Bronchiolitis

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Viral bronchiolitis is the most common cause of admission to hospital for infants in high-income countries. Respiratory syncytial virus accounts for 60–80% of bronchiolitis presentations. Bronchiolitis is diagnosed clinically without the need for viral testing. Management recommendations, based predominantly on high-quality evidence, advise clinicians to support hydration and oxygenation only. Evidence suggests no benefit with use of glucocorticoids or bronchodilators, with further evidence required to support use of hypertonic saline in bronchiolitis. Evidence is scarce in the intensive care unit. Evidence suggests use of high-flow therapy in bronchiolitis is limited to rescue therapy after failure of standard subnasal oxygen only in infants who are hypoxic and does not decrease rates of intensive care unit admission or intubation. Despite systematic reviews and international clinical practice guidelines promoting supportive rather than interventional therapy, universal de-implementation of interventional care in bronchiolitis has not occurred and remains a major challenge.

Introduction

Bronchiolitis is an acute viral infection of the lower respiratory tract that affects infants and young children worldwide. It is most commonly caused by human respiratory syncytial virus (RSV). Estimates suggest that RSV disease results in more than 30 million cases of lower respiratory tract infection in children younger than 5 years annually, with 3·2 million hospitalisations and 200 000 deaths worldwide each year.[1–4] Death from bronchiolitis occurs disproportionately in low-income countries, and bronchiolitis is the leading cause of infant hospitalisation in high-income countries.

Numerous guidelines exist to aid clinicians in the diagnosis and treatment of bronchiolitis (table). Despite two decades of messaging suggesting that less treatment is better and promoting supportive rather than interventional therapy, universal de-implementation of interventional care has not occurred and remains a major challenge. This Seminar builds on previous work to synthesise available evidence[12–14] and establish the extent to which it can be generalised for the recognition, pathophysiology, diagnostic pathways, management, and prevention of bronchiolitis.

Search strategy and selection criteria

We searched the Cochrane Collection Library for systematic reviews and PubMed for scientific articles in English only from Dec 17, 2015, (the date of our previous search for the Australasian bronchiolitis guideline) to Oct 21, 2020, using a combination of MeSH headings and keywords (using truncation appropriately) of the search terms "bronchiolitis" or "respiratory syncytial virus", and combined these with the following search terms: "natural history", "epidemiology", "severity of illness index", "diagnosis", "differential diagnosis", "physical examination", "diagnostic imaging", "urinalysis", "nasal lavage fluid", "risk factors", "intensive care units", "morbidity", "prevalence", "mortality", "asthma", "bronchodilator agents", "steroids", "anti-inflammatory agents", "leukotriene antagonists", "hypertonic saline", "oximetry", "oxygen inhalation therapy", "oxygen", "blood gas analysis", "continuous positive airway pressure", "positive pressure respiration", "positive end respiratory pressure", "physical therapy modalities", "suction", "saline drop", "nasal saline", "rehydration solutions", "enteral feeding", "parenteral feeding", "bacterial infection", "antibacterial agents", "sepsis", "urinary tract infection", "infection control", "primary prevention", "patient isolation", "immunization", and "vaccine". In addition, we reviewed references and available technical reports from Dec 17, 2015, to Oct 21, 2020, and national guidelines from Australia and New Zealand, the UK, the USA, Canada, Italy, France, and Spain.

Definition

Historically, there has been a lack of consistency in the definition of bronchiolitis, due in large part to the intrinsic underlying heterogeneity of the condition.[15] Bronchiolitis typically affects infants and young children presenting with signs of respiratory distress and lower respiratory tract infection. Although diagnosed solely on clinical criteria,[5,16] these criteria differ from region to region,[17] resulting in difficulties comparing research and guidelines internationally.[18] Consistency is lacking with respect to age (<12 months or <24 months; table), signs of a viral upper respiratory infection, presence of examination findings such as rales (crackles) with or without wheeze, first or subsequent episode,[18] and responsiveness to bronchodilator or corticosteroids.[5,17–19] This inconsistency results in a heterogeneous collection of phenotypes grouped under the term bronchiolitis.[17,19,20]

Epidemiology and microbiology

Bronchiolitis accounts for up to 15–17% of all hospitalisations in children younger than 2 years, and 15% of emergency department presentations in infants.[21] In children younger than 6 months, 45–54% of hospital admissions are due to RSV,[4,22] with more than 90% of children by age 2 years having been infected with this virus.[23,24]

Most commonly, the underlying infective organism in bronchiolitis is RSV, an RNA virus of the

Paramyxoviridae family ubiquitous within all communities worldwide.[16,19] Together with rhinovirus (8–29%), RSV accounts for 60–80% of bronchiolitis presentations in infants.[19,25,26] RSV has two antigenic strains (RSV-A and RSV-B) that can co-circulate with alternating dominance annually, although RSV-A is associated with higher morbidity.[24] Other viruses associated with bronchiolitis that frequently occur

	Australia and New Zealand, 2016[5]	NICE (UK), 2015[6]	AAP (USA), 2014[7]	CPS (Canada), 2014[8]	Italy, 2014[9]	France, 2013[10]	Spain, 2010[11]
Target population	Infants aged <12 months (can be used in those aged 12–24 months)	Children with bronchiolitis	Children aged 1–23 months	Children aged ≤2 years	Infants and children aged <12 months	Infants aged <12 months	Children aged <24 months
Diagnostic testing							
Chest x-ray	Not recommended	Not routinely recommended; consider when intensive care proposed	Not routinely recommended; consider in severe disease requiring ICU care or signs of airway complication (eg, pneumothorax)	Not routinely recommended; consider when diagnosis is unclear, rate of improvement not as expected, or disease severity indicates other diagnoses	Not routinely recommended	Not routinely recommended; consider if asymmetrical breath sounds are heard, diagnostic uncertainty, cardiac disease, chronic lung disease, or immunodeficiency	Not routinely recommended; consider if diagnostic uncertainty, atypical presentation, severe disease, or progressive disease course
Full blood count	Has no role in management	Not routinely recommended	Not recommended	Not recommended	Not routinely recommended	Obtain if undergoing investigations for a septic work-up	Not recommended
Blood culture	Has no role in management	Not routinely recommended	No mention	Not routinely recommended	Not routinely recommended	Not routinely recommended; recommended for infants aged <1 month as part of full septic work-up; not needed for infants aged 1–3 months unless presenting with signs of severe sepsis	Not routinely recommended
Blood gas	No mention	Not recommended; only if there is concern for severe worsening respiratory distress or impending respiratory failure	No mention	Not routinely recommended; only if there is concern for respiratory failure	Not routinely recommended	No mention	Not routinely recommended; might be useful for severe distress or impending respiratory failure
Virological testing (nasopharyngeal swab or aspirate)	No role in management of individual patients	No mention	Not routinely recommended	Not routinely recommended	RSV antigen recommended in hospital setting for cohorting and potentially decreasing antibiotic use	Not routinely recommended	Not routinely recommended; RSV testing might assist with cohorting
Urine microscopy or culture	Can be considered if temperature >38°C in an infant aged <2 months with bronchiolitis	No mention	Not recommended	Not routinely recommended	No mention	No mention	Routine urine test not indicated; UTI must be considered in patients aged <3 months with bronchiolitis and fever
Treatments							
β 2 agonists	Not recommended (including individuals with a personal or family history of atopy)	Not recommended	Not recommended	Not recommended	Not routinely recommended; carefully monitored trial might be appropriate	Not recommended in first episode of wheezing; consider trial in child with recurrent wheeze depending on atopic history, case history, and clinical features	Not routinely recommended; if used, must undergo carefully monitored trial
Corticosteroids	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Adrenaline or epinephrine	Not recommended except in peri-arrest or arrest situation	Not recommended	Not recommended	Not recommended; carefully monitored trial might be appropriate	Not recommended	Not routinely recommended	Not recommended

