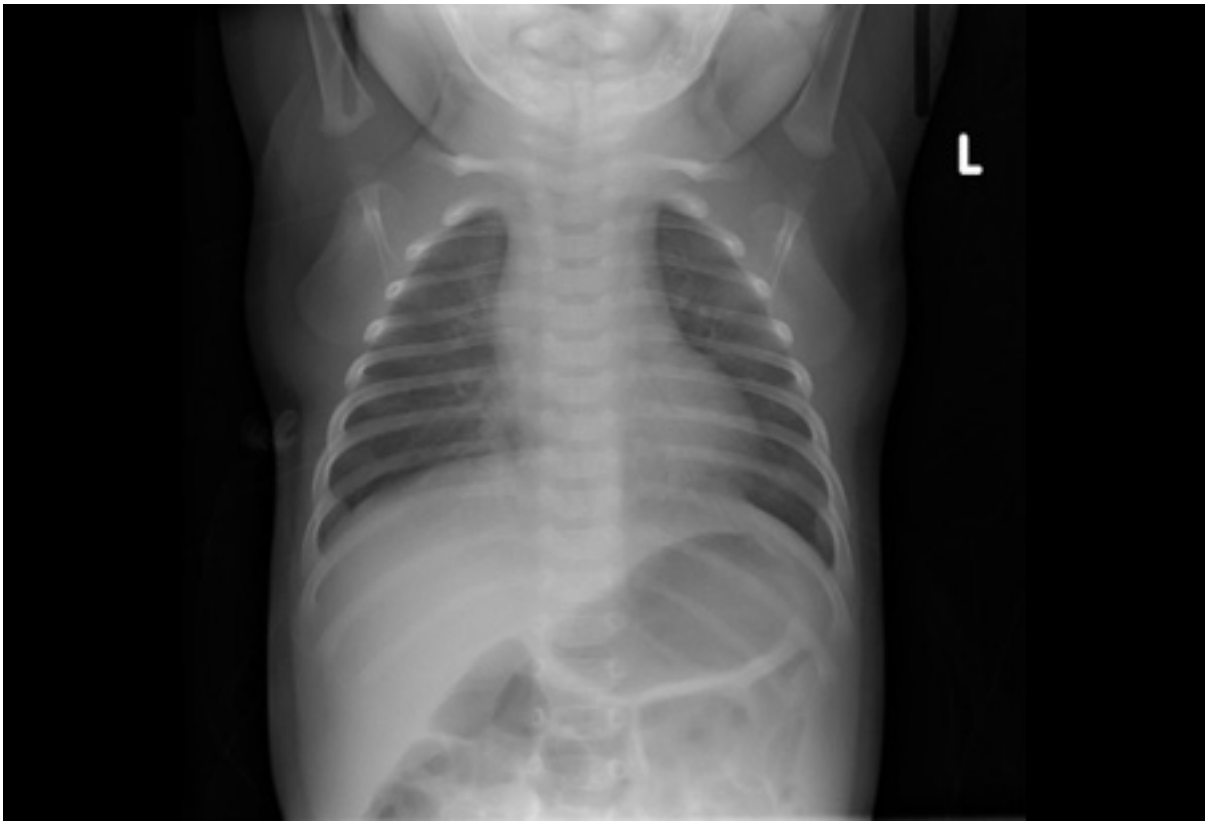

Figure 3: Air trapping and peribronchial cuffing

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BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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