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SUMMARY WITH CRITICAL APPRAISAL

Vibrating Mesh Nebulizers for Patients with Respiratory Conditions: Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

COI	conflict of interest
ED	emergency department
ICU	intensive care unit
JN	jet nebulizer
MDI	metered-dose inhaler
MV	mechanical ventilation
RCT	randomized controlled trial
RT	respiratory therapist
SD	standard deviation
VAP	ventilatory-associated pneumonia
VMN	vibrating mesh nebulizer

Context and Policy Issues

Patients with a variety of respiratory conditions in acute care settings may require aerosolized medications. These respiratory conditions include chronic obstructive pulmonary disease (COPD), asthma, bronchitis, bacterial pneumonia, bronchiectasis, and emphysema.[1,2] Medications used to treat these conditions include various antibiotics[1] and bronchodilators, such as tiotropium bromide,[2] arformoterol tartrate,[2] formoterol fumarate,[2] albuterol sulfate,[2] ipratropium bromide,[2] albuterol-ipratropium,[2] acetylcysteine,[3] racemic epinephrine,[3] and levalbuterol[3] and corticosteroids such as budesonide.[3] Patients with respiratory conditions in acute care settings may have particular requirements such as need for invasive mechanical ventilation; the aerosolized medication devices may therefore have unique clinical effectiveness profiles in this population.

Devices used to generate therapeutic aerosols for these patients include metered-dose inhalers (MDIs), slow mist inhalers, dry powder inhalers, jet nebulizers (JNs), ultrasonic nebulizers, and vibrating mesh nebulizers (VMNs), and there are strengths and limitations of each.[2] JNs are the most commonly used nebulizers, and have remained a relatively consistent standard for over 20 years, but JNs require a compressed gas source whereas MDIs and VMNs do not.[1] MDIs require less labour and are less likely to be a source of contamination, however they often require patient coordination and appropriate doses may be more difficult to deliver.[2,4] In contrast, VMNs have been associated with increased labour requirements as compared to JN,[4,5] require cleaning after every dose,[2,4] and have a high upfront investment cost.[4] VMNs however do not require patient coordination, can deliver high doses faster than JN, are quieter,[2,4] lighter and portable,[1,2] and have been associated with lower undelivered drug volumes.[1,6]

The purpose of this report is to retrieve and appraise the evidence for the clinical effectiveness, safety, and cost-effectiveness of VMN as compared to JN and MDI for patients with respiratory conditions in acute care settings. Additionally, this report aims to retrieve and review current evidence-based guidelines regarding effective use of VMN in acute care settings.

Research Questions

1. What is the clinical effectiveness regarding the use of vibrating mesh nebulizers for patients with respiratory conditions in acute care settings?
2. What is the cost-effectiveness regarding the use of vibrating mesh nebulizers for patients with respiratory conditions in acute care settings?
3. What are the evidence-based guidelines relating to the use of vibrating mesh nebulizers?

Key Findings

Evidence of limited quality from three studies was identified on the comparative clinical effectiveness of vibrating mesh nebulizers for patients with respiratory conditions in acute care settings. In the findings presented in this report, vibrating mesh nebulizers were shown to be either more effective or not detectably different than metered-dose inhalers and jet nebulizers. One randomized controlled trial that enrolled a total of 72 patients found asthma patients treated with vibrating mesh nebulizers spent fewer days in intensive care than patients treated with metered-dose inhalers, but there were no differences between groups for days of mechanical ventilation. This RCT did not find any significant difference in the clinical effectiveness of vibrating mesh nebulizers and jet nebulizers for patients with asthma in the emergency department. A retrospective study of 228 patients did not observe statistically significant differences in effectiveness outcomes for vibrating mesh nebulizers compared to metered-dose inhalers. Another retrospective observational study identified that patients treated with vibrating mesh nebulizers experienced significantly lower total albuterol dose, more discharges from hospital, fewer admissions to hospital, and shorter emergency department length of stay compared to patients treated with jet nebulizers. Important context for all identified clinical effectiveness findings was lacking due to an absence of information on adverse event measurement or reporting. Future high-quality studies are required to make conclusions regarding the comparative clinical effectiveness and safety of vibrating mesh nebulizers. No cost-effectiveness evidence or relevant evidence-based guidelines were identified.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Ovid Medline, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was vibrating mesh nebulizers. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and June 13, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed

for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults and pediatric patients with respiratory conditions (e.g., chronic obstructive pulmonary disease) in acute care
Intervention	Vibrating Mesh Nebulizer
Comparator	Metered Dose Inhaler and aero-chamber; standard jet nebulizer (e.g., small, medium, or large volume nebulizers)
Outcomes	Q1: Clinical effectiveness (e.g., function, increased inspiratory lung, symptom control, length of stay, ventilation days, mortality) Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, and guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1.

