Comparative Effectiveness Review
Number 68

Effective Health Care Program

Noninvasive Positive-Pressure Ventilation (NPPV) for Acute Respiratory Failure

Executive Summary

Background

Acute respiratory failure is a life-threatening condition characterized by an inability to maintain normal levels of oxygen and/or carbon dioxide gas exchange due to dysfunction of the respiratory system. In its most basic sense, the respiratory system comprises a gas exchanging organ (lung) and a ventilatory pump (respiratory muscles and controllers, chest wall). Respiratory failure is classified based on failure of one or both of these elements, as well as the timing of such failure. Acute respiratory failure develops over minutes to several days. Respiratory failure is deemed chronic when derangements occur over several days or longer. Acute-on-chronic respiratory failure occurs when a patient with chronic respiratory failure suffers an acute deterioration in gas exchange; this is most commonly seen in patients with severe chronic obstructive pulmonary disease (COPD).

The epidemiology of acute respiratory failure is not fully known. In the United States, millions of patients are admitted to the intensive care unit (ICU) each year, and acute respiratory failure is the most common cause.[1] Acute respiratory failure is severe enough to require life support with invasive mechanical ventilation for approximately 800,000 Americans a year, a high proportion of whom do not survive the episode.[2] Epidemiological studies have estimated the annual incidence of acute respiratory failure to be between 77.6 and 430 patients per 100,000.[1,3-5] The estimated

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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health care costs related to critical care are approximately 0.7 percent of the annual gross domestic product, and the human and financial costs are only expected to increase with an aging population.[6-9]

Supplemental oxygen is a mainstay of therapy for acute respiratory failure. In severe cases, acute respiratory failure requires respiratory support with invasive mechanical ventilation. Invasive ventilation (also known as conventional mechanical ventilation) is a form of life support in which positive pressure delivers a mixture of air and oxygen through an endotracheal or tracheostomy tube to central airways, which then flows distally to the alveoli. Despite the benefits of invasive ventilation in patients with respiratory failure, up to 40 percent of such patients die in the hospital; some of these deaths are directly attributable to the complications of invasive ventilation and artificial airways.[10-13] In addition, many survivors of acute respiratory failure require prolonged invasive ventilation and suffer persistent decrements in quality of life and functional independence.[14-16]

An increasingly recognized option in the management of selected cases of acute respiratory failure is to employ noninvasive positive-pressure ventilation (NPPV). NPPV refers to a form of mechanical support in which positive pressure delivers a mixture of air and oxygen throughout the respiratory tree via a noninvasive interface. Patient-ventilator interfaces for NPPV include a face mask, nasal mask or plugs, or a helmet that covers the head. NPPV collectively includes several modalities of noninvasive ventilation, which can be delivered via a standard ICU ventilator or a portable device. Continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP) are the two most commonly used modes of NPPV. CPAP is applied throughout the respiratory cycle of a spontaneously breathing patient and is physiologically identical to constant positive end-expiratory pressure. BPAP delivers two pressure levels according to the respiratory cycle and improves ventilation, oxygenation, and alveolar recruitment. BPAP provides both an inspiratory positive airway pressure and a continuous expiratory positive airway pressure, and the difference between these reflects the volume of air displaced with each breath. NPPV can provide modes nearly identical to standard ICU ventilators, such as pressure, volume, assist control, or even proportional assist ventilation.

The use of NPPV for support during the treatment of respiratory failure is attractive because it does not require either endotracheal intubation or moderate and/or deep sedation and can be safely initiated or discontinued as needed. It is also associated with few of the nosocomial complications recognized with endotracheal intubation, such as ventilator-associated pneumonia, critical illness-associated weakness, pneumothorax, delirium, and infections associated with the invasive monitoring typically required during invasive life support.[11,14] NPPV is not appropriate for some patients, such as those with cardiopulmonary arrest or shock, where greater airway control is required, or those with facial trauma, where the interface (e.g., mask) cannot be used appropriately.

NPPV has been evaluated in a large number of trials, often with clinically important benefits, but use of NPPV remains highly variable across institutions and geographical regions.[17-21] Surveys in the United States have shown high variability in estimated use across hospitals.[21] Barriers to use include a lack of physician knowledge, low rates of perceived efficacy, lack of standard protocols and team-based care at some hospitals, and, among older clinicians, little training or experience with NPPV.[22] A specific knowledge gap is uncertainty about the efficacy of NPPV for patients with acute respiratory failure for conditions other than COPD or acute cardiogenic pulmonary edema (ACPE). In addition, NPPV is a resource-intensive modality and requires a substantial amount of training and experience to implement successfully. As a result, some experts have questioned whether the benefits of NPPV seen in highly specialized settings are replicated in routine practice.

