Optimal delivery of aerosolized medication to mechanically ventilated pediatric and neonatal patients: A scoping review

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Objectives: Delivering aerosolized medication to patients during mechanical ventilation is a common practice in respiratory therapy for adult, pediatric, and neonatal populations. However, aerosol delivery in pediatric populations is inconsistent and challenging, impacting how the drug is delivered. Some factors that influence drug delivery efficiency are directly under the purview of the clinician or therapist administering the drugs. However, excessive variability exists amongst clinicians and therapists working at the same site and between different sites. This review aims to systematically summarize the literature to identify current practice variations, identify common practices, and provide suggestions to guide future research in this area. In addition, this scoping review aims to identify the available evidence and knowledge gaps in the literature regarding the delivery of aerosolized medication to pediatric populations during mechanical ventilation. More specifically, the question that guided our research was: What are the best strategies for optimizing aerosol delivery of medication to pediatric patients, including neonates, while on mechanical ventilation?

Methods: A scoping review, using the Joanna Briggs Institute methodology, was conducted until September 2022 in the CINAHL, EMBASE (Ovid), and Medline (Ovid) databases. Our initial search yielded 248 articles. After screening the titles, abstracts, and full text of the articles according to inclusion and exclusion criteria, five articles were analyzed.

Results: We identified three main topics for discussion: the type of device used for administering aerosolized medication, appropriate mechanical ventilation settings, and optimal placement of the nebulizer delivery system.

Conclusion: Of the three topics we intended to discuss, we only found enough evidence to suggest using mesh nebulizers to increase aerosol deposition. We found conflicting or outdated results for the other two topics. This demonstrates a significant gap in the literature since aerosol medications are routinely administered to mechanically ventilated neonatal and other pediatric patients.

Key Words: *aerosol therapy; mechanical ventilation; pediatric; scoping review; optimization of medication delivery*

INTRODUCTION

Delivering aerosolized medication during mechanical ventilation is considered common practice. Ehrmann et al. [1] conducted a worldwide survey of physicians who regularly worked in intensive or intermediate care units about their use of aerosol medication during mechanical ventilation; 99% reported that this was routine practice at their hospital. It is especially common for aerosolized medication to be prescribed in countries such as Canada and the United States, where respiratory therapists (RTs) are well-established and are responsible for delivering them to patients. Surprisingly, standard or best practices for delivering aerosolized medication are still evolving along with growing knowledge and advancements in delivery devices [1]. There remains much variability amongst physicians regarding the types of devices, the circuit placement of the devices, and the ventilator settings used [1]. However, the survey did not discriminate between practices used with adult versus pediatric patients.

According to Dhand and Guntur [2], the factors that influence the efficiency of aerosolized drug delivery can be grouped into five categories: (1) ventilator-related, (2) circuit-related, (3) device-related, (4) drug-related, and (5) patient-related. Some patient-related factors (e.g., airway obstruction severity or the target site for medication delivery) remain out of RTs' control [2]. Similarly, certain drug-related factors (e.g., the type of medication) also remain out of RTs' control. However, some factors depend entirely on the RT, especially regarding the method of medication delivery. For instance, clinicians or RTs decide whether to deliver medication in-line the ventilator circuit or manually ventilate the patient while administering the medication [2].

In adult populations, beta-adrenergic and anticholinergic medications are most commonly administered in metred doses rather than with a nebulizer [2]. The optimal protocols for delivering aerosolized medication seem to be well established, even though they are not necessarily always followed [1, 3, 4]. However, administering aerosol therapy to pediatric patients is more challenging than in adult patients [5]. Supplemental factors such as humidification, smaller tidal volumes, and patient coordination are required to ensure accurate inhalation and delivery, which impacts drug delivery [5]. These factors must be considered when providing aerosolized medication to young children, including neonates [5]. Unfortunately, practices around delivering aerosolized medication to neonatal and pediatric patients are not standardized and remain highly dependent on the individual providing the medication or the local hospital's standards of practice [5].

