Does the use of a vibrating mesh nebuliser through a high flow nasal cannula compared to the jet nebuliser improve nebuliser tolerance among toddlers with respiratory distress?

An integrative review

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Abstract

Aim: To determine if using a high-flow nasal cannula circuit for nebuliser administration improves nebuliser tolerance in infants, which hastens clinical improvement in respiratory distress.

Design: An integrative literature review.

Background: Tolerance during nebuliser administration is poor in the infant population when administered through the traditional device of a jet nebuliser, which is distressing for all participants required when administering the nebuliser correctly. High-flow nasal cannula therapy has recently been introduced for respiratory support in paediatrics. With this, the vibrating mesh nebuliser has been introduced within the high-flow circuit, which remains controversial as minimal research has been conducted.

Method: Four electronic databases were searched, which included reviewing reference lists of studies relevant to the research question. The author approached sales representatives for high-flow nasal circuit equipment, and the Aerogen device was approached about relevant research they conducted.

Results: Four studies were identified that met the requirements of the inclusion criteria, and two were randomised cross-over studies with a low risk of bias. The remaining two were a case study and a retrospective chart review with a high risk of bias. All of the studies described improved nebuliser tolerance in infants to be more with the high flow nasal cannula and vibrating mesh nebuliser group compared to the high flow nasal cannula and jet nebuliser group, with improved distress and increased heart rate confirming bronchodilator effect from the nebuliser treatment. Parents also noted improved nebuliser tolerance and favoured the vibrating mesh nebuliser in the two RCT studies conducted, as they were not required to restrain or distract during the nebuliser therapy, and the infant was calm and relaxed. All four studies lacked evidence of clinical improvement when nebuliser tolerance was present.

Conclusion: Improved nebuliser tolerance displayed by less distraction and agitation as well as an increased heart rate was present when the vibrating mesh nebuliser was delivered within the high flow nasal cannula circuit, whilst there was decreased nebuliser tolerance when using the jet nebuliser, which was displayed by agitation, causing difficulty of assessing physiological parameters

due to distress. More research should be conducted to evaluate nebuliser tolerance when an infant requires nebuliser therapy, such as including the jet nebuliser within the high-flow nasal cannula circuit, like the vibrating mesh nebuliser device. Further research should include older infants and toddlers, as they can be more combative, and more asthmatic patients less than four years of age, to assess tolerance and the physiological response.

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Glossary of Terms

CCU	Critical Care Unit
HFNC	High flow nasal cannula
HFT	High flow therapy
ICU	Intensive Care Unit
RCT	Randomised crossover trial
TA	Thematic analysis
WOB	Work of breathing
VMN	Vibrating Mesh Nebuliser

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CHAPTER 1: INTRODUCTION

Nebuliser therapy is a common treatment for infants with respiratory distress, transforming liquid medication into droplets that suspend in gas (1, 2). Traditionally, medication is aerosolised using a face mask through a jet nebuliser. However, nebuliser therapy has advanced with new types of nebulisers being designed, such as the vibrating mesh nebuliser (VMN) and how you can administer it (1)

High flow therapy (HFT) through nasal cannulas is commenced as a supportive therapy for infants with increased work of breathing due to respiratory distress. Improving work of breathing by flushing of the dead space of the nasopharyngeal cavity, resulting in less overall dead space and more alveolar ventilation as a fraction of minute ventilation (3). HFT delivers humidified high inspired gas flows that exceeds the patient's intrinsic inspiratory flow rate (4-6). Currently, the two nebulisers commonly used through this circuit are the jet nebuliser and the VMN (4).

Numerous studies have been completed, investing in the efficiency of a jet nebuliser compared to a VMN using a high-flow nasal cannula in paediatric patients (4, 7-11). Further research has looked at how breathing patterns can affect aerosol deposition (12), analysing the different patient interfaces (13) or flow rates (14, 15) and narrative reviews looking at all aspects of aerosol therapy via an HFNC circuit (16-18). Still, more research is required to investigate how well the child tolerates the administration of the nebuliser through different devices. Nebuliser therapy was initially designed for adults, so for infants, it becomes a complex procedure due to inadequate administration because of differing anatomy, poorly fitted masks, and the child being frightened or scared and resisting the application of the nebuliser mask (19). When dispensing a nebuliser, jet or vibrating mesh, through the high flow circuit, it would be more practical as there are minimal changes which avoid infant stimulation enabling the infant to receive a more significant amount of medication while also remaining calm and taking even spontaneous breaths (1, 6).

During my nursing profession, I have worked in both rural critical care units (CCU) and large intensive care units (ICU) within New Zealand, Australia and Europe. Despite the different locations, the challenges faced when administering nebuliser therapy to infants admitted due to worsening respiratory systems with increased work of breathing (WOB), remain the same. Supportive therapy like high flow nasal cannulas (HFNC) therapy is commenced as early treatment. Still, when a nebuliser is introduced to improve respiratory effort and reduce WOB, the opposite occurs and worsens the infant's situation. Infants are becoming increasingly stressed, worsening vital signs and making the infant go backward in their treatment due to their distress.

Infants and toddlers cannot comprehend the importance of nebuliser therapy due to their cognitive ability. However, they do know that they do not like the mist that has suddenly appeared in front of their face due to being either cold or noisy with a sudden occurrence. Nebuliser therapy becomes not only a distressing experience for the infant but also for the parent/caregiver, who is present due to the constant negotiation or restraining the infant requires to receive the nebuliser therapy.

In my experience, it is not as traumatic for older paediatric patients. Explanation of the treatment and negotiation of changes in the interface ensured it was more comfortable and pleasant experience. Lastly, older paediatric patients can communicate their concerns and feel and recognise the improvements from the nebuliser therapy treatment.

This review investigates nebuliser tolerance in paediatric patients aged 0-4 years with respiratory distress utilising the VMN device via the HFNC circuit, which could reduce distress and trauma. Improved nebuliser tolerance may decrease distress for all involved while administering nebuliser treatment, including patients, parents/caregivers and health care workers.

- Chapter Two discusses the background information of nebuliser therapy and devices and what will be reviewed within this literature review.

- Chapter Three discusses the processes for obtaining relevant information to the research question.
- Chapter Four analyses the results of the included research studies.
- Chapter Five discusses the results in the context of the relevant research and topics discussed throughout the integrative review.
- Chapter Six discusses conclusions and recommendations for practice and research.

CHAPTER 2: BACKGROUND

Within this chapter, the author will discuss nebuliser therapy and the various components involved, such as what affects nebuliser delivery, the standard nebuliser devices used, challenges when administering nebulisers to infants and toddlers, how the anatomy differs from adults, common respiratory illnesses for infants, high-flow nasal cannulas that provides respiratory and how to administer nebuliser therapy and how it has evolved over time with where it is applied.

2.1 Nebuliser Therapy

Nebuliser therapy is an essential component in the treatment of paediatrics patients with respiratory illness. Transforming liquid medication into an aerosol, suspended within a gas and delivered through an interface to the patient (18, 20-22). Multiple factors affect efficiency of nebuliser therapy, such as nebuliser device, interface selection and deposition (7). Nebulisation only delivers 10-15% of the drug compared to 100% when administered via an oral or intravenous route (12). Nebuliser therapy delivers medication directly to the lungs, increasing therapeutic effects with a smaller drug requirement, faster onset and minimal side effects (10, 12, 23).

Traditional aerosol therapy devices are metered dose inhalers and various nebuliser devices (16). The most common are the jet nebuliser, which uses a gas source, and the VMN, which uses an electrical source (16, 21). For spontaneous breathing patients, the most common interfaces are oral, with the mouthpiece being the most efficient compared to the face mask (13, 22). Patients who require respiratory support can also have either the metered dose inhaler or nebulisers placed within the invasive and non-invasive circuits while providing supportive respiratory treatment (16). Placing a

T-piece, the connector for the nebuliser device, within the circuit either before or after the expiratory port, with the positive pressure from the invasive ventilation aiding the aerosol particles to be directed to the patient (24). Recently, it has become popular to deliver nebuliser therapy via an HFNC. Nebuliser therapy efficiency via non-invasive and invasive circuits depends on the nebuliser device, placement of the device, patient interface and the gas flow within the circuit (16, 25).

An important component for nebuliser therapy when using a mouthpiece or a face mask is having a tight seal between the interface and the patient's face, preventing drug loss whilst improving drug efficiency (7). Face masks are the preferred interface as the patient requires no skill with coordination. However, a tight seal is necessary to maximise the amount of drug delivered whilst preventing drug deposition into the patients face and eyes (7, 13, 22, 26). Therefore, in infants and toddlers who cannot coordinate a tight seal of the nebuliser device for the length of the treatment time, other interfaces should be considered (10, 18, 21, 26, 27). When selecting the patient interface, the health professional should consider the patient's size, age and the ability to adhere to treatment (13).

The advantage of nebuliser therapy is that it can be delivered with no required breathing pattern, making it more comfortable for the patient. The nebulised drug can be delivered directly to the lungs (10, 20), with the ability to mix more than one drug within the device chamber (19). Disadvantages include long treatment time (10, 19), requiring a source of gas or electricity to deliver the drug therapy (10), and an increased loss of the drug during exhalation, whether it is being administered continuously or intermittently (10).

2.1.1 Factors affecting nebuliser therapy

The particle size of the aerosol impacts how it is delivered to the lungs, with 1-5 microns being the optimum size for an increased deposition into the lower respiratory tract (10, 19, 21, 25, 28) in adults. Minimal research has been conducted on optimal delivery for children, so the optimum size is still being determined (18, 19). Particle size greater than 5 microns causes aerosol particles to deposit within the oropharyngeal tract. If the particle size is less than 1 micron, it may remain within the suspension or exhaled (10, 18, 19, 21).

2.2 Jet Nebuliser

The jet nebuliser is a first-generation nebuliser (18) and was created around the 1800s. It is commonly used in hospitals and homes (1) to treat patients with respiratory diseases (22). The jet nebuliser requires compressed gas, air or oxygen (27, 29) to convert the solution into a mist (21). The fast flow rate of the gas draws the medication, a liquid solution or suspension (21, 28), through a tube within the reservoir, which creates multiple particle sizes directed to the baffle. The large particles return to the baffle, which reduces the particle size (1, 22, 29). The small particles exit the nebuliser, where the patient inhales it via a facemask or mouthpiece interface once it has been diluted by air (21, 29).

The aerosol's droplet size depends on multiple factors, such as the nebuliser model, breathing pattern (27), and flow of the compressed gas, which is dependent on the device being used (22). For optimal aerosol particles, gas flow must be at 8L/min. If the flow is decreased to 6L/min, it affects the particles' output by making larger droplets (22), whilst increasing the flow makes the droplets smaller (21). The efficiency of the nebuliser administration and particle size depends on the solutions (28). The jet nebuliser causes the liquid solution to cool during administration and becomes more concentrated due to evaporation loss (28). Further factors affecting drug delivery via the jet nebuliser are patient cooperation, breathing pattern, coughing and the type of mask used.