(Table continues on next page)

	Australia and New Zealand, 2016[5]	NICE (UK), 2015[6]	AAP (USA), 2014[7]	CPS (Canada), 2014[8]	Italy, 2014[9]	France, 2013[10]	Spain, 2010[11]
(Continued from previous page)							
Hypertonic saline	Do not administer nebulised hypertonic saline	Not recommended	Not recommended in emergency department; weak recommendation for inpatients with average length of stay >72 h	Not recommended in emergency department or outpatient setting; might be beneficial in inpatients with long length of stay	Recommended	Recommended for inpatients who have moderate to severe bronchiolitis	Recommended for inpatients
Antibiotics	Not recommended (including azithromycin)	Not recommended	Not recommended unless concomitant bacterial infection, or strong suspicion of it	Not recommended unless clear and documented evidence of secondary bacterial infection	Not recommended unless clear and documented evidence of secondary bacterial infection	Not recommended; consider with signs of secondary bacterial infection or severe difficulty with ventilation	Not recommended unless clear bacterial infection
Antivirals	Not indicated	No mention	No mention	Not recommended	Not recommended	No mention	Not recommended; might be a role for ribavirin in severely immunocompromised patients
Suctioning	Not routinely recommended; superficial nasal suction can be considered in individuals with moderate disease to assist feeding; nasal saline drops can be considered at the time of feeding	Do not routinely perform; consider upper airway suctioning in individuals with respiratory distress or feeding difficulties due to upper airway secretions; use if apnoea present	Insufficient data; routine use of deep suctioning might not be beneficial	Superficial nasal suctioning at frequent intervals; avoid deep suctioning and long intervals between suctioning	Superficial nasal suctioning recommended; deep suctioning not recommended	Superficial nasal suctioning recommended if nasal congestion	Superficial nasal suctioning recommended before feeding, sleeping, and assessment
Chest physiotherapy	Not indicated	Not routinely recommended unless relevant comorbidities present (eg, spinal muscular atrophy or severe tracheomalacia)	Not recommended	Not recommended	Not recommended	Not recommended unless relevant comorbidities (eg, muscular dystrophy or cystic fibrosis) or profound difficulty ventilating	Not recommended
Supplemental oxygen	Use if oxygen saturation is persistently <92%	Use if oxygen saturation is persistently <92%	Not recommended if oxyhaemoglobin >90% without acidosis	Use if oxyhaemoglobin saturation <90% to maintain saturations ≥90%	Use if oxygen saturation is persistently <90–92%	Use if oxygen saturation is <92% or if oxygen saturation is <95% and there are signs of severe respiratory distress	Use if severe respiratory distress or oxygen saturation <92%
Heated humidified high-flow oxygen or air via nasal cannulae	Can be considered in the presence of hypoxia (oxygen saturation <92%) and moderate to severe recessions; use without hypoxia should be limited to RCT setting only	Use is becoming widespread without demonstration of additional efficacy; multicentre RCT and weaning strategies would be of benefit	Future research required	Insufficient evidence to recommend	No recommendation (studies currently ongoing to assess efficacy)	No mention	No mention
CPAP	Can be considered in severe bronchiolitis	Consider CPAP in children with bronchiolitis who have impending respiratory failure	No mention	No mention	For respiratory failure	No mention	Use with severe respiratory difficulties, hypercapnia, or recurrent apnoea
Monitoring or pulse oximetry	Observations as per local hospital guidelines and EWTs; continuous oximetry should not be routinely used to dictate medical management unless disease is severe	Intermittent pulse oximetry monitoring recommended to be measured and monitored at all secondary care centres and primary care centres if available	Not recommended if supplemental oxygen is not required, or if oxyhaemoglobin saturation >90%	Not recommended unless patients are high-risk and in acute phase of disease; intermittent checks appropriate	No mention	No mention	Intermittent pulse oximetry; no clear recommendation for continuous monitoring

(Table continues on next page)

	Australia and New Zealand, 2016[5]	NICE (UK), 2015[6]	AAP (USA), 2014[7]	CPS (Canada), 2014[8]	Italy, 2014[9]	France, 2013[10]	Spain, 2010[11]
(Continued from previous page)							
Hydration or nutrition	When non-oral hydration is required either intravenous or nasogastric hydration are appropriate; if intravenous fluid is used it should be isotonic (0·9% sodium chloride with similar); ideal volume of intravenous or nasogastric fluids required to maintain hydration remains unknown (60–100% of maintenance fluid is an appropriate volume to initiate)	Nasogastric or orogastric fluids first in infants who cannot maintain oral hydration; isotonic intravenous fluids in individuals who cannot tolerate nasogastric or orogastric fluids, or with impending respiratory failure	Nasogastric or intravenous fluids for infants who cannot maintain hydration	Nasogastric or intravenous fluids for infants who cannot maintain hydration	Nasogastric or intravenous fluids for infants who cannot maintain hydration	Nasogastric or intravenous fluids for infants who cannot maintain hydration; consider restricting fluid intake to 66% of normal maintenance in severe bronchiolitis due to risk of SiADH	Nasogastric or intravenous fluids for infants who cannot maintain hydration

AAP=American Academy of Pediatrics. CPAP=continuous positive airway pressure. CPS=Canadian Pediatric Society. EWT=early warning tool. ICU=intensive care unit. NICE=National Institute for Health and Care Excellence. RCT=randomised controlled trial. RSV=respiratory syncytial virus. SiADH=syndrome of inappropriate antidiuretic hormone excretion. UTI=urinary tract infection.

Table: **National bronchiolitis clinical practice guidelines**

as co-infections include: human metapneumovirus (1·7–16·8%), adenovirus (1·0–9·0%), parainfluenza (2·6–6·0%), influenza (0·5–5·0%), human bocavirus (0·6–27·0%), and human coronaviruses (HCoV NL63 and HKU1).[19,25] Occasionally, non-viral co-infections are reported with *Bordetella pertussis* and other atypical bacteria (*Mycoplasma pneumoniae* as well as *Chlamydia pneumoniae* and *Chlamydia trachomatis*).