While studies on aerosol delivery to adult patients are extensive and provide both in vivo and in vitro data, the evidence for pediatric patients is limited and often derived from in vitro studies alone [6]. In pediatric

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populations, the evidence supporting best practices remains inconsistent and has not been systematically summarized. As such, we aimed to systematically summarize the literature to identify current practice variations, identify any common practices and provide suggestions to guide future research in this area. This scoping review aims to identify the types of available evidence and knowledge gaps in the literature regarding the delivery of aerosolized medication to neonatal and pediatric populations during mechanical ventilation.

METHODS

To identify relevant published articles, we conducted a scoping review following the Joanna Briggs Institute (JBI) methodology [7]. Our research question was informed by the JBI framework, which recommends searching the literature by population (i.e., pediatric/neonatal), concept (i.e., aerosolized medication), and context (i.e., mechanical ventilation). Such a review allows researchers to cover a broader "scope" in the literature. This scoping review was not pre-registered with PROSPERO because (1) it was primarily done to inform our other research projects and, after conducting the scoping review, we felt the results warranted publication to inform the body of knowledge, and (2) scoping reviews are not eligible for inclusion in PROSPERO. We conducted a preliminary search in the Cochrane and JBI databases to ensure no similar review was ongoing.

A search of peer-reviewed journals using key terms (i.e., nebulizer, position, aerosol, deposition) and related terms was initially conducted on May 6, 2021, and rerun on September 14, 2022, in the CINAHL, EMBASE (Ovid), and Medline (Ovid) databases. Appendix A[1] includes the search strategy. No additional articles were retrieved when the search was rerun. No filters or limits were applied to the search. An additional article by Berlinski and Willis [8] was identified when a background search on aerosol optimization in pediatric and neonatal patients was conducted for a different project. This article was screened using the same process described below, and it was unanimously decided to be included in the scoping review. A total of 506 articles were identified, with Medline (Ovid) yielding the largest number (n = 248), followed by EMBASE (Ovid) (n = 223) and CINAHL (n = 34). After uploading 506 articles to Rayyan™ (https://www.rayyan.ai), 258 were identified as duplicates and removed, leaving 248 articles to undergo screening [9].

Screening was conducted by three individuals using defined inclusion and exclusion criteria. Publications were included if they met the following four criteria: (1) explores the effect of nebulizer position on aerosol deposition, (2) utilizes invasive ventilatory means, (3) focuses on pediatric and/or neonatal populations or animal trials, and (4) published in English or French. Criteria for exclusion included (1) no title or abstract, (2) conference or poster abstracts, (3) explicit focus on adult populations or use of non-invasive ventilatory means, and (4) written in a language other than English or French. Articles using animal models were included as they are often used to explore the effects or impact that would occur in humans when ethical considerations make it difficult to study certain populations, such as pediatric populations [10–12]. Although there are anatomic and physiologic differences, animal models provide additional routes to quantify measurements, such as aerosol deposition [10, 13]. During background searches, the number of articles on this subject was limited. Thus, we decided to include animal models to ensure a maximal number of relevant studies were found. Criteria for exclusion included (1) no title or abstract, (2) conference or poster abstracts, (3) explicit focus on adult populations, (4) use of non-invasive ventilatory means, and (5) written in a language other than English or French.

Articles underwent three stages of screening as proposed by the JBI model [7]. Firstly, titles were screened against inclusion and exclusion criteria. After title screening, articles underwent abstract screening, followed by full article review using the same inclusion and exclusion criteria described above. Throughout the process screeners were blinded to each other's responses. Once each step was complete (e.g., title screening, abstract screening, and full article review) all discrepancies were reviewed and resolved through discussion. No additional reviewers were required to resolve conflicts. Figure 1 presents our Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [14].

RESULTS

As indicated in Figure 1, of the 248 publications that underwent both title and abstract screening, 237 did not meet the inclusion criteria and were excluded from this scoping review. This left 11 articles to undergo full-text screening. During that stage, four were identified as conference or poster abstracts and were excluded. Two other publications were excluded as they discussed the chemical properties of medications, which was irrelevant to our research question and objectives. This left a total of five articles that met all our inclusion criteria and were included.