The advantages of the jet nebuliser are that the device is easy to use and increases patient compliance (22). The disadvantages of the jet nebuliser are prolonged treatment time, residual drug within the reservoir and continuous generation of aerosol.

1. Prolonged treatment time: can vary between 5 to 15 minutes (19, 27) due to re-aerosolisation of the larger particles that are returned to the reservoir. However, once sputtering occurs, the delivery of the drug is no longer productive, and the nebuliser should be stopped (19).
2. Residual drug within the reservoir: 0.8-1.2ml of the residual drug remains within the device post nebulisation therapy (1, 22). If the fill volume within the reservoir is less than 2ml, it does

not function properly. Recommendations of increasing the fill volume to 4-5ml, improve delivery of the drug therapy (22).

3. Continuous generation of aerosol: new models have been created to be breathe-enhanced to reduce loss of drug therapy (22). Traditionally, the nebuliser delivery would run continuously throughout the patient's breathing cycle, resulting in loss of the aerosol on expiration (1, 21, 22).

2.3 Vibrating Mesh Nebuliser

The vibrating mesh nebuliser (VMN) is a new innovative nebuliser (27) that was introduced in the 1980s (30) and requires electricity to function (1, 22, 29). Within the VMN, there is a small mesh plate that rapidly contracts and expands. Generating a mist that is ejected out of the nebuliser device to either a spontaneously breathing patient or to a patient requiring positive pressure ventilation (29). Inside the mesh plate, there are multiple plates drilled with small laser holes that move against the drug solution (18, 19, 22, 27-29). The drug solution is thrust through the plate that forms liquid jets. Once it reaches a certain length, it then transforms into droplets (30). The position of the reservoir, where the drug solution is inserted, is above the mesh plate (28), and the droplet size delivered depends on the size of the holes on the mesh plate (1, 28, 29).

Further advantages of the VMN are short treatment times, no requirement of extra gas flows (11, 22, 27, 28), and smaller residual volumes (1, 22, 27, 28). The VMN provides a higher dose of drug delivered than the jet nebuliser due to smaller residual volumes (22). It is also a portable and silent device when delivering nebuliser therapy that requires power to function (10, 22). The disadvantages of VMN are cost and the possibility of the mesh pores becoming clogged if the drug solution is viscous (10).

2.4 Nebuliser therapy challenges for infants

Historically, the delivery of nebuliser therapy has been problematic for the infant and toddler population (1, 25), with the design of many interfaces being adapted from the adult version or children over six years of age (29). The intolerance of the interfaces causes ineffective administration (11, 25,

31), and an inadequate breathing pattern. Therefore, the nebuliser therapy is administered incorrectly, resulting in the drug not being delivered to the lower airways (19, 23). Lastly, infant and toddlers undergo many changes within the first two years of their life that can affect nebuliser delivery, such as airway size, lung volume, breathing pattern and their respiratory rate (18, 29).

Infants and toddlers are obligatory nose breathers, making the mouthpiece interface an unviable option (16, 32). Due to behavioural and emotional factors, infants and toddlers cannot co-ordinate breathing for some interfaces that require a tight seal and quiet breathing therapy during administration (1, 7, 18, 19). Making the patient interface an essential component for adherence for effective delivery of the nebuliser treatment whilst creating a therapeutic response (1). When a face mask interface is applied for nebuliser therapy, several factors should be taken into consideration, such as the weight of the device, the patients' anatomic contours and seal (1, 18). Mask seal is a vital component to ensure maximum delivery of the nebuliser therapy. However, if there is a leak because the child becomes distressed and begins moving their head from side to side or crying, there is an increased loss of nebuliser dose and decreased lung deposition of the nebulised drug (1, 18, 19, 26, 33). The blow-by delivery method is used to administer the nebuliser mist by wafting it in front of the infant or toddlers face who is upset, crying and un cooperative. This technique is considered ineffective due to the loss of nebuliser dose to the atmosphere (1, 18, 19). When the face mask is 1cm away from the face when delivering the nebuliser via the blow-by method, 50% of the dose administered is lost, and if the mask is 2cm from the face, it increases to 80% (19). Another delivery method is to apply the nebuliser device to the infant or toddler while are asleep, hoping that the nebuliser therapy does not cause them to wake up and become agitated (1, 19). An *in vivo* study found that 70% of infants wake up during this form of administration (32).

The facemask interface is the preferred option, but it requires to be well fitted to the contours of the face to increase the amount inhaled (18, 27). Infant and toddlers who are unwell become irritated easily by the noise and cool mist that the jet nebuliser generates when using this interface (16, 17). Ari and Fink reported that 49% of infants or toddlers become distressed when using the facemask interface (1). In contrast, Janssens and Tiddens say that a third of infants become distressed during

nebuliser administration (32), resulting in a loose seal, causing aerosol to leak significantly and reducing the efficiency of the nebuliser delivery, resulting in an increased amount of nebuliser being deposited to the upper airway and the face and eyes (1, 23, 27, 33). Crying during nebuliser therapy reduces the amount of the drug delivered compared to infants and toddlers who are breathing normally (16, 27). When the infant or toddler is distressed, the breathing pattern changes to prolonged expiration followed by fast and short inspiration, which also causes deposition into the upper airways (7, 18, 23, 26, 27). Parent/caregiver and the health care team are then required to comfort and distract the child (1, 27), leading to the parent/caregiver having a preference in interface due to easy use and more tolerance from the child (18).

The nasal cannula has become an alternative interface to the face mask, with the placement of the nebuliser device within the high-flow circuit (11, 16, 17). Once the nasal cannula has been applied to the infant's face, it reduces the amount of manhandling, no repositioning of the interface is required, and less contact with the infant as you do not need to try and keep the interface in place (11, 16). Using the HFNC circuit on the infant or toddler to receive nebuliser therapy allows hydration therapy as they can tolerate nasogastric or oral feeds (6).

2.5 Respiratory system in infants that differ from adults

An infant's respiratory system goes through constant changes as they grow (27, 34), whilst the adult respiratory system is robust and can manage increased respiratory compromise before respiratory failure develops (34). The neurological respiratory controls in infants are undeveloped and unstable, which leads to hypoventilation and apnoea, making them predisposed to respiratory failure (34). Hypoventilation results from the respiratory muscles not being well developed, causing the infant to fatigue easily, resulting in escalation of care and possibly mechanical ventilation (34).

Anatomically, infants have smaller airways, which causes higher resistance with fewer alveoli available for gas exchange (25, 27, 34). The chest wall is made of cartilage and is exceptionally compliant, causing it to deform easily and reduces recoil, which aids in lung expansion and inflation of

the alveoli (34, 35). As the infant grows, so does the neurological respiratory control: the chest wall becomes less compliant, and airways increase in size as well as the number of alveoli, allowing the respiratory system to cope with an increased amount of stress when applied to the respiratory system (27, 34).

Infants 12 months and under are obligatory nose breathers (16, 29). The nose is known to create the highest resistance to flow, and paediatric nasal resistance exceeds that of an adult (19, 34). Within the nasal cavity are turbinate structures that alter with age. As the infant ages, the cartilage stiffens, and the turbinate structures are less likely to collapse. They play an essential part in warming, humidifying and filtering the air inhaled (1, 25).

The upper airway of the infant also differs to the adult respiratory system. Infants have a large head compared to the size of their body. When lying supine, there is excessive flexion on the neck, which creates airway obstruction (34). The mouth is large and fills the small oral cavity (34). The larynx is located posteriorly and is composed of cartilage that is not yet ossified, causing it to be softer and more pliable, increasing airway obstruction risk (19, 34). The epiglottis is floppy, while there is decreased tone in the pharynx and supraglottic (19). Lung development begins whilst in utero and, for full-term infants, is complete at birth (34). The lower airways are smaller in diameter, resulting in reduced air flow, which makes them prone to obstruction with airway oedema, mucous plugging and inflammation (19, 36). Tidal volume is low, requiring the infant to breathe at a faster and variable rate compared to older paediatrics or adults (1, 19, 27). Infants and children have a higher delivery and deposition of aerosol particles into the upper respiratory tract due to them having smaller airways and being obligatory nose breathers. While in adults, aerosols are deposited higher in the lower respiratory tract (7). Aerosol deposition in infants is affected by the complex structures of the airway (16, 25), with decreased deposition compared to adults due to low tidal volumes and short respiratory cycles (1).

2.6 Respiratory conditions requiring respiratory support

The two most common respiratory conditions that develop respiratory failure are bronchiolitis and asthma, occurring due to the increased demand on the respiratory system. The respiratory system relies on a balance between the muscles that control breathing and the neurological control system. Increased respiratory load places strain on the lungs, thoracic cage, and airways during respiration. The lungs must overcome increased resistance to get enough air into the alveoli. Resulting in respiratory impairment that occurs quickly over hours or days during an acute illness in paediatric patients, especially newborns. The infant can no longer effectively respond to the increased respiratory drive because of the small reserve that becomes quickly depleted (35).

2.6.1 Bronchiolitis

Bronchiolitis is an acute viral infection affecting the lower respiratory tract in infants under two years of age (6, 37-44) who require admission to the hospital within the winter months for supportive treatment (32) (37, 38, 41, 43, 45). It is caused by a viral infection (41), with the respiratory syncytial virus (RSV) being the most common cause (38, 40, 43, 44), affecting 60 – 80% of paediatrics that present to the emergency department (38, 43). Infants have an increased risk of developing bronchiolitis when they are less than two months old, born prematurely or with a congenital heart disease or chronic lung disease (41, 43).

Inflammation and obstruction of the distal bronchioles cause bronchiolitis, reducing airflow in the small airways and creating breathing difficulties (38, 41, 42, 44) such as hyper expansion, lung function changes, increased mucous production, wheezing and atelectasis (38). Symptoms of respiratory distress worsen over the first two days and peak in severity around day 3-5 of illness. Symptoms improve between 7-14 days (38). However, the condition can change quickly due to mucous plugging and the infant being unable to clear their airway of mucous and debris (38).

Diagnosis is determined from the patient's clinical presentation, based on the history of the illness and examination of symptoms. The symptoms typically begin with a runny nose and cough similar to a

common cold (38, 41, 42), followed by further symptom development such as persistent cough, tachypnoea, increased accessory muscle use with scalene and intercostal retractions, grunting, nasal flaring, wheeze on auscultation and a generalised weak condition (38, 39, 42). Infants may also have reduced oxygen levels and difficulty with feeding (39, 42). Hypoxaemia occurs due to airway obstruction and atelectasis (38). There is an increased WOB due to the patient's requirement to exert their muscles to offset the auto-positive end-expiratory pressure (PEEP) and produce inspiratory flow despite the already existing airway resistance (46).

Guidelines recommend supportive care, which involves respiratory support and hydration (6, 37, 39, 42, 44). HFNC therapy is recommended if conventional nasal prong oxygen has failed for infants with hypoxia, oxygen saturations less than 92% (39), with the flow rate of the HFNC set at 2L/kg/min (39). When HFNC therapy is used, it may reduce the need for escalation of care (43, 45) by providing some positive airway pressure, supporting the airways to stay open and improving ventilation (42, 43). Multiple studies have looked into nebulised bronchodilators and ipratropium bromide in infants with bronchiolitis but have shown no improvement on lung function or severity of the condition and may worsen oxygen saturation levels (44, 47). Guidelines do not recommend routine use of bronchodilators in bronchiolitis, confirmed by the Cochrane review of bronchiolitis (38, 43).