Objectives

The literature supporting the use of NPPV for respiratory failure in the acute-care setting has evolved over the last two decades.[12] Although there have been some exceptions, such as a 2010 meta-analysis examining NPPV in acute respiratory failure of multiple causes,[23] the use of NPPV has been most extensively studied in patients with acute respiratory failure due to COPD and congestive heart failure. In addition to these two well-studied uses, there is increasing interest in determining if NPPV is beneficial for other causes of acute respiratory failure (e.g., asthma) or can shorten the duration of invasive mechanical ventilation, either as a method to facilitate early extubation or to prevent extubation failure in high-risk groups.[23] Further, there is uncertainty about whether the beneficial effects demonstrated in randomized controlled trials (RCTs) are replicated in real-world settings where training, experience, organizational factors, and patient factors may differ substantially. Additionally, it is uncertain whether the effects of NPPV vary by clinician experience and

training, the use of protocols, the setting in which NPPV initiation is applied, or by specific patient characteristics.

This comparative effectiveness review (CER) was commissioned by the Agency for Healthcare Research and Quality (AHRQ) to evaluate the evidence for NPPV versus other typical treatments for acute respiratory failure. We conducted a systematic review that is inclusive of all major causes of acute respiratory failure and includes studies of NPPV used for weaning from invasive ventilation. We anticipate that clinicians involved in medical and surgical critical care medicine, emergency medicine, and anesthesiology, along with developers of clinical practice guidelines, will be the primary audience for this report.

We constructed Key Questions (KQs) using the general approach of specifying the population of interest, the interventions, comparators, outcomes, timing of outcomes, and settings. The KQs considered in this CER are:

KQ 1: Is noninvasive positive-pressure ventilation (NPPV) associated with less morbidity (including from intubation), lower mortality, fewer adverse events, or lower medical utilization when compared with supportive medical therapy or invasive ventilation:

a. In adults with chronic obstructive pulmonary disease (COPD) and acute respiratory failure?

b. In adults with acute cardiogenic pulmonary edema (ACPE)?

c. In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?

d. In adults with acute respiratory failure in selective settings including: postoperative setting and post-transplant setting?

KQ 2: Is NPPV with bilevel positive airway pressure (BPAP), compared with NPPV with continuous positive airway pressure (CPAP), associated with less morbidity, lower mortality, fewer adverse events, or lower medical utilization:

a. In adults with COPD and acute respiratory failure?

b. In adults with ACPE?

c. In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?

d. In adults with acute respiratory failure in selective settings including: postoperative setting and post-transplant setting?

KQ 3: Is early extubation to NPPV, compared with usual care, associated with less morbidity, lower mortality, fewer adverse events, or lower medical utilization:

a. In adults with COPD and acute respiratory failure?

b. In adults with ACPE?

c. In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?

d. In adults with acute respiratory failure in selective settings including: postoperative setting and post-transplant setting?

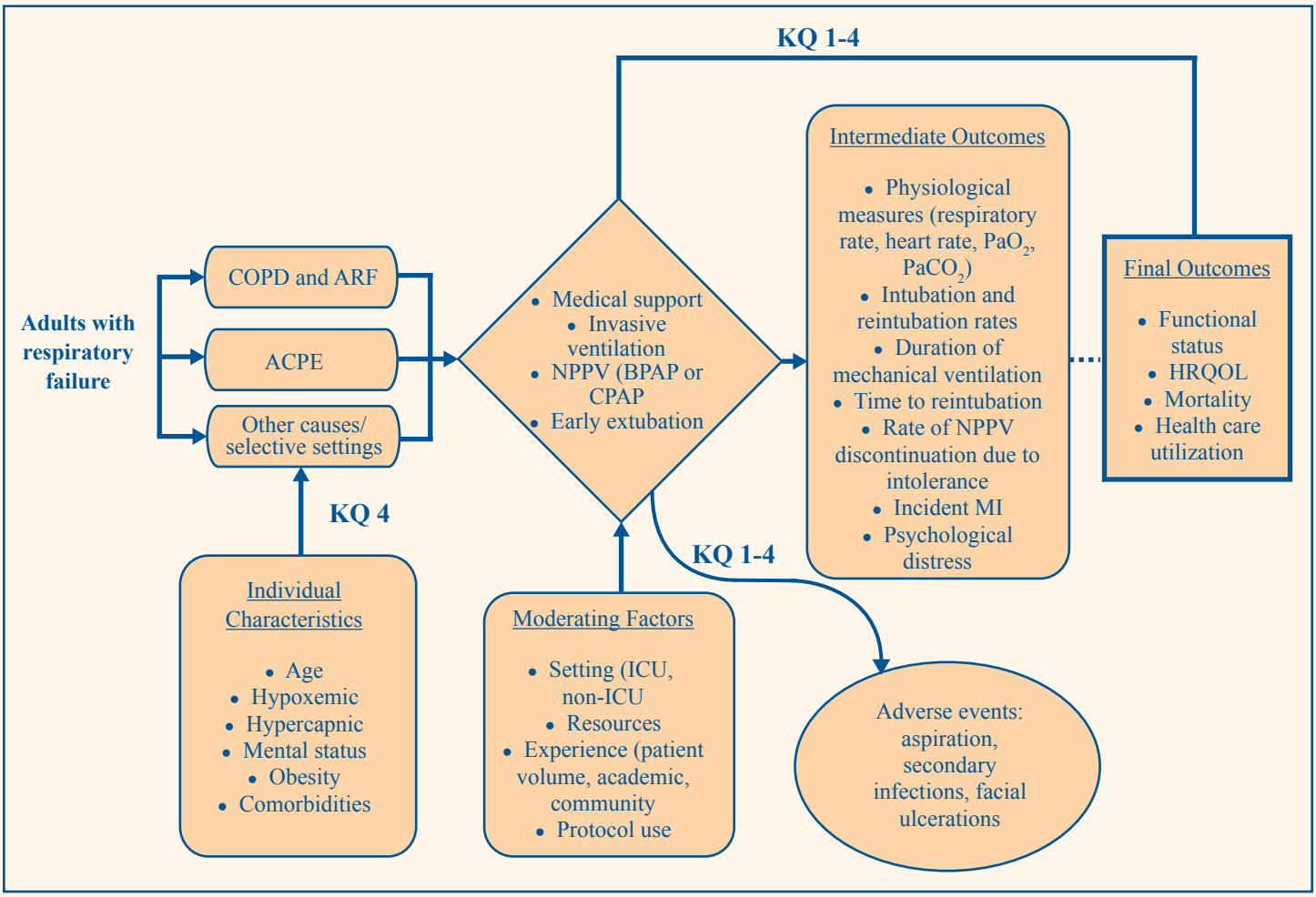
KQ 4: For KQs 1–3, do the effectiveness and risks of NPPV vary by setting and associated resources, experience and training of clinicians, and use of protocols or by patient characteristics (e.g., morbid obesity, mental-status changes, overall disease burden)?