Critical Appraisal of Individual Studies

One reviewer critically appraised the included primary clinical studies using the Downs and Black checklist,[7] and the economic study included in Appendix 5 using the Drummond checklist.[8] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study was described narratively.

Summary of Evidence

Quantity of Research Available

A total of 272 citations were identified in the literature search. Following screening of titles and abstracts, 258 citations were excluded and 14 potentially relevant studies from the electronic search were retrieved for full-text review. One additional potentially relevant publication was retrieved from the grey literature search for full-text review. Of these 15 potentially relevant articles, six were excluded for not taking place in an acute care setting, four were excluded for lacking clinical effectiveness outcomes, and two were excluded for being narrative reviews. Three publications met the inclusion criteria and were included in this report; these comprised one randomized controlled trial (RCT), and two non-randomized clinical studies that examined the clinical effectiveness of VMN for patients with respiratory conditions requiring nebulization in acute care settings. No cost-effectiveness studies met the inclusion criteria and no relevant guidelines for the use of VMN were identified. Appendix 1 presents the PRISMA[9] flowchart of the study selection.

An additional reference of potential interest is provided in Appendix 5. This financial impact study, published in 2016, compared actual costs, including labour and capital costs, of switching from metered-dose inhalers for ipratropium-albuterol administration to VMN for mechanically ventilated patients in the United States.[5] This study did not incorporate

clinical-effectiveness outcomes into the analysis and was therefore not included in this report.

Summary of Study Characteristics

Study Design and Country of Origin

The three primary clinical studies included in this report consisted of an RCT, and two non-randomized studies.[3,10,11] The RCT was conducted in Egypt, published in 2017, and enrolled 72 patients.[11] The two non-randomized studies were both conducted in the US, and examined clinical-effectiveness outcomes following an institutional switch to VMN from another aerosol generating device.[3,10] One study, from 2018, was a non-randomized intervention,[10] and the other was a retrospective cohort study that was published in 2017 and examined 228 patient records.[3]

Patient Population

The RCT by Moustafa et al. enrolled patients of all ages with a previous asthma diagnosis admitted to the respiratory intensive care unit (ICU) with an acute exacerbation requiring invasive ventilation.[11] Patients that had participated in a research study within the previous six months were excluded.[11]

Dunne and Shortt examined patients of all ages with acute respiratory distress in the emergency department (ED) that were prescribed an initial dose of albuterol.[10] Baseline heart rate averaged approximately 101 beats per minute and baseline respiratory rate averaged approximately 21 breaths per minute.[10]

Dubosky et al. examined mechanically ventilated adult patients prescribed aerosol therapy while excluding patients with tracheostomy, patients that received less than 24 hours of invasive mechanical ventilation, patients that received a combination of aerosol generating device therapy, and patients who were extubated and re-intubated during hospitalization.[3] The median Acute Physiology and Chronic Health Evaluation II (APACHE II) evaluation for the 228 patients was 17 and the discharge diagnoses were comprised of 18% respiratory, 14% cardiac/vascular, 24% neurological, 12% sepsis, and 32% other.[3]

Interventions and Comparators

The RCT compared VMN (Aerogen Solo, Aerogen Ltd, Ireland), MDI with chamber (AeroChamber Vent, Trudell Medical International, Canada), and JN (Oxycare, Ceren Uretim A.S., Turkey).[11] Each aerosol generating device was also examined with and without humidification for a total of six treatment groups in this study. The aerosolized medication was not specified.[11]

Dunne and Shortt examined a JN (VixOne, Westmed, Inc., Tucson, AZ) operated at 8 L/min O_2 from a 50-psi source with a mouthpiece or aerosol mask, compared to a VMN (Aerogen Solo, Aerogen Ltd, Ireland).[10] The VMN with mouthpiece was operated with no added O_2 flow, however a valved-mask was used for patients who were unable to coordinate a mouthpiece treatment as determined by the respiratory therapist (RT). For patients requiring a valved-mask a minimal added O_2 flow was used as per label (1-2 L/min for pediatric patients and 2-6 L/min for adult patients). Both interventions were administered by trained RT staff. Both aerosol-generating devices delivered an initial dose of 0.083% 2.5 mg/3 mL albuterol sulfate solution, and patients were administered higher doses when clinically indicated as determined by the attending physician.[10]