Of the five studies that met our inclusion criteria, all were primary studies published between 1991 and 2020 (see Appendix B[1] for summary). The majority of included articles are from North America. Two [8, 15] are from the United States, while those by Esmaeilizand et al. [16] and Mandhane et al. [5] are from Canada. The one remaining article by Cameron et al. [10] is from Europe, specifically England.

Four of the five studies utilized simulated lung models [5, 8, 15, 16], while the remaining study used an animal (rabbit) model [10]. One article assessed metred-dose inhaler (MDI) delivery [5], while the others focused on aerosolized agents [8, 10, 15, 16]. Four articles assessed deposition of albuterol [5, 8, 10, 15]. Two specified that they used ultraviolet (UV) spectrophotometry at 276 nm to measure absorption of the deposition; the others did not specify frequency. One article assessed budesonide deposition using UV spectrophotometry at 243 nm [16]. The study involving an animal model used sequential gamma camera imaging and then assessed for tissue radioactivity to measure lung deposition [8].

As mentioned previously, clinicians and RTs are able to control some factors when administering aerosol therapy. In what follows, we discuss in more detail common factors shared between the articles as identified by Dhand and Guntur [2]. These factors include (1) the type of device used for medication administration (device-related factor), (2) the mechanical ventilation settings that should be used when administering aerosolized medication (ventilator-related factor), and (3) optimal placement of the nebulizer delivery system (circuit-related factor). For each of these factors, we provide a narrative summary of what was included in the articles and additional information to guide future research.

DISCUSSION

Device used (device-related factor)

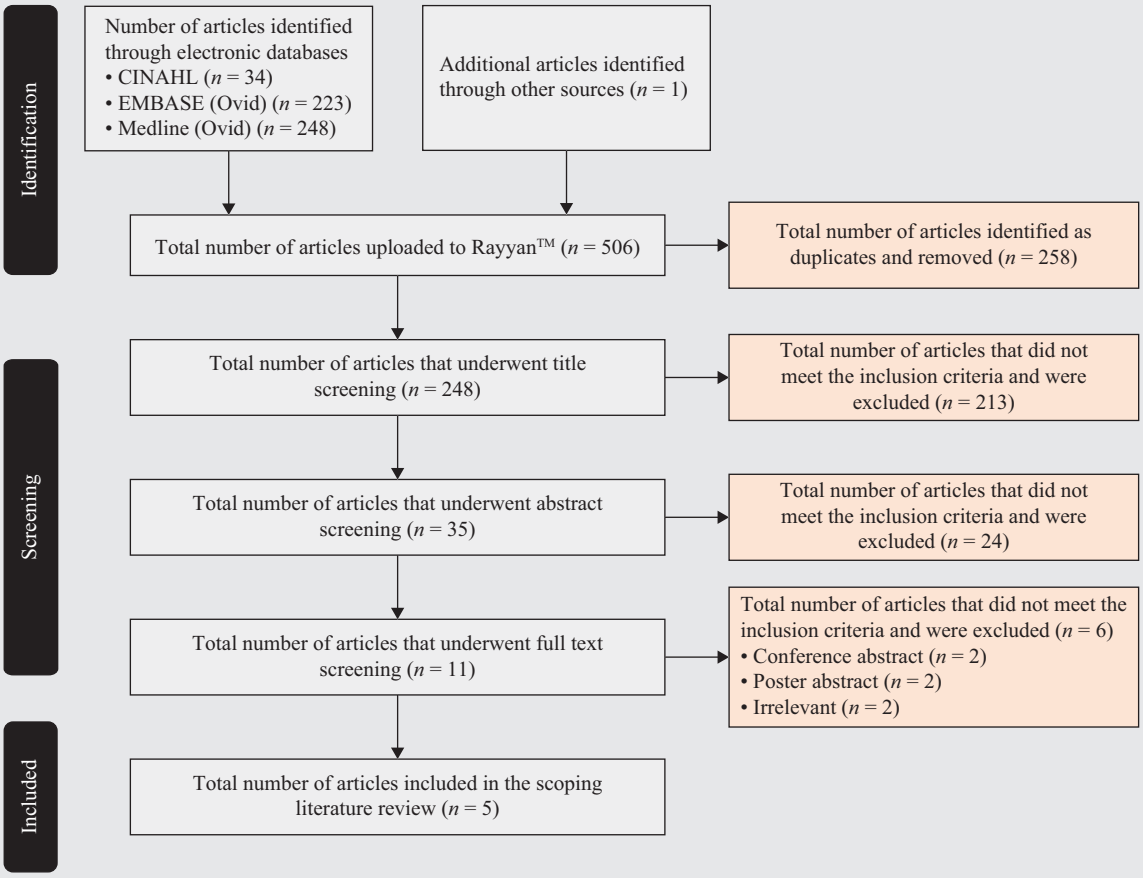
Three of the five studies compared different types of devices used for delivering aerosolized medication. Two studies compared nebulizers (i.e., jet, ultrasonic, or mesh), and one compared spacers for MDIs (Appendix B[1]). Our review of the two studies that compared nebulizers confirms the superiority of mesh nebulizers and inferiority of jet nebulizers for delivering albuterol to pediatric patients. As Berlinski and Willis [15] state, "[they] speculate that the vibrating mesh device achieved a higher lung dose because of its design and operation characteristics" (p. 1131). This includes reduced dead space in the design as well as "not [adding] extra flow to the ventilator circuit" [15]. This concurs with other studies of aerosolizing devices that were outside our search [8, 15, 17].