Analytic Framework

Figure A shows the analytic framework for this project.

In general, the figure shows that this CER compares morbidity, mortality, adverse events, and health care utilization for patients receiving NPPV with supportive medical therapy or invasive ventilation (KQ 1), patients receiving NPPV with BPAP with NPPV with CPAP (KQ 2), and patients receiving early extubation to NPPV with those receiving weaning strategies that do not utilize NPPV (KQ 3). Subgroups considered for KQs 1–3 included adults with COPD and respiratory failure; adults with ACPE; adults with acute respiratory failure due to pneumonia, asthma, obesity-hypoventilation syndrome, or interstitial lung disease; and adults with acute respiratory failure in postoperative or post-transplant settings. Adverse events considered are aspiration, secondary infections (including pneumonia and sinusitis), and facial ulcerations. Intermediate outcomes included physiological measures (respiratory rate, heart rate, partial pressure of oxygen in arterial blood [PaO_2], and partial pressure of carbon dioxide in blood [$PaCO_2$]); intubation and reintubation rates; duration of mechanical ventilation; time to reintubation; rate of NPPV discontinuation due to intolerance; incident myocardial infarction; and psychological distress. Final outcomes assessed are functional status, health-related quality of

Figure A. Analytic framework



ACPE = acute cardiogenic pulmonary edema; ARF = acute respiratory failure; BPAP = bilevel positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; HRQOL = health-related quality of life; ICU = intensive care unit; KQ = Key Question; MI = myocardial infarction; NPPV = noninvasive positive-pressure ventilation; $PaCO_2$ = partial pressure of carbon dioxide in blood; PaO_2 = partial pressure of oxygen in arterial blood

life, mortality (in-hospital and 30-day), and health care utilization (ventilator-dependent days, rate of ventilator dependence at hospital discharge, length of hospital stay, length of intensive care unit stay, and total hospital costs). The report also considers whether the effectiveness and risks outlined in KQs 1–3 vary by setting and associated resources, experience and training of the clinicians, use of protocols, or by patient characteristics (e.g., mental status, obesity, and comorbidities).

Methods

Input From Stakeholders

The methods for this CER follow those suggested in the ARHQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter referred to as the Methods Guide).[24] During the topic refinement stage, we solicited input from a group of Key Informants (KIs) representing medical professional societies/clinicians in the areas of pulmonology, critical/intensive care, and respiratory therapy; scientific experts; payers; and Federal agencies to help define the KQs. These KQs were posted on AHRQ's Web site for public comment for 4 weeks, beginning in late December 2010. The comments received were considered in the revision of the KQs and in the development of the research protocol. We next convened a Technical Expert Panel (TEP) to provide input on defining populations, interventions, comparisons, and outcomes, as well as for identifying particular studies or databases to search. The TEP members provided the same range of viewpoints and expertise as are described for the KI group, with the addition of a methodologist with experience in trial efficacy-effectiveness assessment. The KIs and members of the TEP were required to disclose

any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Any potential conflicts of interest were balanced or mitigated. KIs and members of the TEP did not perform analyses of any kind or contribute to the writing of the report. All methods and analyses were guided by the protocol; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[25]

Data Sources and Selection

We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews to identify relevant published literature. Our search strategies used the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature and text words for NPPV and eligible study designs. We used validated search filters for randomized study designs where possible (the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version [2008 revision] in PubMed, and the Cochrane search filter for identifying randomized trials in Embase[26]). We included studies conducted in adults and published in English from 1990 through our final search date of January 31, 2012. We limited studies to 1990 forward because standards of care have changed significantly since 1990. All searches were designed and conducted in collaboration with an experienced search librarian.