Typically, there is seasonal variation in infectivity that is highest during the winter months in temperate zones,[16,27–32] with less variability in tropical zones.[27,33] This variation occurs because RSV favours cool temperatures and high humidity, meaning cool, dry winters have less illness related to RSV than warmer, wetter conditions.[24] In tropical areas, large aerosol droplets are formed due to higher humidity and stable temperatures resulting in less variability across the year.[27]

There have been few reports of co-infection with SARS-CoV-2 infection in bronchiolitis.[34] Public health measures associated with management of SARS-CoV-2 infection have resulted in considerably reduced presentations with bronchiolitis during lockdowns, physical distancing, and closure of schools and early childhood education centres.[35] However, relaxation of public health measures has resulted in a return of bronchiolitis disease burden in infants and peaks in atypical bronchiolitis seasons.[36]

Pathophysiology, clinical presentation, and assessment

The pathophysiological processes occurring in bronchiolitis relate to distal bronchiolar inflammation and obstruction, resulting in reduced airflow into the small airways and alteration in exhalation capacity, which lead to lung hyperexpansion, lung function alterations, increased mucus production, atelectasis, and wheezing. Immunopathology associated with RSV is characterised by the expression of pro-inflammatory cytokines with subsequent perivascular or peribronchial infiltration by mononuclear cells, mainly neutrophils (80%) and lymphocytes, triggering an unbalanced response between T helper 1 and T helper 2 cells.[37,38] Extrapulmonary manifestations can include encephalitis, cardiomyopathy, and hepatitis in more severe disease.[1,39]

The diagnosis of bronchiolitis is clinical, based on typical history and examination, and has not changed appreciably in many decades. A prodrome of symptoms of an acute viral upper respiratory tract infection with rhinorrhoea with or without fever for up to 2 days is followed by progression to the lower respiratory tract with one or more symptoms including persistent cough, tachypnoea, increased work of breathing shown by scalene and intercostal retractions, grunting or nasal flaring, and wheeze or rales on chest auscultation. Presentation can vary by age with young infants presenting with apnoea and fine rales on auscultation and older infants presenting with wheeze on auscultation. Symptoms and signs of respiratory distress and reduced feeding typically worsen over the first few days, with peak severity around day 3–5 of the illness, although with some heterogeneity.[40,41] Improvement of symptoms and signs occur over the next 7–14 days, with 90% of infants having resolution of cough within 3 weeks.[40] In assessing infants with bronchiolitis, clinicians should be aware of the minute-to-minute variation in clinical findings that can occur in patients secondary to alternating plugging and clearing of the airways of mucus and debris. This variation can confound assessment, and often a period of

observation is required to confirm a trend of clinical stability or deterioration. Furthermore, the variation contributes to a scarcity of robust criteria for measuring the immediate effects of possible pharmacological interventions.

The differential diagnosis of bronchiolitis includes both infectious and non-infectious causes. Absence of a viral upper respiratory prodrome should promote consideration of non-infectious causes in young infants, including congenital heart disease, congenital airway abnormalities, and foreign body aspiration. Consolidation, bronchial breathing, persistent local rales on auscultation, new fever, or respiratory deterioration outside classic natural history of bronchiolitis should promote consideration of pneumonia. Apnoea or paroxysms of cough should promote consideration of pertussis.

Several scoring instruments are available for bronchiolitis. The most commonly used clinical signs in these instruments include respiratory rate, wheeze, and retractions. Universally, the instruments have modest predictive ability and cannot be solely relied upon for clinical decision making. The utility of scoring instruments is further limited by the scarcity of robust score constructs and large prospective validation studies in independent settings. A 2018 systematic review of 32 scoring instruments concluded that further work is needed to develop and comprehensively validate better instruments.[42]

The most consistently identified risk factors associated with progression to severe bronchiolitis include gestational age less than 37 weeks, chronological age at presentation younger than 10 weeks, exposure to cigarette smoke, breastfeeding for less than 2 months, failure to thrive (poor nutrition), chronic lung disease, chronic heart conditions or neurological conditions, identified as Indigenous infants (eg, Australian Aboriginals and Torres Strait Islanders, Canadian First Nations peoples, and New Zealand Māori), and disadvantaged socioeconomic status.[22,27,43,44] Infants with any of these risk factors are more likely to deteriorate rapidly and to require escalation of care compared with infants without risk factors. Furthermore, the majority of studies identifying risk factors have identified these factors as independent variables, suggesting that they are additive, although the degree of increased risk with multiple risk factors is imprecise. Although the presence of multiple risk factors does not mandate admission, clinicians should take these risk factors into account when assessing infants with bronchiolitis, particularly when presenting early in illness—strategies include safeguards for those discharged or consideration of admission for those deemed to be high risk.

Host genetic polymorphism in immune responses has been associated with increased susceptibility to RSV infection.[45] Furthermore, individuals with particular genetic variation in Toll-like receptors (TLR1 and TLR10) have shown increased risk of later childhood asthma after RSV infection in infancy.[46] However, uncertainty remains regarding whether a genetic predisposition for allergic disease and asthma is the risk factor for severe bronchiolitis or if severe bronchiolitis is the risk factor for the development of subsequent asthma and allergic disease.[47] The immature, innate immunity of the infant requires further targeted evaluation and research to explain the severity of bronchiolitis in younger infants.[48] Human challenge models are advancing understanding, for example, in identifying neutrophil inflammation preceding RSV infection as a prime for more severe disease.[49] Confirming these findings, then identifying and reducing inflammatory priming in infants, is an area of further research.[49]

Diagnostic investigations

Despite the availability of high-quality international guidelines for the diagnosis and management of bronchiolitis (table), unnecessary diagnostic investigations are still routinely conducted.[50] Recommendations related to blood gas, complete blood counts, serum electrolytes, and urinalysis or urine culture have not changed in the past decade.[12] Blood gas measurements are not indicated except when there are signs of severe respiratory distress or impending failure. Serious bacterial infections associated with bronchiolitis are rare, and guidelines universally recommend against complete blood counts and cultures unless young infants are undergoing an evaluation for possible sepsis. Hydration status should be assessed and monitored by clinical examination; the routine measurement of serum electrolytes is unnecessary. The estimated prevalence of urinary tract infection in infants presenting with bronchiolitis and fever is 0·8% (95% CI 0·3–1·4).[51] Routine testing of urine is not supported and can lead to exposure to invasive procedures for urine collection, misdiagnosis of urinary tract infection, and unnecessary exposure to antibiotics, laboratory tests, and imaging.