Dubosky et al. compared an MDI (unspecified) with a VMN (AeroNeb Solo, Aerogen Ltd, Ireland). Medications were not pre-specified by the study design; however, they were reported retrospectively.[3] The MDIs delivered a combination of albuterol sulfate and ipratropium bromide to 67% of the examined patients, albuterol alone to 27%, and ipratropium bromide alone to 6%. Medication doses delivered by MDI were not reported. The VMN delivered a combination of albuterol sulfate solution (2.5 mg/0.5 mL) and ipratropium bromide (0.02%) to 43% of the examined patients but was also used to deliver acetylcysteine, racemic epinephrine, budesonide, and levalbuterol in unreported combinations and doses.[3]

Outcomes

Moustafa et al. reported baseline and response clinical parameters of partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), blood oxygen saturation (O_2 SAT%), pH, respiratory rate, and heart rate. This study also reported outcomes of length of ICU stay, mechanical ventilation time, and mortality.[11]

The included non-randomized studies reported outcomes of total albuterol dose,[10] median length of stay,[10] respiratory rate,[10] heart rate,[10] length of ventilation,[3] mortality,[3] incidence of ventilator-associated pneumonia,[3] and number of treatments.[3] Patients examined by Dunne and Shortt[10] were reported as admitted, discharged, or under observation in the Clinical Decision Unit, and rates of admission, discharge, and under-observation were reported; however, the categorization of “under-observation” was not defined clinically, nor was follow-up information reported for these patients.

Summary of Critical Appraisal

Randomized Controlled Trial

The included RCT had some important strengths, including providing patient characteristics, clear patient inclusion criteria and descriptions of the intervention and outcomes, and an outline of statistical methodology.[11] The study did have limitations that introduced substantial uncertainty to the conclusions. The authors did not include information on important aspects of the methodology including randomization, patient recruitment, and the training level of RT staff with the device interventions. The study was also an open-label study and allocation concealment was not mentioned. No information on adverse events and no conflict of interest (COI) statement were provided. The methodology included collection of baseline and post-treatment clinical parameters that were reported narratively without sufficient detail. The lack of a statistical power calculation in this study of 12 patients per treatment group suggested the findings may be prone to Type II error, and the authors acknowledge this possibility. The authors discuss some aspects relevant to external validity in the discussion including effective use of the aerosol generating devices, but it was not clear what aspects might be specific to the Egyptian setting in which the trial was conducted and whether findings are generalizable to the Canadian context.[11]

Non-randomized Studies

As non-randomized, retrospective studies Dunne and Shortt[10] and Dubosky et al.[3] had potential selection and measurement bias due to study design however Dunne and Shortt attempted to minimize the potential for data dredging by not conducting ad-hoc retrospective chart review.[10] Treatment groups were also separated temporally in both studies introducing potential chronological bias where confounding factors can arise over time.[3,10] While neither study provided a statistical power calculation both had larger patient

sample sizes of 1,594[10] and 228[3] patients than did Moustafa et al. who studied 12 patients in six treatment groups each.[11] Both non-randomized studies were industry-sponsored as described in the provided COI statements. Neither study provided any information on adverse events.[3,10] These studies did not define a patient population with a specific indication and such broad inclusion criteria may overlook important clinical efficacy results for particular patient subgroups.[3,10] Dubosky et al. had broad inclusion criteria that limited the internal validity in that patients were treated with different medications between groups, and doses for all medications were not specified.[3] Dunne and Shortt reported an outcome of "under observation" where patients were further evaluated, however no follow-up information on the outcome was provided, the outcome was not sufficiently defined, and its impact on the outcomes of admitted frequency, discharged frequency, and length of stay were not clear.[10] Common strengths of the non-randomized study evidence included clearly stated (although broad) patient inclusion criteria, a description of appropriate statistical methods, and reported patient characteristics of the treatment groups.[3,10] Dunne and Shortt also provided a clear description of the intervention, mentioned device training for RT staff, and accounted for confounding in the analysis.[10]

A tabulated summary of the strengths and limitations of the included publications is provided in Appendix 3.

Summary of Findings

Clinical Effectiveness of Vibrating Mesh Nebulizers

Appendix 4 presents a table of the main study findings and authors' conclusions.