We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles.[23,27-46] All citations were imported into an electronic bibliographic database (EndNote® Version X4; Thomson Reuters, Philadelphia, PA). As a mechanism to ascertain publication bias, we searched ClinicalTrials.gov to identify completed but unpublished studies.

We used two approaches to identifying relevant grey literature: (1) a request for scientific information packets submitted to device manufacturers; and (2) a request submitted to the U.S. Food and Drug Administration for any unpublished RCT data available for devices used to provide noninvasive positive-pressure ventilation.

Using the criteria described in Table A, two investigators independently reviewed each title and abstract for potential relevance to the Key Questions; articles included by either investigator underwent full-text screening. At the full-text screening stage, two investigators independently reviewed the full text of each article and indicated a decision to "include" or "exclude" the article for data abstraction. When the paired reviewers arrived at different decisions about whether to include or exclude an article, or about the reason for exclusion, we reached a final agreement through review and discussion among investigators. Articles meeting eligibility criteria were included for data abstraction.

Table A. Inclusion/exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	Adults (age ≥ 18 years) with: • COPD and acute respiratory failure • ACPE • Acute respiratory failure due to other causes, including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease • Acute respiratory failure in selective settings including: postoperative setting and post-transplant setting	• Population composed entirely of children (< 18 years of age) • Adult populations where NPPV is contraindicated, such as cardiopulmonary arrest, shock, and facial trauma
Interventions	• NPPV including CPAP, BPAP, and closely related noninvasive positive airway pressure modes delivered through any interface (e.g., face mask, nasal mask or plugs, or a helmet that covers the head)	• Invasive ventilation only

Table A. Inclusion/exclusion criteria (continued)		
Study Characteristic	**Inclusion Criteria**	**Exclusion Criteria**
Comparators	KQs 1, 2, and 4: • Supportive care, invasive ventilation, or another form of NPPV KQ 3: • Any approach to weaning that does not utilize NPPV	• No comparator
Outcomes	A clinical or utilization-related outcome of interest, including: • Intermediate outcomes: – Physiological measures such as respiratory rate, heart rate, PaO_2, and $PaCO_2$ (KQs 1–3) – Intubation (KQs 1, 2, 4) and reintubation (KQs 3, 4) rates; duration of mechanical ventilation (KQs 1–4); and time to reintubation (KQ 3) – Rates of discontinuing NPPV secondary to the patient being unable to tolerate the treatment (KQs 1–4) – Incident myocardial infarction (KQs 1–3) – Psychological distress (e.g., anxiety) assessed by using a validated measure • Final outcomes: – Functional status measured by using a validated questionnaire or performance-based measure at hospital discharge or the 30-day followup (KQs 1, 3, 4) – Health-related quality of life measured using a validated questionnaire at hospital discharge or the 30-day followup (KQs 1, 3, 4) – In-hospital and 30-day mortality rates (KQs 1–3) – Medical utilization (KQs 1–4), including ventilator-dependent days, rate of ventilator dependence at hospital discharge, length of hospital stay, length of ICU stay, and total hospital costs • Adverse events (KQs 1–4), including rates of: – Aspiration – Secondary infections (including pneumonia, sinusitis) – Facial ulcerations	• No relevant clinical or utilization-related outcome of interest reported (note that studies reporting only physiological measures such as respiratory rate, heart rate, PaO_2, and $PaCO_2$ were excluded)

Table A. Inclusion/exclusion criteria (continued)		
Study Characteristic	**Inclusion Criteria**	**Exclusion Criteria**
Timing	• Studies of any duration	• None
Setting	Hospital settings, including: • ICUs • Emergency departments • Postoperative and post-transplant settings • General medical units	• Nonmedical settings such as home use • Long-term care settings such as nursing homes • Perioperative uses to prevent acute respiratory failure
Study design	RCTs	• Non-RCT study designs[a] • Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series)
Publications	Published literature: • English-language only[b] • Published from 1990 on[c] • Peer-reviewed article Gray literature: • Report must be publicly available and have sufficient detail for abstraction (e.g., a full report similar in detail and quality to peer-reviewed literature)	• Non-English language publication[b] • Not published in peer-reviewed literature or one of the specified grey literature sources (Scientific Information Packets; FDA analyses) • Published before 1990[c]

ACPE = acute cardiogenic pulmonary edema; BPAP = bilevel positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; FDA = U.S. Food and Drug Administration; ICU = intensive care unit; KQ = Key Question; NPPV = noninvasive positive-pressure ventilation; $PaCO_2$ = partial pressure of carbon dioxide in blood; PaO_2 = partial pressure of oxygen in arterial blood; RCT = randomized controlled trial

[a]Although non-RCTs may be particularly pertinent to addressing effectiveness, confounding by indication makes it unlikely that these studies would yield a valid estimate of effect.