Similarly, viral testing is not routinely recommended; test results do not change clinical management of bronchiolitis in individual patients. RSV testing is suggested in some jurisdictions to aid in cohorting of patients and to reduce antibiotic use, although neither strategy is supported by robust evidence (table).[52] However, there is increasing evidence of differential mechanistic pathways used by different viruses causing bronchiolitis, and these differences could be responsible for some of the heterogeneity observed in therapeutic interventions. Therapeutic management tailored to virological diagnosis in bronchiolitis is an area of future research.[53]

The use of imaging should likewise be restricted. Chest radiography is not recommended as a routine investigation, particularly in infants without fever or hypoxaemia.[54] The use of radiography to potentially allay fears of missing a bacterial lower respiratory tract infection exposes infants to the associated dangers of

unnecessary ionising radiation and increased prescription of antibiotics.[55,56] Yet, in some jurisdictions, chest radiography is used in more than 50% of patients admitted with bronchiolitis.[54] Lung ultrasound, which has the benefit of not being associated with a risk of ionising radiation like chest radiography, requires further evaluation of its utility in clinical management of infants with bronchiolitis.[57]

Therapeutic management

Respiratory support

High-flow and continuous positive airway pressure therapies

The airway obstruction and atelectasis occurring in bronchiolitis can result in hypoxaemia. Traditionally, the hypoxaemia has been treated with low-flow or standard subnasal oxygen administered via nasal prongs at ceiling rates of up to 2–3 L/min or face mask at ceiling rates of up to 15 L/min. Advances in management of hypoxaemia and respiratory failure associated with bronchiolitis include the use of high-flow therapy. High-flow therapy, in which humidified and heated air is blended with oxygen and delivered via nasal cannula, is thought to work by providing a degree of positive airway pressure that reduces upper airway resistance and washout of the nasopharyngeal dead space.[58–60] High-flow has been variably defined; in general it refers to a flow rate of up to 2–3 L/kg per min with a ceiling rate of 40–60 L/min.[58–60] The use of high-flow therapy was initially limited to neonatal and paediatric intensive care units and was part of the armamentarium to treat respiratory failure in bronchiolitis that ranged from high-flow to nasal continuous positive airway pressure, intubation, and mechanical ventilation. The introduction of high-flow for bronchiolitis was based on observational and low-quality evidence suggesting reduced need for intubation and mechanical ventilation following introduction of high-flow to intensive care environments.[59] Over the past decade, the use of high-flow has migrated to emergency departments, inpatient paediatric wards, and patient transfers while improving the evidence base with randomised controlled trials[61–66] and systematic reviews.[58,59]

The absence of a consistent definition for high-flow is reflected in intervention arms of randomised controlled trials in which flow rates vary from 6–8 L/min to 1–3 L/kg per min, a multiple of 4–6 of the minute ventilation volume.[58] Regardless, these trials provide clear evidence for the place of high-flow in bronchiolitis management. The largest randomised controlled trial compared high-flow at 2 L/kg per min versus subnasal oxygen at up to 2 L/min in 1472 children with bronchiolitis and oxygen saturations of less than 92–94% (depending on the institution) at 17 hospitals in Australia and New Zealand. Fewer treatment failures occurred in the high-flow group than the standard oxygen group (7% *vs* 16%; p<0·001).[60] A trial at 17 French hospitals compared high-flow at 3 L/kg per min versus subnasal oxygen at up to 2 L/min in 268 children with bronchiolitis and oxygen saturation under 95%. There was no statistically significant difference in treatment failure requiring escalation in care (14% *vs* 20%; p=0·21).[67] A single-centre trial in Australia compared high-flow at 1 L/kg per min versus subnasal oxygen at up to 2 L/min in 202 children with bronchiolitis and oxygen saturations 90% and above.[68] No statistically significant difference between groups in length of oxygen treatment (20 h *vs* 24 h; p=0·61) was found although high-flow had fewer treatment failures (14% *vs* 33%; p=0·0016). Together, these trials show no difference between high-flow and controls in intensive care admission rates, intubation rates, or hospital length of stay, and show that the intervention is safe with pneumothoraces occurring rarely.[58,59] Importantly, in the 200 combined patients in whom treatment with standard subnasal oxygen failed in the two Australasian trials,[60,68] high-flow rescued 61%.[59] Together, these data indicate that high-flow should not be used as a primary treatment modality in bronchiolitis with hypoxaemia. Rather, use of high-flow should be reserved for escalation of therapy if standard subnasal oxygen fails (figure 1).

Establishing a precise definition of treatment failure for subnasal oxygen therapy and its treatment effect, and refining the appropriate population in which to use high-flow therapy, is a priority to de-implement inappropriate high-flow therapy in infants with bronchiolitis.[69] Hypoxaemia while receiving subnasal oxygen, although an obvious objective definition of failure, is rare. Observational evidence suggests that the heart rate, respiration rate, and paediatric early warning scores of infants with bronchiolitis and hypoxaemia settle in the first 4–5 h when responding to oxygen therapy.[70] These objective criteria were used in the largest randomised controlled trial of high-flow, in which treatment failure required at least three of four predetermined physiological failure criteria. The treatment failure rate with these objective criteria was 16% in the standard subnasal oxygen arm, increasing to 23% when a less objective definition was used (clinician decision).

In intensive care units, high-flow at 2 L/kg per min has been shown to have greater failure rates at 24 h compared with nasal continuous positive airway pressure at 7 cm H_2O (142 participants; 51% *vs* 31%; p=0·001);[71] although high-flow can rescue those who do not respond to nasal continuous positive airway pressure (82% have no need for further respiratory support). When comparing high-flow at 3 L/kg per min with 2 L/kg per min there appears to be no advantage, but increased rates of patient discomfort (43% *vs* 16%; p=0·002).[72]

Continuous positive airway pressure is used widely as a respiratory support strategy to avoid invasive ventilation, particularly in intensive care. A Cochrane review of three studies (122 participants) found low-quality evidence that continuous positive airway pressure could decrease respiratory rate in infants with bronchiolitis compared with subnasal oxygen and recommended further adequately powered studies for the outcomes of hospital length of stay and intensive care unit admission.[73]