The RCT studied six different treatment arms of 12 patients each that examined three aerosol generating devices each operated either dry or humidified.[11] Two statistically significant differences were observed. Patients treated with dry VMN had fewer ICU days than dry MDI patients, and, when both humidity conditions were pooled together, all VMN patients had fewer ICU days than all MDI patients. The authors also reported non-quantitatively that there was no significant impact on measured clinical response parameters (i.e., pO_2, pCO_2, O_2 SAT%, pH, respiratory rate, and heart rate) and no mortalities were observed in any of the treatment arms. The authors acknowledged the small patient sample size and recommended increasing the number of patients in future studies to confirm these clinical effectiveness findings.[11]

Evidence from non-randomized studies came from two retrospective comparative studies. Dunne and Shortt observed that in comparison to JN, VMN resulted in fewer ED admissions, more ED discharges, and a shorter length-of-stay in the ED.[10] About 15% of both JN and VMN patients were neither admitted to nor discharged from the ED, and were reported as "under-observation"; however, this outcome was not defined and how it contributed to ED length-of-stay was unclear. When broken down into age categories, VMN patients aged 19 to 50 years and 51 years or more experienced less admissions than similarly-aged JN patients. Additionally, for patients aged greater than 50 years, more discharges were observed for patients treated with VMN than those treated with JN. Differences for other patient age groups were not statistically significant. A greater proportion of patients who were treated with VMN had a lower total dose of albuterol (2.5 mg) as compared to JN patients, a greater proportion of whom received a higher total dose of albuterol (7.5 mg). In addition, 23.4% of JN patients received a total dose of 7.5 mg or greater while no VMN patients received such high total doses.

Dubosky et al. did not observe any statistically significant differences between MDI and VMN devices in outcomes of ventilation time, number of treatments, incidence of ventilator-associated pneumonia (VAP), or in-hospital mortality.[3] Dubosky et al. acknowledged the possibility that the study was underpowered with 48 patients in the MDI and 180patients in the VMN treatment groups. None of the identified studies had any information on the occurrence or methodology to report adverse event outcomes.

Cost-Effectiveness of Vibrating Mesh Nebulizer

No cost-effectiveness evidence was identified. One financial impact study was identified; this study did not meet the inclusion criteria for the present report, since it only considered costs, independent of the relationship with effectiveness. This study is described in Appendix 5.

Guidelines

No relevant evidence-based guidelines were identified; therefore, no summary can be provided.

Limitations

Collectively the evidence identified for this report was of insufficient quantity and quality to make conclusions regarding the comparative clinical effectiveness of vibrating mesh nebulizers. No evidence specific to pediatric patients or patients with COPD was identified. The RCT was conducted in Egypt and the applicability to the Canadian health care system was unclear. The degree of independence was unclear as two of the included studies were industry-sponsored and one lacked a conflict of interest statement. No cost-effectiveness evidence or evidence-based guidelines were identified.

Conclusions and Implications for Decision or Policy Making

One RCT and two non-randomized primary clinical studies that evaluated the clinical effectiveness of VMN for patients with respiratory conditions in acute care settings were identified.[3,10,11] To compare VMN and MDI, the RCT[11] examined patients with an asthma diagnosis and one non-randomized retrospective study[3] examined all adult patients with an order for aerosol therapy with mechanical ventilation. To compare VMN and JN, the RCT[11] examined patients with an asthma diagnosis and the other non-randomized retrospective study[10] examined adult and pediatric patients prescribed albuterol for acute respiratory distress in the ED.

The RCT found that patients treated with VMN (dry or humidified) experienced fewer ICU days than patients treated with MDI (dry or humidified), and VMN delivered without humidification also resulted in fewer ICU days than MDI delivered without humidification. For the primary outcome of mechanical ventilation days, there were no significant differences between VMN and MDI.[11] One retrospective comparative study did not find any statistically significant differences between VMN and MDI for similar outcomes (i.e., days of ventilation, in-hospital mortality, number of treatments, and incidence of VAP).[3] This study did not have a consistent intervention limiting the ability to attribute the lack of clinical effectiveness difference to VMN or MDI in isolation.[3] The authors of both studies acknowledged that larger prospective studies are required to examine the comparative clinical effectiveness of VMNs and MDIs for patients in acute care settings.[3,11]

The RCT and one retrospective study examined the comparative clinical effectiveness of VMN versus JN in the ED. In the RCT, no significant differences between VMN and JN were identified for the clinical effectiveness outcomes examined (i.e., length of ICU stay, length of mechanical ventilation, or mortality).[11] The retrospective study reported significantly lower total dose of albuterol, fewer admissions, more discharges, and shorter ED length-of-stay, in patients treated with VMN compared with those treated with JN.[10] Again the authors of both studies reported that future studies are required to confirm and extend these findings.[10,11] Moreover, the authors of the retrospective study acknowledged that a more clearly defined patient population in future randomized controlled trials might improve clinical efficacy evidence for different patient populations.[10]

None of the identified studies reported any adverse event information or device reliability data (e.g., device malfunctions, time spent monitoring) and therefore important context for some clinical effectiveness outcomes was lacking.[3,10,11]

No cost-effectiveness evidence or evidence-based guidelines were identified.