[b]English language: Given the high volume of literature available in English-language publications (including the majority of known important studies), and concerns about the applicability of non-English publication studies to settings in the United States, we excluded non-English articles.

[c]The rationale for this was that standards of care have changed significantly since 1990.

Data Extraction and Quality Assessment

The review team created forms for abstracting the data elements for the KQs. Based on their clinical and methodological expertise, a pair of researchers was assigned to abstract data from the eligible articles. One researcher abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus could not be reached by the first two investigators.

We designed the data abstraction forms for this project to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). We used an efficacy-effectiveness instrument[47] to assess seven domains: population and setting, restrictiveness of eligibility criteria, health outcomes, flexibility of the intervention and study duration, assessment of adverse effects, adequate sample size for important health outcomes, and intention-to-treat approach to analyses. We rated each of the seven items as effectiveness (score = 1) or efficacy (score = 0); scores were summed and could range from 0 to 7. Final efficacy-effectiveness scores were based on the mean of two independent ratings. We classified the etiology of acute respiratory failure based on study inclusion criteria (e.g. acute respiratory failure secondary to COPD) and the description of included patients. When the etiology was mixed, we classified the study by a single condition if at least 70 percent of the sample had that condition; otherwise, the sample was described as "mixed." We prioritized abstraction of clinical outcomes reported for the duration of the ICU or hospital stay, along with any longer term outcomes. In addition, we described comparators (especially supportive therapy) as carefully

as possible given the (sometimes limited) information provided in the study publications, as treatment standards may have changed during the period covered by this review. The safety outcomes were framed to help identify adverse events, including hospital-acquired pneumonia and facial ulcerations. Data necessary for assessing quality and applicability, as described in the Methods Guide,[24] were also abstracted.

To assess the risk of bias/methodological quality of individual studies, we used the key criteria for RCTs described in the Methods Guide[24] and adapted for this specific topic. These criteria include adequacy of randomization and allocation concealment, the comparability of groups at baseline, blinding, the completeness of followup and differential loss to followup, whether incomplete data were addressed appropriately, the validity of outcome measures, and conflict of interest. These general criteria were customized for each major outcome. To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, and poor, based on the studies' adherence to well-accepted standard methodologies and the adequacy of the reporting. For each study, one investigator assigned a summary quality rating, which was then reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement could not be reached.

We graded the strength of evidence (SOE) for each outcome assessed using the approach described in the Methods Guide.[24,48] In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains considered were strength of association (magnitude of effect), and publication bias. For risk of bias we considered basic (e.g., RCT) and detailed study design (e.g., adequate randomization). For directness, we considered whether the interventions of interest were compared directly (i.e., head-to-head) and the directness of the specific outcome vis-à-vis our KQs. For example, we considered ICU length of stay to be an indirect outcome because it does not capture overall resource utilization, including the time and personnel required to implement NPPV. We used results from meta-analyses when evaluating consistency (forest plots, tests for heterogeneity), precision (confidence intervals), strength of association (odds ratio [OR]), and publication bias (funnel plots and test statistics). Optimal information size and considerations of whether the confidence interval crossed the clinical decision threshold using a therapy was also used when evaluating precision.[49]

These domains were considered qualitatively, and a summary rating of "high," "moderate," or "low" SOE was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make, for example, when no evidence is available or when evidence on the outcome is too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of "insufficient" was assigned. This four-level rating scale consists of the following definitions:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient—Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis and Analysis

We began by summarizing key features of the included studies for each KQ. To the degree that data were available, we abstracted information on study design; patient characteristics; medical settings; type of NPPV, including the interface; and intermediate, final, and adverse events outcomes. We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Based on the frequency of reported outcomes and the relative importance of these outcomes, we determined that quantitative syntheses were indicated for: mortality, intubation or reintubation, myocardial infarction, and hospital-acquired pneumonia; other outcomes were summarized using descriptive statistics. Length of stay was analyzed qualitatively because the data reported for this outcome were often highly skewed, and because this outcome is biased due to the mortality benefit associated with NPPV treatment. For this qualitative synthesis, we focused our analysis on the larger studies that had greater power to detect a clinically and statistically significant difference in length of stay. We did not synthesize physiological outcomes because there were sufficient data to draw conclusions based on final outcomes and more clinically relevant intermediate outcomes. Other clinical

outcomes that were reported infrequently, such as rates of sinusitis, facial ulceration, and discontinuation due to intolerance, are summarized descriptively.