2.6.2 Asthma

Asthma is a chronic childhood disease (13, 48) and the leading cause of childhood morbidity (47). Boys have a higher prevalence than girls due to their smaller airways in relation to their larger lungs (48). There are no prevention strategies other than reducing maternal smoking (48).

Asthma is associated with airway inflammation and airway modelling (48-50). Airway damage from chronic airway inflammation includes smooth muscle hypertrophy, epithelial hyperplasia and airway connective tissue deposition, causing bronchoconstriction, collagen deposition, and increased mucus production, which narrow the airways (51). Repeated inflammatory episodes to the lungs, with repair, produce structural changes known as airway remodelling (50). Exacerbations of asthma occur due to airway narrowing from oedema, secretions and smooth muscle constriction of the bronchi (47),

generally require the paediatric patient to present to the emergency department to be treated with steroids and nebulised short acting beta agonists (SABA) such as salbutamol (13, 47).

Risk factors include genetics, respiratory infections early in life and smoke exposure (50-52). Symptoms are non-specific but include wheezing, shortness of breath, chest tightness and cough (48, 49), and expiratory wheeze on auscultation. Treatment aims to reduce symptom burden and decrease the risk of exacerbations (48). Treatment is pharmacological based on review and re-evaluation of symptom control, risk factors, side effects, and patient satisfaction on assessment (48). Standard treatment includes conventional oxygen therapy, bronchodilators and administration of steroids (47, 50). Current pharmacological recommendations for the treatment of mild to moderate exacerbation of asthma that present to the emergency department are three SABA via nebuliser or pressurised metered dose inhalers every 20 minutes over an hour. Severe exacerbation requires three doses of SABA and ipratropium bromide to be administered every 20 minutes or the equivalent dose continuously over one hour (13). HFNC therapy may be beneficial during exacerbations by reducing WOB. The heated and humidified gas reduces bronchoconstriction with dry cold gas (40, 46, 47). Humidification improves cilia movement to remove mucous plugs (40, 47). Showing improvement in heart rate, respiratory rate, fraction oxygen requirement and carbon dioxide level within 24 hours of treatment and avoiding escalation in severe cases (47).

Asthmatic children are associated with a greater risk of poor health, decreased daily activity, lower fitness levels, decreased social activities, and poor performance in school in math and reading. Those with severe asthma and poor asthma control have increased school absences (48, 49). Within New Zealand, the financial burden due to asthma was approximately $799 million in 2011. The healthcare system’s costs were due to hospitalisation, prescription and GP visits. The patient’s family also have a financial burden due to hospitalisation with transport, time off work, childcare, and food, as well as stress, anxiety and lack of sleep (47).

2.7 High-Flow Nasal Cannula Therapy

HFNC therapy was introduced in the early 2000s (6, 35, 40, 53) for patients with acute respiratory failure (10). HFNC therapy is defined as therapy that uses heated, humidified and blended gases, air and oxygen delivered by nasal cannula with a flow rate up to 60L/min (38, 40, 46, 53, 54). Improving patient comfort and sputum clearance (3, 35, 54) while allowing higher flow rates not typically tolerated in the conventional nasal cannula system (35). The increased flow rates exceed the patient's own intrinsic flow rate (10, 37, 53-55), which may vary with the patient's age and weight, 2-60L/min (40, 46). The high flow creates positive expiratory pressure, decreasing physiological dead space, lowering upper airway resistance from nasopharyngeal distension and improving WOB and expiratory efforts (3, 10, 38, 39, 46, 54, 56, 57). The heated and humidified gas improves lung compliance and reduces metabolic demand (35, 58).

The nasal cannula comprises of a soft silicone that fits within the nares (40) and is secured via straps or fasteners. For the infant population, the straps also include a cap or cradle (35). Cannula size is chosen depending on the patient's age and weight and does not exceed 50% of the nares, as this causes increased airway pressure (4, 40, 46). When the nasal cannula is applied to the infant's face, it should be applied with even pressure to prevent leaks but not too much force to prevent pressure sores from developing (35). Flow rate delivered via nasal cannula interface should not exceed 2-3L/kg/min. The nasal cannulas allow the infant or toddler to interact with their parent/caregiver and continue with oral feeding (35).

HFNC therapy reduces the likelihood of patients requiring intubation or escalation of care (37); however, close observation is necessary to detect this (38, 46). HFNC therapy is increasingly being used for the treatment of respiratory support in patients within the ICU who have or have had hypoxic respiratory failure (46, 59). HFNC therapy is contraindicated in patients with upper airway abnormalities that will make the treatment ineffective, life-threatening hypoxia, haemodynamic instability, pneumothorax and trauma to either facial bones or the base of the skull (3).

There are several advantages when implementing HFNC therapy: patient comfort, ease of use (37, 40, 59), decreased mouth dryness (54) with improvement in respiratory effort occurring within 60 minutes of treatment (3, 6, 35, 37) displayed by changes in respiratory rate, oxygen saturation (57). HFNC therapy decreases WOB with decreased airway resistance and improved oxygenation, decreasing the need for invasive ventilation (10, 39). Some patients struggle with the HFNC circuit due to the humidification, confusion and discomfort if the patient also has a nasogastric tube (54). Adverse outcomes include stomach distension, nasal pressure sores and epistaxis (37). Disadvantages include delayed intubation and increased mortality rate (10). If the patient is fitted with a cannula that is too large for the size of the nares, it may cause barotrauma (3).

2.7.1 Nebuliser therapy via high-flow nasal cannula

Aerosol therapy can be included in the HFNC circuit, and gas within the circuit becomes the carrier for aerosol therapy (16, 17). The nebuliser device should be implemented into the circuit to prevent disrupted treatment (16). Discontinuation of therapy increases the patients' respiratory efforts when in acute respiratory distress and should be continued when the jet nebuliser is administered via mask or mouthpiece (17). Aerosol is lost using the HFNC circuit due to the loss of the aerosol particles within the circuit and to the atmosphere from the high flow rate being delivered (9, 10). It can also increase deposition to the upper airway for the same reason (10, 39). Removing the HFNC interface to administer aerosol therapy can disrupt the delivery of oxygen and positive airway pressure (16).

Nasal delivery of nebuliser therapy for infants and toddlers is more effective than oral delivery, possibly because they are obligatory nose breathers (26). Humidification affects the delivery of nebulised drugs by altering the particle size, which results in it becoming deposited within the humidified circuit (5). Placement of the nebuliser device within the HFNC circuit is preferred, filtering large particle sizes within the humidifier, with the remaining particles being smaller and travelling to the cannula, reducing nasal and oropharyngeal deposition and increasing alveolar deposition (10).

When implementing the jet nebuliser into the HFNC circuit, it is crucial to review the gas flow rate to ensure it is greater than 6L/min for the nebuliser device to operate, altering the oxygen delivery, total flow and pressure that is generated by some HFNC devices (17). In comparison, when implementing the VMN, it is placed upstream or downstream of the humidification circuit. Only 10% of the drug is delivered to the lungs, less than conventional nebuliser delivery methods but an adequate amount to produce clinical effects (40), whilst research conducted by Reminivac et al. in 2016 found that the VMN is best placed before the humidifier to improve drug delivery (7). Research conducted by Perry et al. in 2013 suggested a reduced clinical response due to the particle size, cannula size and the accumulation and condensation at the nares causing skin irritation (26).

2.8 Migration of high flow nasal circuit from intensive care unit to paediatric wards

HFNC therapy was first introduced as a form of respiratory support for paediatric patients within the ICU department (38, 39). Still, over the last ten years, it has migrated to being used within the emergency department and paediatric wards (35, 39). Increasing the previous option of vital signs, observation, supportive care and improving the fraction of oxygen concentration (35). Patients have been found to have significant improvements in heart rate, respiratory rate and oxygen saturation when HFNC therapy was commenced within the ward setting (54). However, the ward staff are required to be aware of the patient's potential to deteriorate into severe respiratory failure by knowing how to recognise early signs of deterioration whilst using appropriate monitoring to detect it (37, 54, 55, 57), avoiding poorer outcomes that may have resulted if escalation of treatment was delayed (37, 54, 55, 57).

Recent research has shown that HFNC therapy is easy to use with minimal complications and is known to have positive outcomes in paediatrics admitted with respiratory distress. Zemach et al. undertook prospective observational research outside of the ICU to evaluate dyspnoea in paediatrics with hypoxic respiratory failure before and after HFNC therapy was used. It showed that within the first 30 minutes of treatment, 81% of patients experienced less dyspnoea and improved physiological response (57).

2.9 Aim

The main objective is to improve nebuliser delivery to infants aged 0-4 years by reviewing the literature on two different nebuliser delivery techniques, such as jet and vibrating mesh, in conjunction with the HFNC circuit. Evaluating both approaches on how well they are tolerated in the infant population with respiratory symptoms.

3.0 Summary

Nebuliser therapy is a common treatment for infants and toddlers admitted with respiratory illnesses that present with moderate to severe WOB. The jet nebuliser was traditionally used to administer drugs directly to the lungs. However, many challenges are faced due to the device delivering a noisy cold mist and having a long treatment time. In recent years, the HFNC circuit has evolved to enable nebuliser therapy.

This integrative review examined if the VMN via the HFNC circuit improves nebuliser tolerance with an improved clinical response.

CHAPTER 3: METHOD

A systematic review was initially intended as per the study protocol in Appendix 1., but due to a lack of randomised control studies for the research question, the review approach was expanded to an integrative review. Much of the research on nebulisation administration in paediatric patients investigates the different interfaces and how well medication deposits within the lungs. A small amount of research involves comparing techniques that improve nebuliser tolerance for the paediatric population when in respiratory distress. Therefore, it was decided that the integrative method would be more appropriate for the purpose of this literature review. Integrative reviews experimental and non-experimental research to ensure that the research question is comprehensively analysed (60). Dhollande et al. (61) and Whittlemore & Knafl (62) outline the systematic approach of an integrative review to include formulation of the purpose of the literature review, research question, study search and selection, quality assessment, analysis and synthesis, discussion, and conclusion.

3.1 Search strategy

The six steps outlined by Dhollande et al.(61) and Whittlemore & Knafl (62) served as a guide for conducting the systematic search. The PICO template was used to create the research question, assisting in the four components of the template to be included (61), as indicated in Table 1.