This report identified limited quality evidence on the comparative clinical effectiveness of VMN as compared to MDI and JN devices for patients with respiratory conditions in acute care settings. Further high-quality research is required to definitively demonstrate comparative clinical effectiveness of VMN, JN, and MDI.

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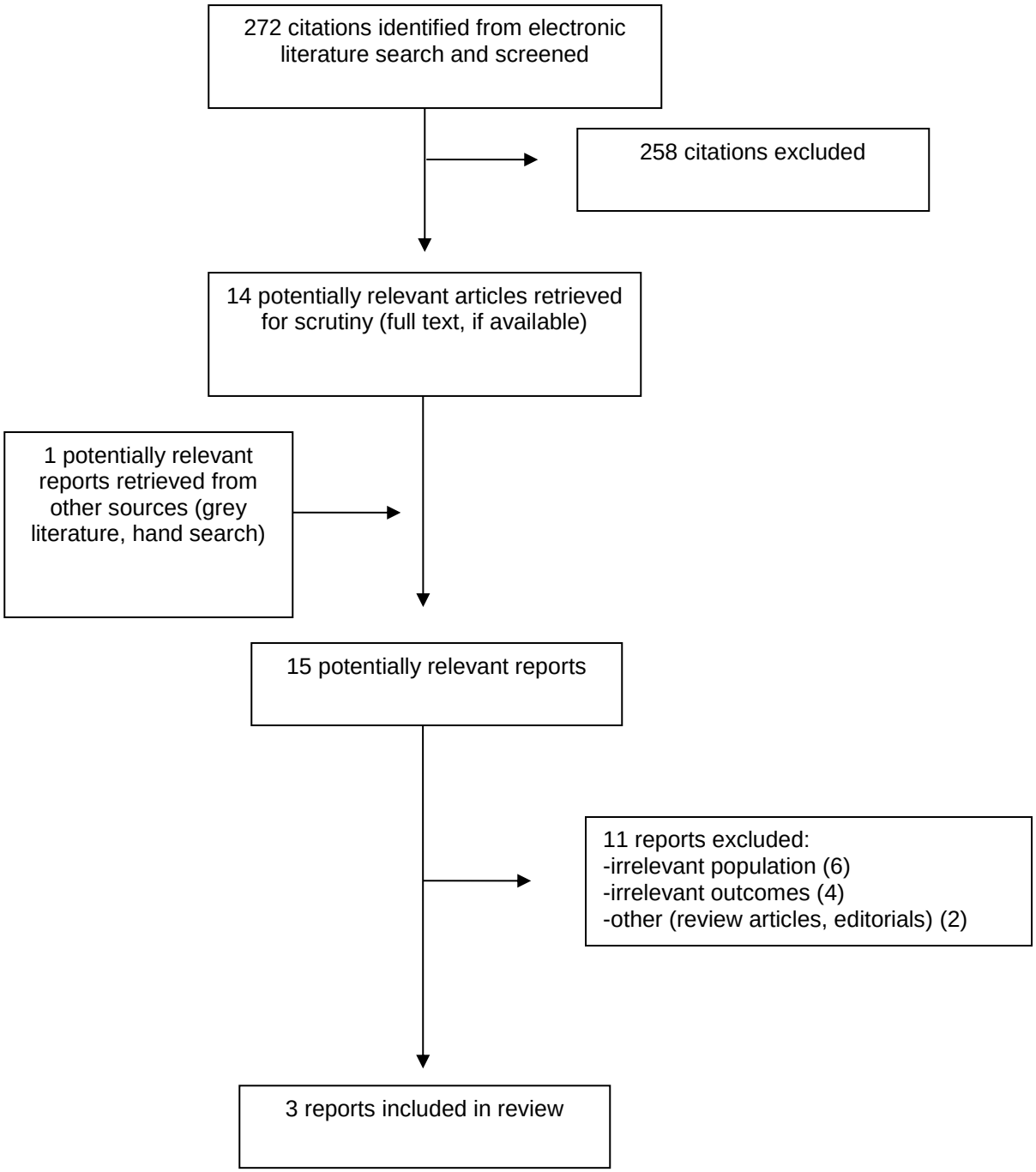
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trial				
Moustafa et al. 2017, [11] **Egypt**	RCT (n = 72)	Patients with previous asthma diagnosis that had been admitted to respiratory intensive care unit with acute exacerbation receiving invasive ventilation. Exclusions were patients that had taken part in research study during previous 6 months.	VMN (Aerogen Solo, Aerogen Ltd, Ireland) w/ humidification (n = 12) VMN (Aerogen Solo, Aerogen Ltd, Ireland) w/o humidification (n = 12) MDI w/ vent (AeroChamber Vent, Trudell Medical International, Canada) w/ humidification (n = 12) MDI w/ vent (AeroChamber Vent, Trudell Medical International, Canada) w/o humification (n = 12) JN (Oxycare, Ceren Uretim A.S. Turkey) w/ humidification (n = 12) JN (Oxycare, Ceren Uretim A.S. Turkey) w/o humification (n = 12)	● Clinical Response parameters included: pO_2, pCO_2, O_2 SAT%, pH, respiratory rate, and heart rate. ● Length of ICU stay ● Mechanical ventilation time ● Mortality
Non-randomized Studies				
Dunne and Shortt 2018,[10] **US**	Non-randomized intervention; Comparative Study using chronological patient groups (n = 1,594)	Adults and pediatric patients prescribed albuterol (initial dose 0.083% 2.5mg/3mL solution) for acute respiratory distress in the ED and administered higher dose if clinically indicated as determined by attending physician.	JN (VixOne, Westmed, Inc., Tucson, AZ) (n=879), operated at 8L/min O_2 VMN (Aerogen Solo with valved adapter (Aerogen Ltd., Galway, Ireland) (n=715) operated at 1-2L/min for pediatric patients and 2-6L/min for adults	● Admission Rate ● Discharge Rate ● Under Observation Rate ● Total albuterol dose ● Median length of stay ● Heart rate ● Respiratory rate