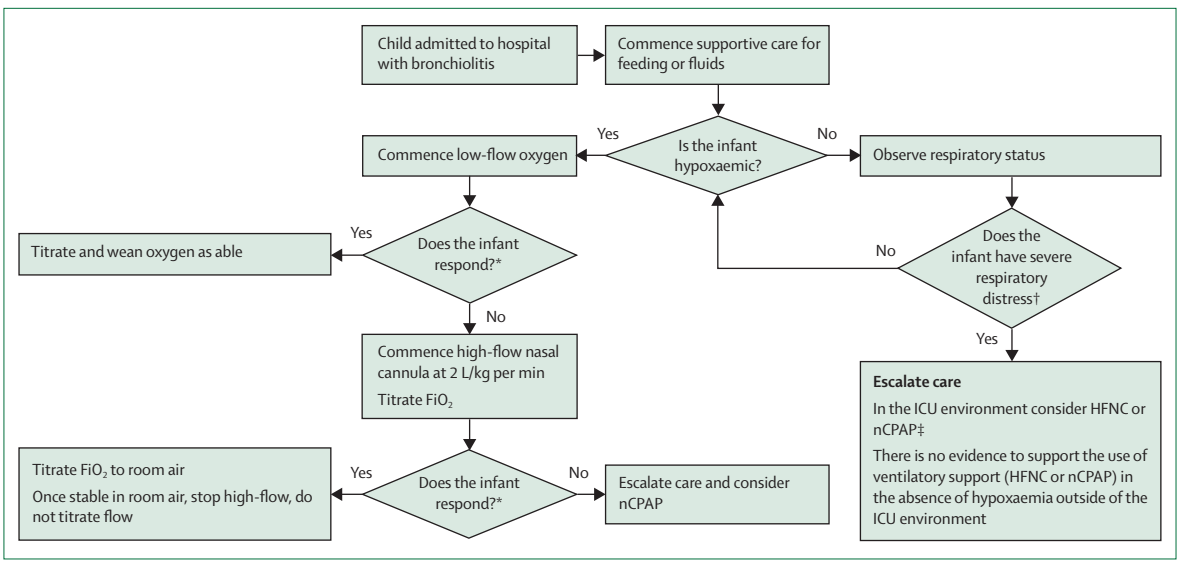

Figure 1: **Evidence-based approach to the use of HFNC for bronchiolitis**
FiO_2=fractional concentration of inspired oxygen. HFNC=high-flow nasal cannula. ICU=intensive care unit. nCPAP=nasal continuous positive airway pressure. *Response to therapy (low-flow oxygen or HFNC) is determined by a reduction in respiratory rate, a reduction in heart rate, or a paediatric early warning score within 4 h of commencing therapy. †If at any time the infant has severe respiratory distress, escalate care. Respiratory distress is a subjective finding. Severe respiratory distress is a level where a senior clinician determines that escalation in care is required, transferring the patient to emergency department resuscitation area, paediatric ward resuscitation area, high dependency unit, or ICU. Junior staff should escalate concerns regarding severe respiratory distress to senior colleagues. ‡For infants aged <6 months in intensive care, nCPAP seems superior to HFNC. Reproduced from O'Brien and colleagues,[59] by permission of John Wiley and Sons.

International guidelines recommend consideration of continuous positive airway pressure in infants with impending respiratory failure or severe disease (table).

Any infant deteriorating on subnasal oxygen who is escalated to non-invasive respiratory support (high-flow or continuous positive airway pressure) requires close observation so that any further escalation to invasive ventilation occurs in a timely manner.

Oxygen supplementation

The benefit of supplemental oxygen therapy in bronchiolitis is based on assumptions from first principles, data on supplemental oxygen therapy from other respiratory conditions, observational studies, and randomised controlled trials.[6,74–76] There is no evidence of the benefit of oxygen in infants with bronchiolitis without hypoxaemia and evidence shows that maintaining an oxygen saturation of at least 91% prolongs length of stay in hospital without benefit.[62,63,65,74] A randomised, double-blind, parallel-group trial involving 615 infants found an oximetry target to commence oxygen supplementation of 90% or less was as effective as a target of 94% or less without negative sequelae.[74] In this trial, infants had their oximetry readings artificially elevated (actual value of 90% displayed as 94%). These infants had similar time to resolution of cough, but had less time on supplemental oxygen, less time in hospital, and returned to normal earlier. A further randomised controlled trial comparing continuous and intermittent monitoring of pulse oximetry in stable inpatients using an oxygen saturation target of 90% showed no difference in clinical outcomes and greater nursing satisfaction with intermittent monitoring.[77] Studies provide high-quality evidence that a lower oximetry threshold of 90%, below which oxygen supplementation is started, is safe in the short term and could reduce length of hospital stay.[62,65,74] However, although the studies undertaken to date show short-term benefit, none have examined long-term neurocognitive outcomes, which could explain the heterogeneity in oximetry threshold recommendations in international guidelines (table).

Suctioning and saline drops

The use of suctioning or saline nasal drops to clear the nares in infants with bronchiolitis is attractive given that infants are obligatory nasal breathers. Unfortunately, no evidence from randomised controlled trials is available for either treatment, with evidence limited to retrospective and observational studies.[6–11] This low-quality evidence suggests that deep suctioning might be associated with adverse events and increase length of hospital stay.[78] Further evaluation of the benefit of suctioning and nasal saline drops is required. Generally, guidelines only support superficial suctioning (table).

Chest physiotherapy

A variety of chest physiotherapy techniques have been used in the management of infants with bronchiolitis, including vibration and percussion plus postural drainage, forced expiratory techniques (in which the thorax is suddenly compressed), and slow flow techniques (in which the thorax and abdominal cavity are slowly compressed). A Cochrane review of 12 randomised clinical trials

(1249 participants) in children with variable severities of bronchiolitis concluded that none of the several different techniques analysed showed a reduction in the severity of disease.[79] Subsequently, a trial of single-day slow flow technique plus triggered coughing showed an improvement in bronchiolitis severity score.[80] A further small randomised trial (103 participants) compared assisted autogenic drainage (manual pressure on the chest) versus intrapulmonary percussive ventilation (bursts of high-flow gas via a fitted mask) versus control, with all groups receiving upright bouncing, nebulised salbutamol, and nasopharyngeal rinsing. Reduced length of stay was found in both the assisted autogenic drainage and intrapulmonary percussive ventilation groups.[81] To date, the evidence does not support routine use of physiotherapy in patients with bronchiolitis, and consideration of physiotherapy is only reserved for those who have relevant comorbidities with difficulty clearing secretions (eg, spinal muscular atrophy or severe tracheomalacia).

Hydration support

Infants with bronchiolitis can have difficulty feeding due to nasal congestion or hypoxaemia related to lower airway disease. If oral hydration is insufficient, nasogastric hydration is recommended over intravenous hydration. Risks of hyponatraemia have been documented with intravenous hydration, with complications uncommon.[82,83] Isotonic fluid is recommended to prevent hyponatraemia.