Table 1. PICO Research Question

Population	Intervention	Comparison	Outcome
Infants aged 0-4 years Respiratory distress	Vibrating mesh nebuliser via high flow nasal cannula	Jet nebuliser	Nebuliser tolerance measured by Improved clinical outcome

A systematic search was completed through four electronic databases: CINAHL plus, Cochrane, Embase and Medline. Within the search criteria, no limitations were made to date to ensure that all relevant studies that were related to the study were found. In vitro studies and animal studies and

studies that were not published in English were excluded. The search strategy was determined by identifying synonyms for each of the search terms within the research question (61). The search terms are described in Table 2 and include all components of the research question. Boolean operators were combined with the search terms, using OR between keywords as well as AND between search terms (61, 62). MESH headings and truncation were used to expand search terms (61, 62). A further systematic search was conducted six weeks later, with increased search terms for high-flow nasal cannula components. Sales representatives for both Airvo (high flow nasal circuit) and Aerogen (nebuliser circuit for vibrating mesh nebuliser) were contacted regarding their internal research.

Table 2. Keyword Research Terms

Population	Intervention	Comparison	Outcome	Outcome	Outcome
Infant, 0-4, toddler, child, p$diatric, kid, small child	Nebuli$er, aerosol, nebuli$er therapy, jet, vibrating mesh nebuliser, VMN	High Flow nasal cannula, HFNC, high flow, high flow nasal prong, nasal cannula, optiflow, airvo, proflow, humidified oxygen, humidified high flow, trans nasal, high flow oxygen	Toleran*, accep*, endur*, permit, allow	Clinical outcome, improv*, better, progress, increase*, recover*, outcome, result	Respiratory failure, respiratory distress, work of breathing, WOB, accessory muscles

3.2 Inclusion and exclusion criteria

Before searching the literature, an inclusion criterion was created (61, 62). Studies would assess nebuliser tolerance in paediatrics via an HFNC circuit.

- Type of participants:

  0-4 years of age

- Type of studies:

  All forms of research - experimental and Non-experimental

- Type of interventions:

  Jet Nebuliser

  Vibrating mesh nebuliser in conjunction with high-flow nasal cannula circuit

- Type of outcomes:

  Improved tolerance to nebuliser treatment – no signs of distress or agitation, characterised by not trying to remove the nebuliser device or requiring the parent to restrain the infant.

  Improved clinical outcome – improved vital signs such as decreased heart and respiratory rate, decreased WOB and wheeze.

- Exclusion: in vitro and animal studies

3.3 Data extraction

Data was extracted from the included research studies and inserted into a matrix table. The matrix table included details, such as; author, publication date, title and type of research, where the research was conducted, intervention and comparison as well as the key findings (60, 61).

3.4 Quality Assessment

Quality assessment is completed to summarise the validity of the studies by assessing the risk of bias in each of the included studies. This review will use the Cochrane Risk of Bias 2 (RoB 2) to analyse the included studies and assess the risk of bias (63-65). The Cochrane RoB assessment tool was initially created in 2005 and was modified in 2014. The RoB 2 was made and is broken down into domains, focusing on different aspects of the research undertaken where bias can occur (63, 64, 66, 67). Five domains assessed for bias are the randomisation process, deviation from the intended intervention, missing outcome data, measurement of the outcome and selection of the reported result (63, 64, 66). The tool requires the reviewer to assess each of the five domains for bias by creating a

judgement of low, unclear or high risk on the information provided within the studies (64, 65, 68). Due to half of the studies obtained being randomised crossover studies, the RoB 2 was used as there was a cross over trials version that could be used to systematically evaluate how the research was obtained from the reported search.

3.5 Data analysis

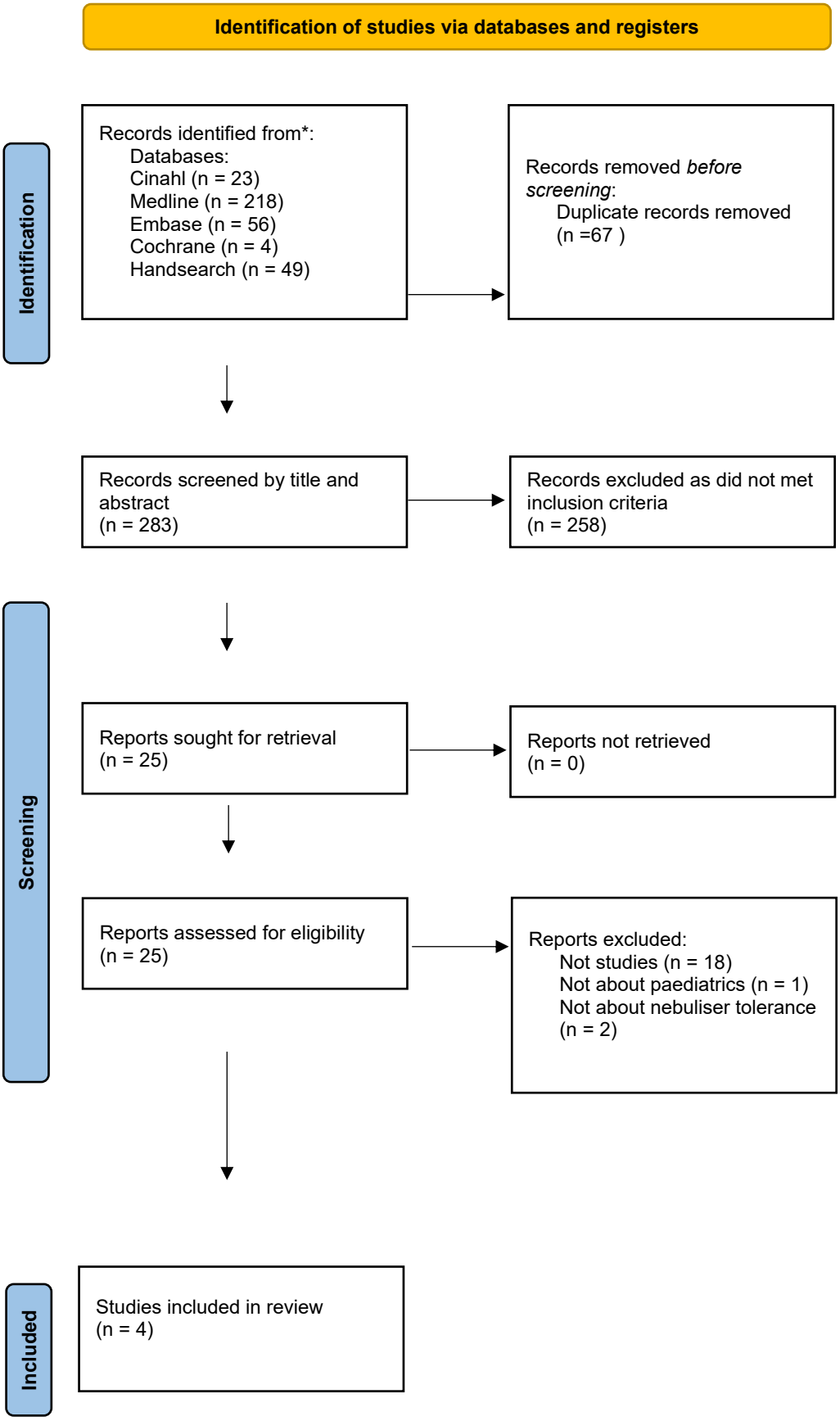
Thematic analysis (TA) is a method that is useful for comparing and contrasting the views of various research participants, highlighting similarities and differences, and producing unexpected findings from the data analysed (69). TA involves a six-step process that facilitates a structure: finding code material, identifying themes, constructing networks, describing and exploring, summarising the thematic network and finally interpreting the patterns (70). TA was used to analyse the data due to its design of finding themes that are significant and relevant to the research question, with the themes being within 50% of the data to be analysed (61, 70, 71).

Chapter 4: Results

4.1 Search results

From the search strategy three hundred and fifty results were retrieved. Reduced to 283 results after duplicates were removed (Figure 1). Once the title and abstract were reviewed, 258 were removed for not meeting the inclusion criteria. The remaining 25 were reviewed by full text. Eighteen did not describe any form of experimental of non-experimental study. One did not include the paediatric population but did discuss nebuliser tolerance and two did not discuss nebuliser tolerance. Four articles remained that were relevant to the research question for analysis.

Figure 1: PRISMA flow diagram



4.2 Study description

Two studies were conducted within the USA. One was from a Paediatric ED in Chicago, and the other was from a paediatric ICU, published in 2015 and 2020. The remaining two studies were conducted in Spain. Both were completed within the paediatric ICU and were published in 2018 and 2022. Morgan et al. (72) reported a case series of 5 infants with bronchiolitis. Al-Subu et al. (73) performed a retrospective chart review of 28 paediatric patients with bronchiolitis and asthma. Valencia–Ramos et al. (74) conducted a randomised cross-over study of 6 infants with bronchiolitis. Valencia–Ramos et al. (75) conducted a further randomised cross-over study that included 33 infants with bronchiolitis. (Table 3).

Table 3: Overview of Literature

Author	Type of Study	Purpose of Study	Sample size and setting	Results
Al-Subu et al., 2020 (73)	Retrospective chart review	Evaluate nebulisers through HFNC at lower gas flows, and if it increases comfort, and reduces respiratory therapist compared to traditional interfaces	28 paediatric patients, Paediatric ICU, Wisconsin, USA	28 children received nebuliser therapy. 60.7% male, median age 32.4 months and median weight 13.5kg. Asthma most prevalent followed by bronchiolitis. Median time in paediatric ICU 31.8 hours, and paediatrics received 4.2 nebulisers per 24 hours. 57% paediatrics did not receive a nebuliser through the HFNC, and remainder received at least one aerosol therapy through HFNC. 2 subjects (7.1%) did not cope with reduction of flow through the HFNC. Higher level of comfort with VMN (87.9%) compared to jet nebuliser (82.9%)
Morgan et al., 2015 (72)	Case Study	Review of aerosol therapy via HFNC in bronchiolitis	5 paediatric patients, Paediatric ED, Chicago, USA	5 infants, 2 males; 3 and 14 months, 3 females; 2-21 months admitted to ED with mod-severe respiratory distress with either RSV or rhinovirus. During VMN administration patients were calm, could sleep through their treatments. Increased heart rate with HFNC and VMN. Comfort and anxiety levels improved for both child and infant during VMN and HFNC.
Valencia-Ramos et al., 2018 (74)	Randomised cross-over study	Evaluate comfort of aerosol delivery that is incorporated into a HFNC circuit compared to jet nebulizer via a face mask	6 paediatric patients, Paediatric ICU, Spain	6 children with moderate bronchiolitis received 113 nebulisations. Median age 1.5 months, median weight 4.35kg. COMFORT-B and visual analog comfort scale used by healthcare workers showed no difference before or after nebulisation for either method, increased comfort during VMN administration. Parents preferred VMN administration over jet nebuliser administration
Valencia-Ramos et al., 2022 (75)	Randomised cross-over study	Assess the hypothesis that comfort is better achieved with a nebuliser incorporated into a HFNC compared to a jet nebuliser	33 paediatric patients, Paediatric ICU, Spain	233 nebulisations administered to 33 patients with acute bronchiolitis. 25 (67%) first episode of bronchiolitis. RSV in 27 children. 109 delivered via JN and 124 via NHF. Greater discomfort with JN. Both health team and caregivers recorded greater discomfort with JN used. HR increased significantly during both systems, however greater with JN during administration. Need to be restrained by parents rose by 48% when receiving JN but remained the same with NHF.