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Baseline patient data: Heart rate: approximately 101 beats per minute Respiratory rate: approximately 21 breaths per minute	Both administered by trained RT staff	
Dubosky et al. 2017,[3] **US**	Retrospective Study examining MDI and VMN at different times following implementation of VMN in acute care (n = 228)	Adult patients with an order for aerosol therapy with mechanical ventilation Exclusions were patients with tracheostomy, required < 24 hours of invasive mechanical ventilation, patients who received a combination of MDI and VMN, and patients who were extubated and re-intubated during hospitalization APACHE II evaluation median approximately 17 Discharge diagnoses: 18% respiratory 14% cardiac/vascular 24% neurological 12% sepsis 32% other.	VMN – 1 year of data post-implementation (n = 180) MDI – 1 year of data prior to VMN implementation (n = 48)	● Ventilation length ● Mortality (in-hospital) ● Incidence of VAP ● Number of treatments

AZ = Arizona; ED = Emergency Department; JN = jet nebulizer; MDI = metered-dose inhaler; O_2 SAT%= blood oxygen saturation; pCO_2 = partial pressure of carbon dioxide; pO_2 = partial pressure of oxygen; RCT = randomized controlled trial; RT = Respiratory Therapist; VMN = vibrating mesh nebulizer; w/ = with; w/o = without.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Clinical Studies using Downs and Black Checklist[7]

Strengths	Limitations
Randomized Controlled Trial	
Moustafa, 2017[11]	
• Patient characteristics provided, and groups were reasonably similar • Clear patient inclusion criteria • Statistical methods described • Clear description of intervention and outcomes	• Randomization not described • No patient recruitment data reported • Single center study • No allocation concealment methodology • Open-label study • Small study (n = 12 per group) • No statistical power calculation • No COI provided • No data or methods for adverse event data • Training not included in methodology • Clinical Response outcomes (and baseline data) not reported
Non-randomized Studies	
Dunne, 2018[10]	
• Patient characteristics provided, and groups were similar (although statistical differences were found between the large samples) • Prospectively identified data set • Clear patient inclusion criteria • Analysis accounted for confounding • RT staff received intervention training • Statistical methods described • Clear description of intervention	• Single center study • Chronologically separate treatment groups • Open-label study • No subgroup analysis for indications • Industry sponsored study • No data or methods for adverse event data • No statistical power calculation • Outcomes of “under observation” not sufficiently described • While patient inclusion criteria were clear they were very broad
Dubosky, 2017[3]	
• Patient characteristics provided, and groups were reasonably similar • Clear patient inclusion criteria • Statistical methods described • Clear description of outcomes	• Single center study • Chronologically separate treatment groups • Open-label study • Industry sponsored study • No data or methods for adverse event data • No statistical power calculation • Training not included in methodology • Unclear variation in administration of intervention • While patient inclusion criteria were clear they were very broad