Of the four different MDI holding chambers assessed by Mandhane et al. [5], the NebuChamber (spacer with valve) reached statistical significance for overall drug delivery and percentage of the loading dose delivered. The deposition values associated with the NebuChamber with valve were between 55.06% and 62.67%, which was "3–6 times larger than the deposition values for the other reservoirs" [5]. As mentioned in the article by Mandhane et al. [5] no other studies have evaluated the impact a valve makes in intubated patients, therefore there are no other studies with the same conclusion. Of the three spacers without valves, the AeroChamber HC MV provided more deposition. Even though the specific brand of AeroChamber was not mentioned, the results found here are supported by [18]; that is, larger chambers

[1]Supplementary materials are available at https://www.cjrt.ca/wp-content/uploads/Supplement-cjrt-2022-044.docx.

FIGURE 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.



Note: This PRISMA diagram reflects the results from the scoping review and was adopted from the article by Page et al. [14].

increase deposition. As Avent et al. [18] describe, larger chambers allow for impaction and evaporation of the particles, which facilitates delivery of smaller particles in the lower respiratory tract. All the other studies investigating the benefits of a valve were conducted on spontaneously breathing patients [19, 20].

Mechanical ventilation settings (ventilator-related factor)

Two of the five studies explore the impact of changing mechanical ventilator settings on aerosol drug delivery. The ventilator parameter settings in the two studies varied in nature and magnitude.

Berlinski and Willis [8] focused exclusively on differences between the set tidal volume. They evaluated the impact of different tidal volumes (i.e., 100, 150, 200, and 300 mL) would have on drug delivery. They concluded that tidal volume did not influence medication delivery [8].

The second study by Cameron et al. [10] manipulated several parameters independent of one another, which included pressure support levels (14 and 28 cmH_2O) and, therefore, tidal volume, inspiratory expiratory (I:E) ratio, respiratory rate, and gas flow rate. Regarding the pressure support level, Cameron et al. [10] early findings support those of Berlinski and Willis [8], where decreasing pressure support levels decreased the amount of aerosol delivery. Cameron et al. [10] found no change in delivery whether the respiratory rate was set at 30 or 60 breaths per minute. However, changing the I:E ratio did have an impact on aerosol delivery. They found an inverse correlation, wherein an increased I:E ratio decreased aerosol deposition. Finally, gas flow rate directly correlated to deposition: increased flow increased in aerosol delivery. The correlation was higher for the I:E ratio than for gas flow, which indicates that increasing delivery time has a greater impact on medication delivery than increasing flow rate. These findings were replicated by O'Riordan et al. [21] using an adult model. However, instead of analyzing each component separately, they amalgamated ventilator settings in what they identified as the "duty cycle," for which tidal volume, flow rate, and respiratory rate are tabulated [21]. Despite strong evidence that minute ventilation has a direct correlation on aerosol deposition, only a few articles were identified evaluating these factors. Furthermore, the articles cited here are relatively old; we could not find more recent relevant research. Further studies are necessary to determine which settings have an impact and how settings can be optimized to enhance aerosol drug delivery to pediatric patients.