Morgan et al. (72) required moderate to severe work of breathing to be included in the case study, whilst Valencia-Ramos et al. (74) required infants less than 24 months of age. Al-Subu et al. (73) excluded intubated patients during their admission to the paediatric ICU. Valencia-Ramos et al. (75) included infants who had been admitted with bronchiolitis within 24 hours and who required respiratory support in the form of HFNC. Exclusion criteria included no parental consent or patients who had contraindications to the use of HFNC, such as upper airway abnormalities, a trauma that affects the structure of the facial bones or skull, and life-threatening hypoxia. Morgan et al. (72) and Valencia-Ramos et al. (74) did not discuss any exclusion criteria.

All four studies had small study sizes, with a varied number of nebuliser treatments depending on the study. Morgan et al. (72) had 5 participants and did not discuss the number of assessed nebuliser treatments. Al-Subu et al. and Valencia-Ramos et al. had an increased treatment size number, and Al-Subu had a larger sample size of participants: 28 participants for 205 nebuliser treatments (73), 6 participants for 113 number of treatments (74). Valenica-Ramos (75) had the most significant study size, with 33 participants and 233 nebuliser treatments. All participants were assessed before and after nebuliser administration (72-75). Al-Subu was the only study not assessing the participant during the nebuliser administration (73). Al-Subu et al. (73) had an average age of 32 months, while the remaining three studies were less than six months of age. All four studies compared jet nebulisers to VMN within the HFNC circuit. Each study described how each of the nebuliser devices were applied for nebulisation delivery.

The randomised cross-over studies completed by Valencia-Ramos et al. (74, 75) had random treatment sequences. They were computer-generated to commence with either the jet nebuliser or the VMN, with it alternating for further drug delivery via the nebuliser system. The remaining studies had no form of randomisation. Valenica-Ramos et al. (74) nebuliser drug and number of treatments were dependent on the participant's clinical presentation and medical criteria. Salbutamol, 3% hypertonic solution or epinephrine were the drugs used. No washout was used to prevent the carry-over effect. Valencia-Ramos et al. (75) nebuliser drug depended on the medical team's decision. Salbutamol, 3% hypertonic solution or epinephrine were the drugs used. There was no discussion of washout being

used to prevent carry-over effects. Al-Subu et al. (73) did not discuss what nebuliser device was used first, while Morgan et al. (72) described two consecutive doses of albuterol delivered via the jet nebuliser device before considering using the VMN device as they were concerned that the participants were having persistent airflow obstruction with an increased concern for fatigue and respiratory failure. .

4.3 Risk of bias assessment of included studies

Analysis from the RoB 2 tool shows that two of the studies show a high risk of bias, whilst another shows some concern due to the randomisation process and measurement of outcome. Valencia-Ramos et al. (75), a randomised crossover trial (RCT), showed the lowest overall risk of bias in all five domains, deeming it the highest quality according to the algorithm and the review author (63, 64). Valencia-Ramos et al. (74), an RCT, showed low to some concern in all domains, with an overall risk of some concern. Both Morgan et al.(72) and Al-Subu et al.(73) are a case study and a retrospective chart review which showed the highest risk of bias overall. The RoB2 tool analyses five domains of bias that can affect the intended results, they are: the randomisation process, deviations from intended interventions, missing data outcome, measurement of outcome and selection of the reported result (64, 66). The risk of analysis for the included studies is summarised in Table 4, with more detail in Appendix D.

4.3.1 Randomisation process

Valencia-Ramos et al. (75) showed low concern as all participants were randomly sequenced via computer-generated numbers to begin nebulisation with either jet or VMN. They then alternated with subsequent nebulisation. The outcome assessors and data analysis were blinded to the allocation, not the participants or health staff, as they would visually be able to see what device was being used. Valencia-Ramos et al. (74) showed some concern about the randomisation process. The intervention was randomised, but there was no discussion in the study if there was any difference in baseline or if the participant, family members, health care workers or assessors were aware of the intervention that the participant was randomised to. However, there was a difference in set-up with the jet nebuliser being applied over the HFNC circuit and the VMN being inserted into the circuit of the HFNC. Morgan

et al. (72) were considered high risk, and Al-Subu et al. (73) were considered some concern due to both studies not being randomised. Subjects were chosen due to their admitting diagnosis to the emergency department.

4.3.2 Deviation from intended interventions

Both RCTs showed low risk of bias as they did not deviate in their intended outcomes (74, 75). Morgan et al. (72) showed some concern of risk in intended interventions as there was no discussion of assigned intervention to the participants, carers or people delivering the intervention. Al-Subu et al. (73) showed a high risk of bias as two participants (7.1%) were unable to tolerate the lowered flow rate of the high-flow nasal circuit, which was required in this study when a nebuliser was being administered via HFNC, so the two participants continued with jet nebuliser over the HFNC.

4.3.3 Missing data outcome

Both RCTs completed by Valencia-Ramos (74, 75) showed a low risk of bias due to randomised interventions and no alterations being conducted or any data missing. Al-Subu et al. (73) showed a high risk of bias as for HFNC to be assessed, the flow rate was weaned before nebulisation and, if not tolerated, was switched to jet nebulisation. Morgan et al. (72) showed a high risk of bias due to the nature of the study design being a case study and information being obtained after the event. Despite this, there was no discussion of any participants being withdrawn or interventions being changed.

4.3.4 Measurement of outcome

The RCTs completed by Valencia-Ramos (74, 75) showed a low risk of bias. The 2018 RCT assessed the participants with two types of tools for comfort for both interventions, and the assessors were given education on how to complete these a month before the study was conducted. The 2022 RCT assessed participants with two types of tools for comfort for both interventions by both health workers and parents/caregivers, and the outcome assessors and data analysts were blinded to group allocations. Al-Subu et al. (73) showed some concern risk of bias as there was no randomisation. However, this study did include nebuliser tolerance as a measurement of outcome. Morgan et al. (72)

showed a high risk of bias as the measurement of outcome was conducted after the intervention had occurred.

4.3.5 Selection of the reported result

All four studies showed a low risk of bias due to the pre-determined assessment tools before the study was conducted. COMFORT-B scale and visual analog were used for the 2018 RCT (74), while the COMFORT-B scale and numerical rating comfort scale were used for the 2022 RCT (75). Al-Subu et al. (73) assessed the child's comfort and physiological response. The case study conducted by Morgan et al. (72) assessed for improved clinical response, which showed nebuliser tolerance subsequently.

Table 3: The revised Cochrane risk of bias for randomised trials analysis

YEAR	TITLE	AUTHOR	TYPE OF STUDY	RANDOMISATION BIAS	DEVIATION FROM INTENDED	MISSING OUTCOME	MEASUREMENT OF THE OUTCOME	SELECTION OF THE REPORTED RESULT	OVERALL BIAS	COMMENTS
2015	High-Flow Nasal Cannula and Aerosolized B agonists for rescue therapy in children with bronchiolitis: A case study	Morgan et al.	Case study	High	Some Concern	High	High	Low	High	Overall high risk of bias due to the nature of the study being a case study.
2018	Incorporating a Nebulizer System into High-Flow Nasal Cannula Improves Comfort in Infants with Bronchiolitis	Valencia-ramos et al.	Prospective, Randomised cross-over study	Some Concern	Low	Low	Low	Low	Some Concern	Increase risk of bias due to concerns regarding randomisation process and how the outcome measurement was conducted
2020	Feasibility of Aerosol Bronchodilators Delivery through High-Flow Nasal Cannula in Paediatric Subjects with Respiratory Distress	Al-Subu et al.	Retrospective chart review	Some concern	High	High	Some concern	Low	High	Overall high risk of bias due to the retrospective aspect of this study
2022	Impact of different nebulisation systems on patient comfort in bronchiolitis: a randomised controlled cross-over study	Valencia-Ramos et al.	Randomised cross-over study	Low	Low	Low	Low	Low	Low	Overall low risk due to randomisation and assessment post each nebulisation according to the measurement outcomes

4.4 Study findings and common themes

Each study was read thoroughly to find common codes that appeared. From here, they were created into themes (61, 71) that examined how nebuliser therapy was administered in conjunction with the HFNC therapy with sub-themes of jet nebuliser and VMN, tolerance during nebuliser administration with a sub-theme of comfort analysis, the involvement of the caregivers, and clinical response.

4.4.1 Placement of nebuliser device within the HFNC circuit

All described the jet nebuliser being applied over the HFNC. Valencia-Ramos et al. (75) described the jet nebuliser over the HFNC and no modification of the flow rate of the HFNC therapy, with the flow rate for the jet nebuliser being at 8L/min. Valencia-Ramos (74) described reducing the flow so that the total flow included the flow required to create the nebuliser to mist, and Al-Subu et al. (73) decreased the flow rate of the HFNC down to 2-L/min before the nebuliser administration. Morgan et al. (72) did not discuss any alternation to the flow rate but set the gas flow rate 3.5 times higher than the expired minute volume or 5-8L/min as per the manufacturer's instruction.

The VMN device was connected to the dry side of the humidifier within the HFNC circuit in all of the studies. Still, Morgan et al. (72) also allowed it to be on either the dry or wet side of the humidifier within the HFNC circuit.

4.4.2 Tolerance during nebuliser administration

All four studies compared infants and toddler's tolerance to a nebuliser administered by either a jet nebuliser or a vibrating mesh nebuliser. All stated how they were to assess nebuliser tolerance.

Valencia-Ramos et al. (75) assessed comfort and satisfaction five minutes before, during and five minutes after nebuliser therapy by completing the COMFORT-B score and a numerical rating scale by healthcare workers and parents/caregivers. The jet nebuliser was found to show more significant

discomfort during nebulisation than when using VMN (P<0.025). Parents/caregivers rated more significant discomfort when using the jet nebuliser (p=0.46). Valencia-Ramos et al. (74) showed no improvement in tolerance using the COMFORT-B score and visual analog comfort scale before or after either nebuliser delivery method. However, during nebulisation, there was improved tolerance when using the VMN (COMFORT-B score P=0.006, visual analog P=0.2). The comfort scales the parents/caregivers assessed showed that 26 out of 113 treatments showed higher comfort and satisfaction during VMN compared to jet nebulisation.

Al-Subu et al. (73) described comfort as infants who remained calm before and during treatment or were unsettled before the nebulisation commenced and then calmed down during nebuliser administration. Comfort assessment assessed behaviour: calm, not crying, no facial tension or aggressive physical movement. The heart rate is used as an indirect assessment of the effect of the bronchodilator. Al-Subu et al. found infants to have 87.9% improved tolerance when using the VMN via the HFNC compared to 82.9% when using the jet nebuliser (73).

Morgan et al. (72) described tolerance as the infant not being agitated, combative or requiring the parent to restrain the patient while administrating the nebuliser. Described comfort and anxiety levels better during the VMN nebuliser via the HFNC, with an increased heart rate to confirm that the bronchodilator was effective. The infant was calm and able to sleep during the nebuliser treatment, whilst during the jet nebuliser was agitated, and the parents were required to hold the mask on the infant's face. The infant's severity asthma scores increased from moderate to severe during nebuliser therapy via the jet nebuliser.