COI = conflict of interest; RT = respiratory therapist.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 5: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized Controlled Trial	
Moustafa, 2017[11]	
MV-days Dry and Humid delivery (mean (SD)), *P* = NS JN 5.71 (1.27) VMN 5.67 (0.96) MDI-AV 5.92 (1.25) **ICU-days Dry and Humid delivery (mean (SD)), *P* = NS** JN 8.50 (2.17) VMN 7.75 (2.23)* MDI-AV 9.17 (2.57)* **P* = 0.039 **MV-days all aerosol generators (mean (SD)), *P* = NS** Dry 5.97 (1.18) Humid 5.56 (1.11) **ICU-days all aerosol generators (mean (SD)), *P* = NS** Dry 8.64 (1.18) Humid 8.31 (2.03) **MV-days (mean (SD)), *P* = NS** JN - Humid 6.0 (1.5) JN - Dry 5.4 (1.0) VMN - Humid 5.8 (1.0) VMN - Dry 5.6 (1.0) MDI-AV - Humid 6.2 (1.1) MDI-AV - Dry 5.7 (1.4) **ICU-days (mean (SD)), *P* = NS** JN - Humid 8.7 (2.5) JN - Dry 8.3 (1.9) VMN - Humid 7.6 (2.5) VMN - Dry 7.9 (2.0)* MDI-AV - Humid 9.7 (2.8) MDI-AV - Dry 8.7 (2.3)* **P* = 0.034 compared to MDI-AV There were no mortalities observed during this study. Neither aerosol generator type nor humidification had a significant impact on the measured clinical response parameters (**pO_2**, **pCO_2**, **O_2 SAT%**, **pH**, **respiratory rate**, and **heart rate**).	"The use of VMN to deliver aerosol to ventilated patient resulted in a trend toward decreased ICU-days compared to JN and MDI-AV. We recommend increasing the number of patients studied to confirm and possibly extend these findings." (p. 45) "No significant effect on patients' clinical status was found in this study from changing humidity during aerosol delivery to ventilated patient. Hence we discourage the practice of turning off the humidifier during aerosol delivery, which might be forgotten in the off position." (p. 45)
Non-randomized Studies	
Dunne, 2018[10]	
Admit to ED - All Ages (% (95% CI)), *P* < 0.05 JN 41.4 (38.2 to 44.7) VMN 28.1 (24.8 to 31.4)	"When compared to the JN, the VMN was associated with increase discharge rate to home, fewer admissions to the hospital from the ED and shorter LOS in the ED with a

Table 5: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Discharge - All Ages (% (95% CI)), *P* < 0.05 JN 43.0 (39.7 to 46.3) VMN 56.1 (52.4 to 59.7) **Under Observation to Clinical Decision Unit – All Ages (% (95% CI)), *P* = NS** JN 15.6 (13.2 to 18.0) VMN 15.8 (13.1 to 18.5) **Frequencies of Total Doses of Albuterol (%)** 2.5 mg, *P* < 0.05 JN 47.9 VMN 85.5 5.0 mg, *P* < 0.05 JN 28.8 VMN 14.5 ≥7.5 mg, *P* = NA* JN 23.4 VMN 0.0 * Ten patients in JN group received doses of albuterol up to 400mg and were not included in this analysis as precise dose was not available **LOS ED - All Ages (hours), *P* = 0.0001** JN 4.8 VMN 4.2 **Heart Rate increased in VMN group and decreased in JN group. No difference in respiratory rate was observed between groups. Statistics on these outcomes were not clearly reported.**	substantial reduction in total albuterol dose required." (p. 645) "Future randomized controlled studies are required to determine the undiluted effect of device type on sub populations of patients with primary respiratory disease such as asthma and COPD, and for prospective cost data collection." (p. 645)
Dubosky, 2017[3]	
Days receiving ventilation (median (IQR)), *P* = 0.14 MDI 5 (3, 8.5) VMN 6 (4, 10) **In-hospital mortality (n/N (%)), *P* > 0.99** MDI 16/48 (33%) VMN 60/180 (33%) **Incidence of VAP (n/N (%)), *P* = 0.72** MDI 3/48 (6%) VMN 9/180 (5%) **Total number of treatments (median (IQR)), *P* = 0.14** MDI 9.5 (4, 20) VMN 7 (3, 16)	"We found no association between an MDI or vibrating mesh nebulizer and our primary outcomes, days receiving ventilation, in-hospital mortality, or VAP, in mechanically ventilated subjects." (p. 391) "Our study might be underpowered for the outcomes of interest. Following exclusions, there were <50 subjects in the MDI group. The odds ratio for VAP was 2.89, which might be clinically important, but it is not significant, probably due to the small number of subjects who received the MDI." (p. 395)