For the outcomes selected for meta-analysis, we used random-effects models to synthesize the evidence quantitatively using the Comprehensive Meta-Analysis software (Version 2; Biostat, Englewood, NJ). When outcomes were reported at multiple time points, we used the longest in-hospital followup duration (e.g., in-hospital mortality instead of ICU mortality). We summarized binary or categorical outcomes using a weighted effect measure for proportions (e.g., OR) and 95 percent confidence intervals (CIs). When we found statistically significant effects, we calculated the risk difference by using the summary OR and median odds of events from the comparator arms of the included studies. If the summary OR varied substantially by study quality, we used the OR from the good-quality studies for this calculation. We tested for heterogeneity using graphical displays and test statistics (Q and I^2 statistics). When there were sufficient studies ($n \geq 10$), we assessed for publication bias using funnel plots and test statistics.[50] If these analyses suggested significant publication bias, we computed an adjusted summary estimate using Duval's trim-and-fill method.[51]

We hypothesized that the methodological quality of individual studies, efficacy-effectiveness score, the training or experience of the interventionists, the characteristics of the comparator, and patients' etiology of acute respiratory failure would be associated with the intervention effects. When there were sufficient studies, we performed subgroup analyses to examine these hypotheses. For these analyses, we categorized studies as mostly efficacy (score of 0–2), mixed efficacy-effectiveness (score of 3–5), and mostly effectiveness (score of 6–7). Since staffing and experience were reported rarely, we grouped studies by geographical region (primarily continents) as a proxy for experience and completed subgroup analyses for this classification.

We conducted a secondary, mixed-treatment meta-analysis to address the effects of CPAP, BPAP, and invasive ventilation compared with supportive therapy by using both direct and indirect comparisons. Mortality is a dichotomous outcome and was fitted using multiple logistic regression analysis. Dummy variables were used for study differences, and treatment variables were used for the three treatment effects. A random-effects model was fitted using the EGRET® software (EGRET for Windows, 1999; Cytel Software Corporation, Cambridge, MA), which estimates both fixed-effect and random-effects parameters and automatically generates the dummy variables for each study ("Logistic-Normal Regression Model" option). Hasselblad 1998[52] describes the application of this methodology to meta-regression problems.

Results

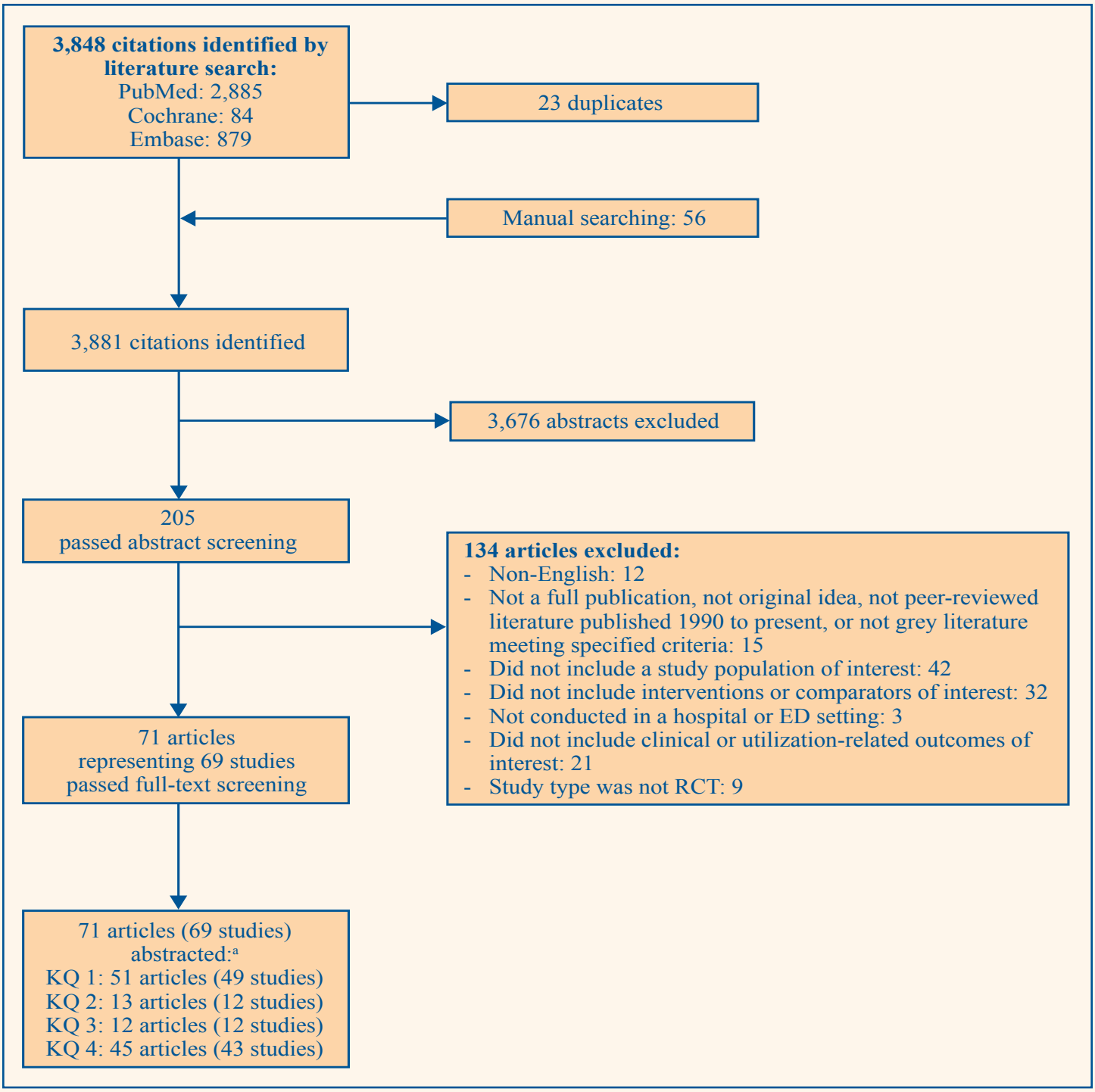
Figure B depicts the flow of articles through the literature search and screening process. Searches of PubMed, Embase, and the Cochrane Database of Systematic Reviews yielded 3,848 citations, 23 of which were duplicate citations. Manual searching identified 56 additional citations, for a total of 3,881 citations. After applying inclusion/exclusion criteria, we included 71 articles (representing 69 unique studies) for data abstraction. As indicated in Figure B, many articles/studies were relevant to more than one KQ. Our search of ClinicalTrials.gov did not find evidence for completed but unpublished studies relevant to our KQs.