4.4.3 Involvement of the parent/caregiver

Valencia-Ramos et al. (74, 75) described parent/caregiver as involved in assessing comfort for both nebuliser devices, using two evaluation forms. Valencia-Ramos et al. (75) found that 48% of infants were required to be held by the parent/caregiver during VMN compared to jet nebuliser therapy (p<0.05). Valencia-Ramos et al. (74) also discussed the parent/caregiver required to restrain the

infant during jet nebulisation treatment. Morgan et al. (72) describe the parent/caregiver involvement as needing to comfort the infant by holding them and assisting in keeping the mask on their face. Al-Subu et al. (73) study involved no discussion of involvement from the parent/caregiver.

4.4.4 Clinical response

Valencia-Ramos et al. (75) study showed that there was an increased heart rate during both methods of nebulisation, with a higher heart rate when the jet nebuliser compared to the VMN ($P<0.001$), there was no significant change in respiratory rate for either method pre, during or after nebulisation. Valencia-Ramos et al. (74) showed an increased heart rate during nebulisation compared to before nebulisation in both groups ($P<.001$, $P<.001$), with no changes in oxygen saturation, breathing frequency or fraction of oxygen required.

Al-Subu et al. (73) study looked at clinical assessment of heart rate, respiratory rate, oxygen requirement and oxygen saturation completed before and after each administration. There was an increase in heart rate, 9.98 beats/min when using both the VMN and 0.64 beats/min when using the jet nebuliser. There was no significant increase in respiratory rate after nebuliser treatment during jet nebuliser delivery ($P=.26$). Morgan et al. (72) study had an increased heart rate when using the VMN. However, there were no changes in respiratory rate or oxygen saturation.

CHAPTER 5: DISCUSSION

5.1 Key messages

The review conducted, investigated if tolerance to nebuliser therapy is higher when using a HFNC circuit, found that only a small amount of evidence is looks at the tolerance of nebuliser treatments for infants and toddlers. Evidence that was found showed that all four studies imply that nebuliser therapy using the VMN via the HFNC is more tolerable to infants than the traditional face mask via a jet nebuliser. This was confirmed by the infant not being agitated, crying or requiring restraint from parents/caregivers to receive treatment. Completing this review shows that this is the first to examine this topic.

5.2 Shortcomings and considerations

When nebuliser therapy was first introduced in conjunction with the HFNC, administration was possible through either removing the HFNC and administering the nebuliser via the traditional face mask or keeping the HFNC in place and wafting the mist close to the nares or applying the facemask over the HFNC (7). Studies have shown that, unfortunately, the jet nebuliser mask causes distress to 49% of infants when receiving a nebuliser via the facemask, resulting in a loss of seal (1, 32). In 2005, Piccuto and Hess's investigation showed that a T-piece in a spontaneous breathing adult was the most efficient interface requiring respiratory support (28). The jet nebuliser device can be inserted within an invasive circuit with a T-piece, allowing the aerosol particles to move upwards and for condensed particles to return to the reservoir to be nebulised again (10). Despite this, not all models of the HFNC devices, such as the Airvo 2, can integrate the jet nebuliser as it alters the gas flow rate with dilution of the oxygen concentration. In these machines, it is recommended for you to either remove the HFNC or apply the facemask over the HFNC (8).

Applying a nebuliser over the HFNC is ineffective as it reduces the aerosol particles when administered (15, 18). However, removing the HFNC circuit to administer a nebuliser can be detrimental to the patient as it interrupts respiratory support, disrupting lung recruitment which is being provided, which can compromise the patient (8, 15, 18). A study completed by Murphy et al. (15)

described varied results in administering a nebuliser while the patient received HFNC therapy, depending on the clinician. 33% interrupted the HFNC therapy to administer the nebuliser, 40% administered the nebuliser by applying the nebuliser mask over the HFNC, and 24% placed the nebuliser device within the HFT circuit.

In vitro studies disclosed that the VMN device placed at the inlet of the humidifier increases aerosol deposition within the lower respiratory tract compared to when placed close to the patient. However, in the infant population, there is an increase in deposition when there is extremely low flow, <0.25/kg/min, when placed close to the patient (17). It has been shown that there is a loss of aerosol particles within the tubing of the HFNC circuit, which reduces the aerosol particle size to 1.6-2.4 microns due to the gas flow and humidity (25).

The majority of the studies looked at participants with bronchiolitis. Infants and toddlers who present with bronchiolitis can have a wheeze. However, they have been ruled out not to have asthma. Instead, the wheeze may be caused by having a small airway, tracheomalacia, dysphagia or inflammation of the airway post a viral illness (76). Bronchiolitis occurs due to an increased airway resistance, which is caused by obstruction from swelling within the airway and plugging from mucous, not from airway constriction (44, 77, 78); therefore, the use of a bronchodilator with has little effect (78).

Salbutamol works on the smooth muscle within the beta2-adrenoreceptors within the lungs and the beta1-adrenoreceptor within the heart, which results in tachycardia (78). Because of this, the smooth muscle contracts and responds to the pharmacological stimulant (34), causing tachycardia, which is a common side effect of salbutamol (44, 79), and also decreases oxygen saturation (77, 79). A meta-analysis completed by Cai et al. (44) revealed that using salbutamol in paediatric patients with bronchiolitis increases their respiratory rate and not their oxygen levels. The smooth muscle of the airways relaxes post administration of salbutamol by increasing airflow and providing relief of symptoms caused by an exacerbation of asthma, such as coughing, chest tightness, shortness of

breath and wheezing (80). Treatment with a bronchodilator has been found to improve the clinical scores a little but not shorten the length of stay. Therefore, they are not a recommended treatment for bronchiolitis (44, 79).

5.3 Comparison with previous literature or reviews

This is the first review of literature looking at nebuliser tolerance for infants. There are numerous studies looking at the efficiency of nebuliser therapy depending on device, flow and interface for the infant population however very little has been completed on how well the infant tolerates nebuliser treatment. Reminiac et al. (81) completed an RCT in 2018, looking at the effectiveness of aerosol therapy being administered via VMN with HFNC compared to the traditional jet nebuliser in adults. The study showed significant tolerance during nebuliser therapy via VMN, with no significant changes in clinical response: heart and respiratory rate. No other studies or reviews were found.

5.4 Limitations of the study

There are several limitations identified for this integrative review.

Firstly, only English studies were included due to the inability to access or translate them. Some titles were not followed through due to being in Japanese and needing help to access the complete study to assess if they were relevant to the research question.

Secondly, only one reviewer was involved in the selection, interpretation and risk of bias of studies. However, a comprehensive search of multiple databases was used to search and find relevant studies, with the search completed again six weeks later. Guides and resources were used when completing the RoB 2 analysis tool to ensure it was completed to the best of the author's ability.

Thirdly, the findings are driven by a small number of variable quality studies, and could easilty reverse these findings if larger, better-quality trials were available.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 Recommendation for practice

The evidence suggests that infants and toddlers showed less distress when receiving nebuliser therapy via a VMN. However, Morgan et al. (72) discussed that not all infants became upset when receiving a jet nebuliser; therefore, treatment should be continued with the jet nebuliser for these paediatric patients. However, in infants already receiving HFNC support or fighting the jet nebuliser, the VMN device through the HFNC circuit should be considered to ensure that treatment is administered with minimal distress.

6.2 Recommendation for research

Firstly, further research is recommended due to the limited amount available on nebuliser tolerance in paediatric patients from 0-4 years of age.

Secondly, a larger sample size of participants would increase the comparison to be reviewed, as the highest number of participants within the current research is 33 and includes participants older than six months, the primary age included in the recent studies. Older infants and toddlers, especially those aged 2-4 years, would be more purposeful in their behaviour, whether acceptance or distress, assisting in examining tolerance during nebuliser therapy. Including more participants with asthma; only one of the research studies had 28 participants, with the majority having the respiratory condition asthma. Increasing the evidence, which currently is lacking, on the physiological response with improved nebuliser tolerance.

Thirdly, further research specific to the HFNC circuit: Incorporating the jet nebuliser within the HFNC circuit as is done when using invasive respiratory support. To assess if the vibrating mesh nebuliser is superior to the jet nebuliser when both are incorporated within the HFNC circuit.

Lastly, expanding the location of where the research is conducted. With HFNC therapy being administered within paediatric wards, it would be interesting to see what nebuliser tolerance is in an environment best suited for the paediatric patient. And looking into an escalation pathway as a sub-theme, if it was required, and when it occurred or not during the treatment process.

Appendix A: Study protocol

STUDY PROTOCOL

Compared to jet nebuliser, does the use of vibrating mesh nebuliser through high flow nasal cannula improve nebuliser tolerance with a shortened clinical recovery time among toddlers with respiratory distress?

1.0 Background

1.1 Description

Nebuliser therapy is a common treatment therapy for infants with respiratory distress, transforming liquid medication into droplets that are suspend in gas (1, 2). Traditionally, medication is aerosolized using a face mask through a jet nebuliser. However, therapy has advanced with new types of nebulisers being designed such as vibrating mesh nebuliser and the way in which you can administer it (1).

1.2 Description of the intervention and arm

High flow therapy through nasal cannulas is commenced as a supportive therapy for infants with increased work of breathing due to respiratory distress. Improving work of breathing by flushing of the dead space of the nasopharyngeal cavity, resulting in less overall dead space and more alveolar ventilation as a fraction of minute ventilation (3). High flow therapy delivers humidified high inspired gas flows that exceeds the patient's own intrinsic inspiratory flow rate (4-6). Currently, the two nebulisers that are commonly used through this circuit are the jet nebuliser and the vibrating mesh nebuliser (4).

1.3 Why is it important to do this review

Numerous studies have been done to compare the efficiency of a jet nebuliser with a vibrating mesh nebuliser, but very little has been done to compare how the child tolerates the nebuliser system. Nebulizer therapy was initially designed for adults so for infants it becomes a complex procedure due to inadequate administration because of differing anatomy, poorly fitted masks, and the child being frightened or scared and resisting the application of the nebuliser mask (19). It is reasonable to think that when dispensing a nebuliser, jet or vibrating mesh, through the high flow circuit would be more practicable as there are minimal changes, avoiding stimulation of the infant. Enabling the infant to receive a greater amount of medication while also remaining calm and taking even normal spontaneous breaths (1, 6).

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2.0 Research Question

2.1 Aim

Improve nebulizer administration in infants aged 0-4 years

2.2 Objective

To compare mesh nebuliser tolerance to the more routinely used jet nebuliser in infants admitted with respiratory distress and receiving high flow treatment via a nasal cannula circuit

3.0 Search Strategy

3.1 Electronic searches:

The databases listed below will be searched for any randomised trials relating to the topic.

- Cochrane
- Medline
- CINAHL
- Embase

Endnote library will be used to download complete citations for review

3.2 **Other searches**:
The reference list of relevant RCTs/articles will be evaluated to see if any other research of interest exists.