A randomised study of nasogastric hydration versus intravenous hydration (759 participants) showed no significant difference in length of hospital stay, adverse events, admission to the intensive care unit, or need for ventilation.[84] Nasogastric hydration was easier to implement and had fewer treatment failures.[84] These data are supported by a pilot randomised controlled trial[85] and a retrospective review of hydration in infants younger than 2 months,[86] neither of which showed any increase in aspiration episodes or adverse events associated with nasogastric hydration. Two observational studies of nasogastric hydration in infants with bronchiolitis on high-flow therapy suggested that feeding-related adverse events are rare, and that enteral hydration is safe while on high-flow therapy.[87,88]

Other therapeutic management

Hypertonic saline

Nebulised hypertonic saline (≥3%) is a potentially attractive therapy in bronchiolitis due to its theoretical ability to hydrate the airway surface, reduce airway oedema, and improve mucus clearance.[89] A 2017 Cochrane systematic review of nebulised hypertonic saline for infants with bronchiolitis found that hospitalised infants had a significantly shorter mean length of stay compared with those receiving nebulised normal saline (17 trials; 1867 participants; mean difference –0·41 days, 95% CI –0·75 to –0·07 days).[90] However, the quality of the evidence was low, with significant heterogeneity between studies. Reanalysis of data, adjusting for heterogeneity, did not support a benefit to hypertonic saline.[91] Two further meta-analyses concluded that hypertonic saline reduces length of hospital stay,[92,93] although the quality of the evidence remains low (including indirect meta-analysis comparisons). The 2017 Cochrane review also suggested reduced risk for hospitalisation when hypertonic saline was used in the emergency department (eight trials; 1723 participants; risk ratio [RR] 0·86, 95% CI 0·76 to 0·98).[91] However, a large randomised controlled trial (777 participants) subsequently failed to find a benefit of hypertonic saline.[94–96] Adverse events (such as worsening cough) reported from hypertonic saline are generally mild and resolve spontaneously.[91,94,97] Large rigorous multicentre trials with standardised designs are required to answer the question of whether hypertonic saline has a place in bronchiolitis management.

Bronchodilators

The use of inhaled bronchodilators in the management of bronchiolitis varies by country and region.[98–100] International guidelines rarely recommend routine use of bronchodilators in managing bronchiolitis (table).[101] Meta-analyses have found no benefit.[102–104] The 2014 Cochrane review of bronchodilators (predominately albuterol and salbutamol) for infants with bronchiolitis found no significant reduction in admission to hospital from the emergency department (ten studies; 710 participants; odds ratio [OR] 0·75, 95% CI 0·46 to 1·21) or inpatient length of stay compared with placebo (11 studies; 349 participants; mean difference 0·06, 95% CI –0·27 to 0·39).[104] These results have been confirmed by network meta-analysis (figure 2).[69] The use of magnesium sulfate as a bronchodilator is also not associated with improvements to inpatient length of stay.[105,106]

Glucocorticoids

Two large trials (600 participants and 800 participants) have examined the benefit of oral corticosteroids for infants with bronchiolitis treated in the emergency department.[107,108] Both showed no statistically significant reduction in admission to hospital with corticosteroids, a finding supported in a subsequent meta-analysis (five studies; 1530 participants [1461 oral treatment; 69 intramuscular]; RR 0·86, 95% CI 0·7–1·06).[20] Only one study (90 participants; six groups) has reported the effect of inhaled corticosteroids on hospitalisation, with no benefit shown.[20] Corticosteroids alone have not been associated with reduced length of stay in inpatients (figure 2).[20,69] Similar to bronchodilators, national and international guidelines do not recommend the use of corticosteroids in managing bronchiolitis (table).

Combination therapy

Bronchodilators and corticosteroids have a synergetic benefit in asthma management, and there is interest in whether this effect holds for bronchiolitis. A multicentre,

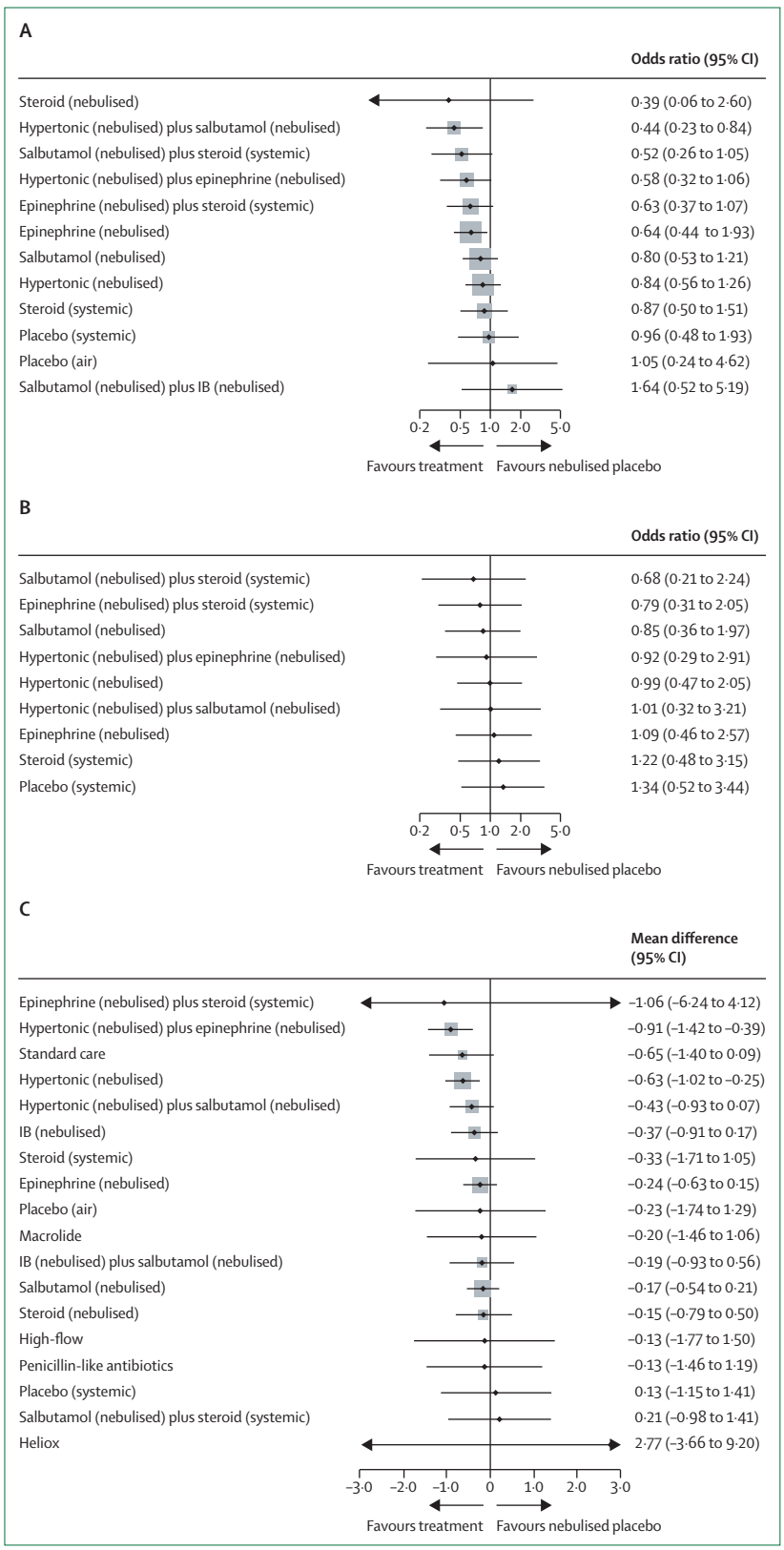

Figure 2: **Network meta-analysis of treatments for bronchiolitis versus placebo in terms of admission rate on day 1 (A), admission rate by day 7 (B), and hospital length of stay in days (C)**
Reproduced from Elliot and colleagues,[92] by permission of the American Academy of Pediatrics. IB=ipratropium bromide.