Key Question 1. NPPV Versus Supportive Care or Invasive Ventilation

Key points from the Results chapter are:

- In patients treated for acute respiratory failure, current evidence supports a reduction in mortality when NPPV plus supportive care is used versus supportive care alone. This evidence is strongest for patients with COPD and ACPE, but limited evidence supports an effect in the postoperative and post-transplant settings.
- In patients treated for acute respiratory failure, current evidence supports a reduction in intubation rates when NPPV plus supportive care is used versus supportive care alone. This evidence is strongest for patients with COPD, but also supports an effect in patients with ACPE and in the postoperative and post-transplant settings.
- In patients treated for acute respiratory failure, current evidence supports a reduction in hospital-acquired pneumonia when NPPV plus supportive care is used versus supportive care alone. This evidence is strongest for patients with COPD.
- The evidence does not support an increase in rate of myocardial infarction related to NPPV.
- Evidence for treatment effects of NPPV in acute respiratory failure is sparse in many other etiologic subgroups, including acute respiratory distress syndrome (ARDS) and asthma.

Figure B. Literature flow diagram



ED = emergency department; KQ = Key Question; RCT = randomized controlled trial

[a]Some studies/articles were included for more than one KQ, so that numbers given in this box total to more than 71 articles/69 studies.

- Effects of NPPV on medical utilization are uncertain.
- Outcomes for psychological response, functional status, or health-related quality of life were not reported. Duration of mechanical ventilation was reported infrequently.

Forty-nine studies involving 4,527 patients met our inclusion criteria for KQ 1. Of the 49 studies, 40 compared NPPV plus supportive medical therapy with supportive medical therapy alone, 5 compared NPPV with invasive ventilation, and 4 were 3-arm trials comparing CPAP, BPAP, and supportive care. Forty-three studies reported mortality, 39 studies reported intubation rates, 7 studies reported myocardial infarction, and 8 studies reported rates of hospital-acquired pneumonia. No studies reported effects on health-related quality of life or anxiety associated with NPPV use. Most studies (60%) were conducted in Europe; six studies (12%) were conducted in the United States or Canada. Of the 49 studies, 22 (45%) were of good methodological quality, 21 (43%) were of fair quality, and 6 (12%) were of poor quality.

Approximately two-thirds of the studies reported a morbidity index (Acute Physiology And Chronic Health Evaluation [APACHE] II or Simplified Acute Physiology Score [SAPS]) that relies primarily on physiological measures. The median predicted mortality for enrolled patients was approximately 12 percent. Table B summarizes the findings and strength of evidence (SOE) for each major outcome. In brief, in patients treated for acute respiratory failure, there is high SOE supporting a reduction in both mortality and intubation when NPPV plus supportive care is used versus supportive care alone. This effect was established most strongly for patients with ACPE, or severe exacerbations of COPD. There is moderate SOE supporting a reduction in pneumonia associated with NPPV, but the evidence does not support a change in rate of myocardial infarction related to NPPV compared with supportive care alone. Evidence for treatment effects is sparse or absent in many diagnostic groups, including those with asthma, interstitial lung disease, perioperative and post-transplant settings.

Table B. Summary of the strength of evidence for KQ 1—NPPV versus supportive care

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**High**
39 (4,111)	RCT/Good	Consistent	Direct	Precise	OR = 0.56 (0.44 to 0.72) RD = 64 fewer per 1,000 (40 to 83)
Intubation rate					**High**
39 (3,792)	RCT/Good	Inconsistent	Direct	Precise	OR = 0.31 (0.24 to 0.41) RD = 217 fewer per 1,000 (177 to 247)
Myocardial infarction					**Moderate**
7 (1,517)	RCT/Good	Consistent	Direct	Imprecise	OR = 1.11 (0.85 to 1.44) RD = not applicable
Medical utilization: hospital length of stay					**Low**
11 (2,499)[a]	RCT/Good	Consistent	Indirect	Imprecise	No study found a statistically significant difference in LOS.
Medical utilization: ICU length of stay					**Insufficient**
5 (523)[a]	RCT/Good	Inconsistent	Indirect	Imprecise	Not estimable; 2 of 5 studies found a statistically significant decrease in LOS.
Hospital-acquired pneumonia					**Moderate**
9 (650)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.27 (0.15 to 0.49) RD = 121 fewer per 1,000 (81 to 144)

CI = confidence interval; ICU = intensive care unit; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

[a]Data are for larger studies with sufficient power to test for a 1-day difference in length of stay.