Aerosol device placement (circuit-related factor)

Authors from four studies looked at different placements of aerosol devices to see which position would optimize medication delivery. Three of them studied nebulizer position [15, 16], and one examined the placement of the holding chamber for MDI delivery [5]. Two of the aerosol device studies compared the delivery of medication when the nebulizer was positioned at the wye and at the ventilator [8, 15]. Two of the studies compared the delivery when placement of device was set at the wye and

before the humidifier [15, 16]. Only one study evaluated placement of the device 30 cm before the wye [15].

Based on the data derived from this review, we suggest the need for further evaluation of device position as results between studies are inconsistent or not reproducible. Esmaeilizand et al. [16] evaluated deposition of budesonide rather than albuterol. Even though the trend showed higher efficiency of delivery when the device was in greater proximity to the patient (i.e., closer to the wye), their results did not reach statistical significance. Berlinski and Willis [15] did show statistical significance, indicating that jet and mesh nebulizers perform better when placed at the ventilator or humidifier and that the ultrasonic nebulizer performs better when positioned at the humidifier. These results replicated an earlier study outside of our search [22]. But their second study [8] refuted the earlier results by showing higher efficiency at the wye. Those results supported another study outside of our search [23]. Optimal placement of devices for delivering aerosolized medication remains unknown.

LIMITATIONS

Although our search design is based on key and related terms, we recognize that some articles relevant to our research question may not have been retrieved from the selected databases based on the search criteria terms. Another limitation is that the type of lung model used to represent pediatric populations varied between the studies, with some using simulators and others using animals. It is possible that conflicting results amongst the studies could partially be attributed to differences in lung models. Finally, although all five studies analyzed how different parameters impact aerosol deposition, they were inconsistent in their choice of parameters. This limits comparison of effects and could possibly explain some of the conflicting results. Lack of consistency across the studies represents a challenge for interpreting the data and highlights the variability in research on devices intended for pediatric physiologies.

CONCLUSION

In this review, we identified three main research topics concerning aerosol delivery of medication to pediatric and neonatal patients: type of device, mechanical ventilation parameters, and nebulizer device placement. Amongst the five studies, we found evidence demonstrating the superior benefits of using mesh nebulizers to increase aerosol deposition in pediatric patient models. The results of the studies addressing settings for mechanical ventilation and aerosol device placement were either conflicting one another or were outdated. When we sought other data to support or refute the findings from our review, we discovered a similar gap in research on aerosolized medication delivery to adult populations [22, 24, 25]. We, therefore, recommend more research on aerosol delivery to inform best practice guidelines. We specifically recommend further investigation of more varied ventilator settings and nebulizer positions on the efficacy of the delivery of different aerosolized drugs.

We also identified that one type of delivery model has not be studied at all, specifically, aerosolized medication via manual hand ventilation. Mandhane et al. [5] surveyed various hospitals on their methods for delivering medication, and half indicated that they used manual hand ventilation. However, no research has been conducted on the nature and effects of this form of ventilation in delivering medicine to pediatric or neonatal patients. Further investigation is necessary because it can have a direct impact on how well patients respond to aerosolized medication, which plays a significant role in patients' disease processes. Thus, our scoping review demonstrates a large gap in the literature, which is especially problematic given the routine administration of aerosol medications to pediatric and neonatal patients in intensive care units.

DISCLOSURES

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Conflicts of interest

All authors declare no conflict of interest.

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Ethical approval

No HREB approval was necessary for this research.

Authors' contributions

Each of the listed authors fulfills the requirements of authorship. The contribution of the first author, Louise Chartrand, was substantial in developing the research strategy, analysis of the literature reviewed, and writing the manuscript. The second author, Victoria Ploszay, was instrumental in organizing the research platform and screening the articles reviewed; this author also contributed to writing a portion of the manuscript. The third author, Sebastien Tessier, developed key search terms and inclusion and exclusion criteria, helped screen articles for relevance, and made revisions to the manuscript.

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