4.0 Selection criteria

4.1 Types of studies
Randomised control trials or trials described as randomised will be included, this will include random cross-over studies who have completed measurements prior to cross over otherwise they will be excluded.
Exclude in vitro and in vivo studies and animal studies.

4.2 Types of participants
Infants aged 0-4 years will be included, as this population of paediatrics have an increased intolerance to nebulizers being administered.

4.3 Types of interventions
Both the jet and vibrating mesh nebulizer units will be used for comparison. Both interventions need to be used in conjunction with a high flow circuit and can be completed in either the ward or the intensive care setting.

4.4 Types of outcomes
First outcome will assess how the infant tolerates the nebulizer being administered, the infant should appear comfortable and not trying to remove the interface from their face. Second outcome will assess the clinical improvement of the infant. This will be on the observation chart of the infant, with improved respiratory rate and decreased work of breathing.

5.0 Data collection and analysis

5.1 Selection of studies
No data restrictions will apply, and only English studies will be included.
Titles and abstracts will be checked to see if they meet the inclusion criteria. Where there is uncertainty, the article will be obtained for further review. Throughout the process, citations will be exported into Endnote.

5.2 Data extraction and management
Data from each study will be entered into a data extraction form, with relevant information relating to the research topic highlighted.

5.3 Data analysis
The data obtained will be evaluated for similarities and differences in relation to the review question.

5.4 Discussion of conclusion
Discussion will occur of the review findings. Recommendations for practice and further research will be made. Conclusion will be a summary of the major findings

APPENDIX 1. Search strategies by database

Medline Search Strategy

1. "Nebulizers and Vaporizers"/or Asthma/ or nebulise*. mp. Or Aerosols/ or Administration. Inhalation/
2. Aerosols/ or Administration, Inhalation or "Nebulizers and Vaporizers"/ or nebulise*.mp. or Asthma/ or Bronchodilator Agents/
3. atomiser.mp.
4. "Nebulizers and Vaporizers"/ or Aerosols/ or atomiser*.mp.
5. Asthma/ or Administration, Inhalation/ or Bronchodilator Agents/ or "nebuliser therapy".mp. or Aerosols/ or "Nebulizers and Vaporizers"
6. 1 or 2 or 3 or 4 or 5
7. Noninvasive Ventilation/ or Oxygen Inhalation Therapy/ or Cannula/ or high flow nasal cannula.mp. or Respiratory insufficiency/
8. Respiratory insufficiency/ or Noninvasive Ventilation/ or Oxygen Inhalation/ or Cannula/ or HFNC.mp. or Bronchiolitis/
9. Respiratory insufficiency/ or Oxygen Inhalation/ or Aerosols/ or airvo.mp. or Cannula/
10. Nasal Cavity/ or transnasal.mp.
11. Oxygen/ or Oxygen Inhalation therapy/ or Cannula/ or Noninvasive Ventilation/ or optiflow.mp.
12. Respiratory Distress Syndrome, Newborn/ or Oxygen Inhalation Therapy/ or Noninvasive Ventilation/ or nasal high flow.mp. or Respiratory insufficiency/
13. 7 or 8 or 9 or 10 or 11 or 12
14. tolera*.mp.
15. accept*.mp.
16. endur*.mp.
17. allow.mp.
18. 14 or 15 or 16 or 17
19. Treatment Outcome/ or clinical outcome.mp.
20. improv*.mp.
21. progress.mp.
22. result.mp.
23. 19 or 20 or 21 or 22
24. "respiratory failure".mp. or Respiratory Insufficiency/
25. "Work of Breathing"/
26. Work of Breathing"/ or WOB.mp.
27. Respiratory insufficiency/ or Asthma/ or Respiratory Muscles/ or accessory muscles.mp. or Respiration/
28. Asthma/
29. Bronchiolitis/ or Bronchiolitis, Viral/
30. 24 or 25 or 26 or 27 or 28 or 29
31. Infant/ or Infant Health/ or Infant Behavior/
32. Toddler.mp. or Child. Preschool/
33. pediatric*.mp. or Intensive Care Units, Pediatric/ or Pediatric Nursing/ or Hospitals/ Pediatric/
34. paediatric*.mp.
35. Child/ or Infant/ or small child.mp. or Child, Preschool/
36. kid.mp.
37. 31 or 32 or 33 of 34 or 35 or 36
38. 6 and 13 and 18 and 23 and 30 and 37
39. randomi*ed.mp.
40. Randomized Controlled Trial/
41. 38 and 39 and 40
42. Case study.mp. or Case Reports/
43. Clinical review.mp.
44. 38 and 42 and 43
45. 38 and 42

CINAHL

1. nebuli*er and high flow nasal cannula and paediatric and tolerance and clinical outcome
2. nebulizer and high flow and pediatric and tolerance and clinical outcome
3. nebulizer and high flow and pediatric and tolerance
4. nebulizer and high flow and pediatric and tolerance and treatment outcome
5. nebulizer and high flow and pediatric
6. nebulize* and “high flow nasal cannula” and p?diatric
7. nebuli?er* and high flow and p?diatric
8. nebulizer and high flow and pediatric and comfort
9. nebuli?er and high flow nasal cannula and p?diatric
10. (nebulizer and vaporizer) and airvo and infant and outcome
11. (nebulizer and vaporizer) and airvo and infant and respiratory insufficiency
12. (nebulizer and vaporizer) and transnasal and infant and respiratory insufficiency
13. Nebulizer and transnasal and pediatric and respiratory insufficiency
14. Nebulizer and high flow and aerosol and pediatric and distress
15. (nebuli?er or aerosol or vapori?er or “nebulizer therapy”) and (high flow or HFNC or airvo or transnasal or optiflow) and (p?diatric or infant or toddler or “small child”) and (comfort or tolera* or allow)
16. (nebuli?er or aerosol or vapori?er or “nebulizer therapy”) and (high flow or HFNC or airvo or transnasal or optiflow) and (p?diatric or infant or toddler or “small child”) and (comfort or tolerab* or allow or permit*) and (outcome or improv* or increase or recover*) and (respirator* or “work or breathing” or WOB or accessory muscles”)

Embase

1. High flow nasal cannula therapy/ or nasal cannula/ or oxygen therapy/ or high flow.mp.
2. Nasal cannula/ or high flow nasal cannula therapy/ or HFNC.mp.
3. Nasal cannula/ or high flow nasal cannula therapy/ or airvo.mp. or oxygen therapy/
4. transnasal.mp.
5. optiflow.mp.
6. Nasal high flow.mp. or high flow nasal cannula therapy/
7. Nasal cannula/ or bronchiolitis/ or humidified oxygen.mp. or oxygen therapy/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Airway resistance/ or asthma/ or nebuli?er.mp.
10. aerosol*.mp. or aerosol generating procedure/ or aerosol/
11. atomizer.mp. or nebulizer/
12. Nebulizer/ or “nebulizer therapy”.mp. or bronchodilating agent/
13. 9 or 10 or 11 or 12
14. Infant care/ or infant/
15. Child health/ or child/ or child health care/ or preschool child/
16. p?diatric*.mp.
17. kid.mp.
18. small child.mp.
19. 14 or 15 or 16 or 17 or 18
20. Respiratory failure/
21. Respiratory distress/
22. Breathing/ or “work of breathing”/ or breathing mechanics/
23. WOB.mp.
24. accessory muscles.mp.
25. Asthma/
26. Bronchiolitis/ or viral bronchiolitis/
27. 20 or 21 or 22 or 23 or 24 or 25 or 26
28. tolera*.mp.
29. accept*.mp.
30. endur*.mp.
31. permit.mp.

32. allow.mp.
33. 28 or 29 or 30 or 31 or 32
34. Clinical outcome/
35. improv*.mp.
36. better.mp.
37. increase.mp.
38. progress.mp.
39. recover*.mp.
40. Outcome assessment/ or patient-reported outcome/ or outcome variable/ or outcome.mp.
41. result.mp.
42. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. 8 and 13 and 19 and 27 and 33 and 42
44. Randomized controlled trial/
45. 43 and 44
46. Case study/
47. 43 and 46
48. review.mp.
49. 43 and 48
50. Find similar to High flow nasal cannula therapy in children: working principles and treatment failure predictors
51. Find similar to Aerosol Therapy During High Flow Nasal Cannula
52. Find similar to Incorporating a nebulizer system into high flow nasal cannula improves comfort in infants with bronchiolitis

References:

1. Ari A, Fink JB. Aerosol therapy in children: challenges and solutions. Expert review of respiratory medicine. 2013;7(6):665-72.
2. Berlinski A. Pediatric Aerosol Therapy. Respir Care. 2017;62(6):662-77.
3. Kwon JW. High-flow nasal cannula oxygen therapy in children: A clinical review. Clinical and Experimental Pediatrics. 2020;63(1):3-7.
4. Ari A. Aerosol Drug Delivery Through High Flow Nasal Cannula. Current pharmaceutical biotechnology. 2017;18(11):877-82.
5. Kesavan S, Amirav I. Is aerosol delivery by high-flow nasal cannula in children an effective alternative to face mask aerosol nebulization? Pediatr Pulmonol. 2019;54(12):1873-4.
6. McKiernan CMD, Chua LCMD, Visintainer PFP, Allen HMD. High Flow Nasal Cannulae Therapy in Infants with Bronchiolitis. The Journal of pediatrics. 2010;156(4):634-8.
7. Goralski JL, Davis SD. Breathing easier: Addressing the challenges of aerosolizing medications to infants and preschoolers. Respir Med. 2014;108(8):1069-74.

Appendix B. Matrix Table

No table of figures entries found.