two-by-two factorial, randomised placebo-controlled trial of infants with bronchiolitis found an unexpected synergistic effect when nebulised epinephrine combined with six oral doses of dexamethasone was used.[108] Results showed a 35% relative reduction in hospitalisation rate (17·1% *vs* 26·4%) and improvement in symptoms (quiet breathing, normal feeding) during the 7 days after enrolment, with most benefit observed in the first 3 days. When adjusted for multiple comparisons, these results were just above the threshold for statistical significance. A phase 3, multicentre, randomised double-blind trial is underway, evaluating whether this particular regimen reduces hospital admissions by day 7.[109]

Network meta-analysis

Unlike their pairwise counterparts, network meta-analyses compare multiple therapies through a network of direct and indirect statistical comparisons. Although indirect comparisons provide conclusions where head-to-head comparisons are not available, they are not randomised and are subject to confounding and bias. Thus, indirect comparisons are of lower quality than pairwise meta-analysis. A 2020 network meta-analysis of common therapies for bronchiolitis included 19 090 participants in 150 studies.[69] The authors found no benefit of epinephrine or salbutamol in reducing either admissions to hospital up to 7 days following a visit to the emergency department or length of stay for hospitalised patients (figure 2).[69] Furthermore, although the combined therapy of nebulised hypertonic saline plus epinephrine reduced hospital length of stay (mean difference –0·91 days, 95% CI –1·42 to –0·39), the strength of evidence was rated as poor, with the suggestion that more rigorous research is required (figure 2). Nebulised hypertonic saline plus salbutamol reduced admission rate at day 1 compared with nebulised placebo (OR 0·44, 95% CI 0·23 to 0·84), but the quality of evidence was considered low. No significant decrease in admission rate on day 7 for any treatment or comparison was seen (figure 2). The authors of this analysis concluded that clinical practice guidelines should recommend supportive measures only.

Antibiotics

Antibiotic use in bronchiolitis remains high (approximately 25%),[110] despite known underlying viral causes, low prevalence of secondary bacterial infections,[111] and use not being recommended across international guidelines. Factors contributing to the high use of antibiotics are the presence of fever, challenges in interpreting chest radiographs, that the infant looks

unwell, and subsequent concern for missing an alternative diagnosis such as pneumonia.[112] Infants undergoing chest radiography are at least 10 times more likely to receive antibiotics (OR 10·9, 95% CI 8·9–13·3).[110] Globally, antimicrobial resistance is increasing, with antibiotic stewardship both in general and in bronchiolitis in particular advocated through many programmes such as Choosing Wisely.[113] Avoiding adverse effects of antibiotics is important for patients and families.

Although bronchiolitis is usually self-limiting, antibiotics have been assessed for persistent respiratory symptoms within 6 months of the acute illness. A meta-analysis of the two randomised controlled trials (240 participants) concluded there is insufficient evidence to recommend antibiotics in this context.[114] Macrolides are attractive for their potential long-term benefit in bronchiolitis, secondary to their anti-inflammatory and immunomodulatory action,[115] and from extrapolation of benefits observed in other respiratory diseases, such as cystic fibrosis.[116] A meta-analysis of four randomised controlled trials (377 participants) found that macrolides are able to reduce interleukin-8 levels, but fail to reduce viral load or provide clinical benefits.[117] Studies are required to definitively answer questions regarding long-term benefits of antibiotics and short-term and long-term benefits of macrolides, particularly for high acute and post-acute bronchiolitis morbidity seen in the indigenous populations of Australia, New Zealand, Canada, and the USA.

Antivirals

Given the burden of disease, antivirals to reduce viral load in bronchiolitis continue to be assessed with early phase work. For example, oral fusion inhibitors specific to RSV (JNJ53718678 and NCT04583280) are undergoing phase 2 evaluation[118] and phase 3 evaluation.[119] To date, no clear clinical benefit of antivirals has been documented. In 2021, the nebulised RSV antiviral ALX-0171 was shown to reduce RSV in nasal mid-turbinate samples without corresponding clinical benefit, suggesting that the dysregulated immune response seen in bronchiolitis occurs earlier in the disease than could be modified by RSV antivirals.[120] Ribavirin is not recommended due to potential teratogenic effects for health-care providers exposed to nebulised forms of the drug and potential haematological toxicity in patients.[121]

Infection control

As viral detection improves, infants with bronchiolitis are more often shown to have multiple viruses at time of hospital presentation. RSV remains the most common virus detected. It is highly transmissible, with a basic reproduction number between 2 and 8.[122] Studies have shown that strict infection control practices, including hand hygiene and use of personal protective equipment (such as gloves, single-use aprons, masks, and goggles), can reduce nosocomial RSV infection rates by around 50%.[123] For nosocomial patient infections, care bundles have proven effective in reducing infection by around 50%. However, it is not currently possible to ascertain which of these measures is most effective in terms of efficacy and value for money.[124] Because many patients are infected with multiple viruses, co-locating inpatients in cohorts based on RSV status might not be beneficial.[124]

Long-term effects

RSV infection is associated with long-term complications, including impaired lung function, recurrent wheezing, and asthma.[125–128] Many children will experience several wheezing episodes during their first year of life, and although more than 50% will outgrow wheezing, a proportion will experience wheezing during later childhood and into adolescence.[129] Although a positive association has been established, it is unclear if infection of the lower respiratory tract by RSV causes long-term wheezing or if individual risk factors predispose infants to both severe bronchiolitis and recurrent wheezing.

A systematic review and meta-analysis of 35 studies appraised the strength of evidence for a causal effect between laboratory-confirmed RSV lower respiratory tract infection before 2 years of age and recurring wheezing illnesses.[130] Results of exposure studies that adjusted for genetic influences showed smaller mean-adjusted OR estimates (OR 2·45, 95% CI 1·23–4·88) compared with studies that did not adjust for genetic influences (4·17, 2·36–7·37). Results were consistent with the hypothesis that a substantial proportion of the association between RSV infection and subsequent wheezing comes from shared genetic predisposition, with insufficient evidence to recommend viral immunoprophylaxis for the prevention of wheezing illness. Long-term follow-up data are needed before presuming that prevention of infection of the lower respiratory tract by RSV could reduce recurrent wheeze or asthma.

A 2019 multicentre prospective cohort study of 716 infants (aged <1 year) across 17 hospitals showed that the risk of developing recurrent wheeze differs between viruses.[131] Infants with rhinovirus C infection, along with IgE sensitisation to food or aeroallergens, were at highest risk. Additionally, these patients had statistically significantly higher risks of recurrent wheeze and asthma by 4 years of age compared with patients infected with only RSV. Although viral testing is not routinely recommended, targeting prevention strategies to this higher risk group of infants could be considered in cases where viral testing has been done.