CI = confidence interval; ED = emergency room; ICU = intensive care unit; IQR = interquartile range; JN = jet nebulizer; LOS = length of stay; MDI = metered-dose inhaler; MDI-AV = metered-dose inhaler with AeroChamber Vent; MV = mechanical ventilation; NA = not applicable; NS = not significant; SD = standard deviation; VAP = ventilator-associated pneumonia; VMN = vibrating mesh nebulizer.

Appendix 5: Additional References of Potential Interest

Loborec et al. conducted a financial impact study of an institutional switch from MDI to VMN in the US in 2016.[5] The authors did not include any clinical effectiveness data in their analysis and therefore this study was excluded from this report. The following three tables describe the characteristics of this study, its strengths and limitations, and its findings.

Table 6: Characteristics of Included Economic Evaluation

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Loborec,[5] 2016, USA	Financial impact study, same 3 month period one year apart, provider perspective	Evaluate financial impact of formulary substitution including associated labour costs	Patients receiving mechanical ventilation (excluding ED) of ipratropium-albuterol administered by an RT	VMN (n = 5,472 RT encounters) vs. MDI (n = 5,075 RT encounters) administration of ipratropium-albuterol	Financial impact study No consideration of clinical efficacy	All respiratory medication RT staff costs VMN capital investment Data for patient-specific spacers not readily available	3 month period was representative of a year No clinical effectiveness data were examined

MDI = metered-dose inhaler; RT = respiratory therapist; VMN = vibrating mesh nebulizer.

Table 7: Strengths and Limitations of Economic Studies using the Drummond Checklist[8]

Strengths	Limitations
Loborec, 2016[5]	
• Research objective clearly stated • Importance established • Alternatives and rationales described • Type of analysis justified • Methods clearly described • Included labour costs • Examined prescription changes between groups • Compliance reported • Conclusions consistent with results • A discussion of study limitations provided • Statement of no conflict of interest	• No clinical effectiveness outcomes incorporated into analysis • Patient group characteristics not detailed • Analysis did not include indication data • Analysis of depreciation of capital investment and/or replacement costs, and life expectancy not provided

Table 8: Summary of Findings of Included Economic Evaluation

Main Study Findings	Authors' Conclusion
Loborec, 2016[5]	
Pharmacy Expenditures - Ipratropium-albuterol MDI (US$)/RT encounters in 3 months Before Exclusive VMN (3 months) $141,588/796 After Exclusive VMN (3 months) $1,205/0 **Pharmacy Expenditures - Ipratropium-albuterol nebulization solution (US$)/RT encounters in 3 months** Before Exclusive VMN (3 months) $3,485/1,003 After Exclusive VMN (3 months) $5,935/1,315 **Labour Costs (US$)** RT workload increase estimate 3.9 hours RT costs (1 FTE hired with benefits) $77,000/year **VMN Technology Capital Expenditures (US$)** Initial investment (150 controllers) $111,130 VMN patient specific kits (124/month) $62,496/year JN patient specific kits (124/month) $788/year **Total Savings (US$)** Extrapolated costs first year $146,806 Extrapolate costs subsequent years $257,936	"An automatic substitution of ipratropium–albuterol nebulization solution for MDIs resulted in a three month savings of $99,359 in drug cost and an extrapolated full-year savings of $397,436. When additional costs associated with the substitution were taken into account, there was an overall savings of $146,806 during the implementation year and a projected savings of $257,936 for each following year." (p. 125) "Compared with jet nebulizers, the previous standard of care in the health system, the VMN device reduces the amount of wasted medication (because there is a smaller residual volume after administration), operates more quietly, and delivers up to four times more medication to the lungs." (p. 122)

FTE = full-time equivalent; JN = jet nebulizer; RT = respiratory therapist; VMN = vibrating mesh nebulizer.