Author	Year	Title	Research Methods	Setting	Devices used	Purpose
Al-Subu, A. M., Nguyen, V. T., AlAli, Y., Yngsdal-Krenz, R. A., Lasarev, M. R., Eldridge, M. W., & Hagen, S. A.	2020	Feasibility of Aerosol Bronchodilators Delivery through High-Flow Nasal Cannula in Paediatric Subjects with Respiratory Distress	retrospective chart review of paediatric patients admitted to the ICU and required nebulisation between December 2017 and June 2018	Paediatric ICU	Opti flow - HFNC with humidification circuit. When HFNC used weaned 2-4L/min prior to nebulisation. Aerogen solo on dry end of the circuit. Kids MED mask.	Evaluate nebulisers through HFNC at lower gas flows, and if it increases comfort, and reduces respiratory therapist compared to traditional interfaces
Morgan, S. E., Mosaskowski, RRT., Solano, P. S., Hall, J. B., & Tung, A.	2015	High-Flow Nasal Cannula and Aerosolized B agonists for rescue therapy in children with bronchiolitis: A case study	Case study	Paediatric ED	HFNC at oxygen gas flow set between 5-8L/min. Jet nebuliser connected to a mask to the HFNC. Nebuliser connected to the dry circuit of the humidified circuit	Review of aerosol therapy via HFNC in bronchiolitis
Valencia-Ramos, J., Miras, A., Cilia, A., Ochoa, C., & Arnaez, J.	2018	Incorporating a Nebulizer System into High-Flow Nasal Cannula Improves Comfort in Infants with Bronchiolitis	Prospective, randomized cross-over trial	Paediatric ICU	Opti flow - HFNC. VMN inserted into HFNC aerogen solo. Jet nebulizer attached to mask with a flow of 8L/min	Evaluate comfort of aerosol delivery that is incorporated into a HFNC compared to jet nebulizer via a face mask
Valencia-Ramos, J., Sangrador, C. O., Garcia, M., Oyaguez, Pl, & Arnaez, J.	2021	Impact of different nebulisation systems on patient comfort in bronchiolitis: a randomised controlled cross-over study	Randomized cross-over trial	Paediatric ICU	HFNC system - Opti flow. Cirrus 2 paediatric mask	Assess the hypothesis that comfort is better achieved with a nebuliser incorporated into a HFNC compared to a jet nebuliser

Author	Respiratory condition	Position of jet nebuliser	Position of VMN	Sample size	Median Age	Inclusion/exclusion
Al-Subu et al.	Asthma and Bronchiolitis	Mask interface, applied over the HFNC interface	VMN connected to the dry side of the humification circuit of the HFNC	28 children - given a total of 205 nebulisations.	Median age 32.4 months (15.9-53.2)	Inclusion - Patient intubated on admission
Morgan et al.	Bronchiolitis	Mask interface, applied over the HFNC interface	VMN connected to either the wet or dry side of the humification circuit of the HFNC	5 infants treated with bronchiolitis in the paediatric emergency department. Age range 2-21 months	Median age 5.6 months	Exclusion -Mod- severe respiratory distress
Valencia-Ramos et al.	Bronchiolitis	Mask interface. If applied with HFNC, mask applied over nasal cannula and final flow would be the nebulizer and HFNC	VMN connected to the dry side of the humification circuit of the HFNC	6 children received 113 nebulisers. 64 nebulisers via HFNC and 49 via jet nebuliser	Median age 1.5 months	Inclusion - less than 24, admitted with bronchiolitis and using HFNC respiratory support system Exclusion - No other underlying disease or factors of severity such as prematurity, cardiopathy, bronchopulmonary dysplasia, neuromuscular disease or immunodeficiency
Valencia-Ramos et al.	Bronchiolitis	Jet mask connected to gas flow at 8L/min, HFNC not removed and flow rate was not modified	VMN connected to the dry side of the humidication circuit of the HFNC	33 children with 233 nebulisations. Median age 3 months	Median age 92 days	Consent not obtained, and contraindications for HFNC such as upper airway abnormalities that may make HFNC ineffective or potentially dangerous, life-threatening hypoxia, haemodynamic instability, facial bone or skull base trauma and pneumothorax excluded

Author	Analysis of nebulizer tolerance	parent involvement	Results/Main findings	Limitations
Al-Subu et al.	HR, RR, oxygen requirement, sp02 before and after each administration. Comfort assessment was assessing behaviour: calm, not crying, no facial tension or aggressive physical movement. HR used as indirect assessment of bronchodilator delivery	nil	28 children received nebuliser therapy. 60.7% male, median age 32.4 months and median weight 13.5kg. Asthma most prevalent followed by bronchiolitis. Median time in paediatric ICU 31.8 hours, and paediatrics received 4.2 nebulisers per 24 hours. 57% paediatrics did not receive a nebuliser through the HFNC, and remainder received at least one aerosol therapy through HFNC. 2 subjects (7.1%) did not cope with reduction of flow through the HFNC	Retrospective. Small study. Comfort levels not assessed using an objective comfort scale.
Morgan et al.	HR, clinical asthma severity score assessments before, during and after each treatment. Agitation or comfort during nebulisation - not described	Parent required to comfort infant by holding them and assist keeping mask on the patients face.	Patient agitation improved when delivered using VMN via the HFNC. All patients increasingly agitated due to the face mask. And parents required to hold the patient to assist keeping mask on the face. During VMN administration patients were calm, could sleep through their treatments. Increased heart rate with HFNC and VMN. Comfort and anxiety levels improved for both child and infant during VMN and HFNC.	Case study. Small study. No objective agitation score used
Valencia-Ramos et al.	Analysis of COMFORT - B and visual analog and numerical score recorded 5 min before, during and 5 minutes after nebulization by 2 nurses	Assessed comfort using COMFORT-B and visual analog. Not documented as patient requiring to hold the child or comfort given them too.	Increased HR during nebulisations in both groups, no change in oxygen saturation, RR or oxygen requirement. Comfort greater with nebulization in HFNC compared to the jet nebulizer in both COMFORT-B and visual analog. Comfort B and visual analog scales used by health care workers showed no difference between both delivery methods for before and after nebulization. Comfort scale assessed by parents showed greater comfort and satisfaction with nebuliser within HFNC circuit	Small study size, total of 113 nebulization measured. Randomized and controlled. Assessment of comfort in different validated medical scales performed by healthcare workers and parents.
Valencia-Ramos et al.	Comfort assessed using COMFORT-behaviour scale and variant of numerical rating comfort scale. HR, RR were analysed	Assessed comfort using comfort and numerical scale. Also discussed about requirement to hold baby during nebulisation	233 nebulisations administered to 33 patients with acute bronch. 25 (67%) first episode of bronchiolitis. RSV in 27 children. 109 delivered via JN and 124 via NHF. Greater discomfort with JN. Both health team and caregivers recorded greater discomfort with JN used. HR increased significantly during both systems, however greater with JN during administration. Need to be restrained by parents rose by 48% when receiving JN but remained the same with NHF.	Performed at a single centre. Comfort and satisfaction were measured by caregivers and personal staff. Noise and brightness levels not recorded that may have effected comfort level.

Appendix C: Revised Cochrane RoB2 template

Revised Cochrane risk-of-bias tool for randomized crossover trials

TEMPLATE FOR COMPLETION

Version of 18 March 2021

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

Study details

Reference	

Study design

☐ Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

X Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:		Comparator:	

Specify which outcome is being assessed for risk of bias	
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions

☐ failures in implementing the intervention that could have affected the outcome

☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

☐ Journal article(s) with results of the trial

☐ Trial protocol

☐ Statistical analysis plan (SAP)

☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)

☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)

☐ "Grey literature" (e.g. unpublished thesis)

☐ Conference abstract(s) about the trial

☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)

☐ Research ethics application

☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)

☐ Personal communication with trialist

☐ Personal communication with the sponsor

Risk of bias assessment

Responses <u>underlined in green</u> are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1a: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		<u>Y / PY</u> / PN / N / NI

1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups at the start of the first period suggest a problem with the randomization process?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain S: Risk of bias arising from period and carryover effects

Signalling questions	Comments	Response options
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?		Y/PY/PN/N/NI
S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?		NA/Y/PY/PN/N/NI
S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?		Y/PY/PN/N/NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from period and carryover effects?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during each period of the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?		Y / PY / PN / N / NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA / Y / PY / PN / N / NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA / Y / PY / PN / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y / PY / PN / N / NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during each period of the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced between interventions?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Risk of bias due to missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?		Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI
5.4 Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Appendix D: Risk of bias assessment table - summary of domains for included studies

Author	Randomisation bias	Evidence	Deviation from intended outcomes	Evidence	Missing outcome data bias	Evidence
Al-Subu et al. (73)	Some concerns	No documentation of randomization, was a retrospective chart review of all patients admitted to the ICU requiring nebulization over a 6-month period	High	2 subject (7.1%) unable to tolerate lowered flow rate, which was required in this study when being administered via HFNC, so continued with jet nebuliser over the HFNC. COMFORT-B scale and visual analog used to assess the infant's comfort during nebulisation, as well as physiological factors such as HR, RR, oxygen saturations and oxygen requirement	High	No randomisation during this study. In order for HFNC to be assessed, flow rate was weaned prior to nebulisation, if not tolerated were switched to jet nebulisation
Morgan et al. (72)	High	Case report of 5 infants treated in ED of a children's hospital All infants were initially treated with two consecutive doses of albuterol delivered by a jet nebuliser	Some Concerns	No discussion of assigned intervention to the participants, carers or people delivering the intervention. Heart rates and Asthma severity assessment score was conducted prior, during and after both the jet nebuliser as well as the VMN	High	A case study was conducted. No discussion of any of the participants being withdrawn
Valencia-Ramos et al. (74)	Some concerns	Case report of 5 infants treated in ED of a children's hospital All infants were initially treated with two consecutive doses of albuterol delivered by a jet nebuliser	Low	Does not discuss if participants were aware, however their median age is 1.5 months. Parents were required to give consent to the study	Low	Data outcome was available for all participants randomized
Valencia-Ramos et al. (75)	Low	Participants were randomly selected using computer generated random numbers to begin nebulisation with either jet or VMN. Then alternated with subsequent nebulisation. Only the outcome assessors and data analysis (not the particpant or health staff) were blinded to the allocation	Low	Participants were not blinded, however the participants were less than 208 days Health care workers administering nebulisation would be aware, therefore theoritically it should be discussed with them the procedures being completed on their infants. Comfort and satisfaction score was completed before, during and after by both the health workers and the caregivers	Low	of the 33 patients, the nebulisation technique was randomised and then alternated with subsequent treatments

Appendix D continued: Risk of Bias Assessment table – summary of domains for included studies

Author	Measurement of the outcome bias	Evidence	Selection of the reported results bias	Evidence	Overall bias	Comments
Al-Subu et al. (73)	Some Concerns	No randomisation, retrospective chart review	Low	Retrospective chart review. Assessment of childs comfort, their HR, RR, flow rate, and oxygen requirement pre and post each nebulisation	High	Overall high risk of bias due to the nature of the study being a case study.
Morgan et al. (72)	High	Heart rate and clinical asthma severity score was conducted before, during and after. Individual outcome conducted after each intervention	Low	Yes - physiological data (heart rate) and asthma severity score	High	Increase risk of bias due to concerns regarding randomisation process and how the outcome measurement was conducted
Valencia-Ramos et al. (74)	Some concerns	Method to measure was COMFORT-B score as well as visual analog score to assess how comfortable the child was when receiving a nebuliser. Measurements were the same for both jet nebuliser and vibrating mesh nebuliser. No documentation, but the jet nebuliser required a face mask while the VMN nebuliser had an adapter inserted into the HFNC circuit. Health workers were provided with education session on the assessment tool a month before implemented	Low	Prior to study commencing, training was completed through an accredited course describing the assessment tools as well as the physiological assessment. Information was inputed and was analysed from the assessment tools used.	Some concerns	Overall high risk of bias due to the retrospective aspect of this study
Valencia-Ramos et al. (75)	Low	Comfort and satisfaction scores were completed by both the caregivers and the health care team as well as physiological factors such as HR, the ability to tolerate a feed or requirement of analgesia. Outcome assessors and data analysts were blinded to group allocations.	Low	Comfort and satisfaction score, heart rate, ability to have a feed or requirement for analgesia	Low	Overall low risk due to randomisation and assessment post each nebulisation according to the measurement outcomes

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