Prevention

To date, the only licensed preventive strategy for RSV infection is the monoclonal antibody palivizumab.[132–134] Palivizumab is administered as five monthly intramuscular injections to infants in their first year of life who are at high risk of severe RSV disease during peak bronchiolitis season. Palivizumab prophylaxis in ex-preterm infants reduces RSV hospitalisations (RR 0·49,

95% CI 0·37–0·64) and intensive care admission (0·5, 0·3–0·81).[132–135] The American Association of Pediatrics recommends palivizumab prophylaxis during peak bronchiolitis season in infants born before 29 weeks' gestation, in infants born between 29 and 32 weeks' gestation with chronic lung disease, and for consideration in infants with haemodynamically significant heart disease.[7] Palivizumab prophylaxis is expensive, and the cost-effectiveness of this strategy prevents universal use, even in infants who are high-risk.[135]

A newer monoclonal antibody, nirsevimab, has the advantage of being administered once only at the start of peak season for RSV. Nirsevimab was evaluated in ex-preterm infants born between 29 and 35 weeks' gestation and showed reduced hospitalisation rates compared with placebo (0·8% *vs* 4·1%; p<0·001).[136] In healthy term and late-gestation ex-preterm infants, nirsevimab reduces medically attended RSV-associated lower respiratory tract infection (1·2% *vs* 5·0%; p<0·001) and hospitalisation (0·6% *vs* 1·6%; p=0·07), highlighting a potential future therapeutic role.[137]

Over the past decade there have been several vaccine candidates developed to prevent RSV infection. The most promising and advanced candidate is a maternal vaccine comprising RSV fusion protein nanoparticles. In a large phase 3 study (4636 women), although the vaccine did not meet its primary efficacy endpoint of reducing RSV lower respiratory tract infections in infants younger than 90 days, it showed promise with respect to secondary endpoints, including hospitalisation for RSV-associated lower respiratory tract infection.[138] Many other potential paediatric and maternal RSV vaccine candidates are undergoing preclinical and phase 1–3 trials.[139]

Cost-effectiveness and quality improvement

The largest cost burden of bronchiolitis is hospital-associated costs (45–85% of total costs),[140,141] which proportionately increase with severity of illness.[142] In low-income countries, medication costs can be substantial and have been shown to contribute to almost a quarter of total hospitalisation costs.[140] Cost-effectiveness analyses have been conducted for several trials of specific interventions. For hydration, the nasogastric route is associated with a small cost benefit.[141] For oxygen therapy in hypoxic infants, standard oxygen (with escalation to high-flow therapy only following treatment failure) is more cost-effective than initial high-flow therapy.[143] Using pulse oximetry as a major determinant of the need for admission to hospital is a substantial influence on cost, with lower oxygen saturations being both safe and less costly to health-care systems and society.[144] Similarly, intensive care unit admissions are a determinant of health-care cost, and further work is required to better understand the global variation in bronchiolitis intensive care unit admissions.

De-implementation of low-value, unnecessary, or wasteful interventions in bronchiolitis is a major goal.[145] Although de-implementation can be challenging, utilising a targeted approach can lead to improved and more cost-effective management. Haskell and colleagues[112] conducted a qualitative study using the Theoretical Domains Framework that showed that concerns (such as misdiagnosis or parental pressure) cause clinicians to act against their knowledge and beliefs about the ineffectiveness and possible harms of interventions such as chest radiography, antibiotics, bronchodilators, or glucocorticoid use. Subsequently, a cluster randomised controlled trial[146] conducted in 26 hospitals (3727 infants) in Australia and New Zealand that compared targeted interventions (ie, educational and promotional materials, clinical leads, train-the-trainer workshop, stakeholder meetings, and audit and feedback) showed that addressing identified clinician concerns, versus passive dissemination of an evidence-based guideline, improved compliance with evidence-based care (adjusted risk difference 14·1%, 95% CI 6·5–21·7%).[147]

Knowledge gaps and future directions

Despite two decades of messaging suggesting that less treatment is better and promoting supportive rather than interventional therapy, universal de-implementation of interventional care in bronchiolitis has not occurred and remains a major challenge. Numerous systematic reviews and meta-analyses cited show supportive care with hydration and respiratory support are the foundations of bronchiolitis management. Undertaking simple management strategies first, such as nasogastric hydration and standard subnasal oxygen, is the approach best supported by randomised controlled trial data.

The absence of a globally agreed definition of bronchiolitis is problematic. This lack of a clear definition is reflected in the limitations with evidence generated from randomised controlled trials. For example, North American trials have tended to restrict their inclusion criteria to first episodes of bronchiolitis, yet there is a consensus that multiple episodes occur. Other trials have limited enrolment to during RSV season only, even though RSV infection represents only about two-thirds of all bronchiolitis cases. In addition, trials restrict enrolment by age (<6, <12, or <24 months). These problems affect the generalisability of the evidence. Bronchiolitis is the most common reason for infants to be admitted to hospital; clinicians and researchers can and must do better in using evidence to guide the care of infants with bronchiolitis.

The field of paediatric emergency care has become a recognised model of international research collaboration.[148] An ongoing randomised controlled trial of combination therapy of inhaled epinephrine and oral dexamethasone to prevent bronchiolitis admission is occurring in Canada, Australia, and New Zealand,[109] and powered for those with bronchiolitis defined both to include second or subsequent episodes (as in the Australia and New Zealand guidelines) and those fulfilling the more stringent North American inclusion criteria. Utilising the definitions of both jurisdictions will

ensure the generalisability of the results and could be a first step in reaching an international consensus regarding a definition of bronchiolitis. This collaborative approach needs to be extended to future research.

Improving management and treatment of bronchiolitis also requires that the highest possible quality of evidence is generated through studies with rigorous design, low risk of bias, and sufficient power to detect clinically meaningful endpoints.[145] The disease burden of bronchiolitis for patients, their caregivers, and the health-care system is dependent on hospitalisation, length of hospital stay, and intensive care unit admission. All trials should address these endpoints. In addition to the question of effectiveness of combination therapy of epinephrine and dexamethasone in reducing hospital admissions, further research is warranted with respect to the effectiveness of each of nebulised hypertonic saline, high-flow therapy in non-hypoxic infants, oxygen saturation threshold targets, and maternal (or infant) immunisation. Aside from randomised controlled trials examining high-flow therapy, there is a paucity of high-quality trials being undertaken in infants with the most severe disease and admitted into intensive care units. Similarly, there is a scarcity of high-quality trials in low-income settings where disease burden is highest. Finally, further robust work in de-implementation of low-value, non-evidence-based and potentially harmful therapies and investigations, such as salbutamol and chest radiography, and sustainability of de-implementation strategies is crucial if clinicians are to provide all infants with bronchiolitis with evidence-based care.

Contributors

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