Outcomes for psychological response, functional status, or health related quality of life were not reported. Duration of mechanical ventilation was reported infrequently.

NPPV was compared with invasive ventilation in only 405 subjects. Compared with invasive ventilation, NPPV lowered hospital-acquired pneumonia (summary OR 0.15; 95% CI, 0.08 to 0.30; SOE = high) but did not reduce mortality or length of stay (SOE = low).

Key Question 2. BPAP Versus CPAP

Key points from the Results chapter are:

- Thirteen RCTs of varied quality showed no statistically significant difference between providing NPPV with BPAP compared with CPAP for the outcomes of:
  - Mortality
  - Need for endotracheal intubation
  - Myocardial infarction
- Current evidence is insufficient to determine if BPAP or CPAP have differential treatment effects for hospital or ICU length of stay, hospital-acquired pneumonia, psychological distress, functional status or health-related quality of life, and mortality rates beyond hospitalization.
- All studies but one included only participants with ACPE, although indirect comparisons included other diagnoses and supported these findings. This limits the applicability of these findings in patients with other causes of acute respiratory failure, such as COPD, as well as those in postoperative and post-transplant settings.

A total of 12 RCTs were included in our analyses for KQ 2. Ten studies enrolled patients from emergency departments, one from unclear settings, and one from a high-dependency unit. The number of patients included in studies ranged from 26 to 1,156, with a total of 1,463 patients. Four studies included three treatment arms (BPAP, CPAP, and supportive care with supplemental oxygen), while the remainder compared BPAP with CPAP alone. Although we aimed to address a variety of populations, all but one study included only patients with ACPE. No studies included in these analyses addressed obesity hypoventilation syndrome, interstitial lung disease, or the perioperative or post-transplant setting. Seven studies were performed in Europe, two in Brazil, one in Tunisia, one in Canada, and one in Australia. Of these, four were of good quality, six were of fair quality, and two were of poor quality.

Table C summarizes the findings and strength of evidence for each major outcome. In brief, 12 RCTs of varied quality showed no statistically significant difference between providing NPPV with BPAP compared with CPAP, for the outcomes of mortality and need for endotracheal intubation (moderate strength of evidence) or myocardial infarction (low strength of evidence). There is currently insufficient evidence to determine if BPAP or CPAP have differential treatment effects for: hospital or ICU length of stay, hospital-acquired pneumonia, psychological distress, functional status, health-related quality of life, and mortality rates beyond hospitalization. All studies but one included only participants with ACPE. The applicability of these findings is uncertain in those with COPD and other causes of acute respiratory failure.

Key Question 3. Early Extubation to NPPV

Key points from the Results chapter are:

- In eligible studies, BPAP was the only NPPV modality evaluated; no studies used CPAP.
- In patients with COPD who are intubated for acute respiratory failure, current evidence supports a reduction in mortality and hospital-acquired pneumonia when NPPV is used to facilitate extubation. These benefits were not observed in studies enrolling patients with mixed etiologies of acute respiratory failure.
- In patients intubated for acute respiratory failure and deemed at high risk for extubation failure, current evidence supports a reduction in reintubation rates and hospital-acquired pneumonia when NPPV is used to prevent extubation failure. A mortality benefit in this group was suggested but was not statistically significant.
- In patients who develop recurrent acute respiratory failure, current evidence does not support a reduction in mortality, reintubation rates, or hospital-acquired pneumonia rates for NPPV use compared with supportive care.
- Few studies had adequate sample sizes to address effects on length of stay. Available evidence does not support a reduction in hospital length of stay with BPAP versus usual care, but suggests a possible decrease in ICU length of stay with early extubation to BPAP. BPAP-assisted weaning was associated with shorter duration of invasive ventilation.
- No studies reported data on myocardial infarction, psychological response, functional status, or health-related quality of life.

Table C. Summary of the strength of evidence for KQ 2—CPAP versus BPAP					
Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**Moderate**
10 (1,338)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.89 (0.58 to 1.35) RD = NA
Intubation rate					**Moderate**
12 (1,463)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.84 (0.51 to 1.38) RD = NA
Myocardial infarction					**Low**
7 (1,056)	RCT/Good	Inconsistent	Indirect	Imprecise	OR = 0.69 (0.34 to 1.40) RD = NA
Medical utilization: hospital length of stay					**Insufficient**
3 (278)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; no study found a statistically significant difference in LOS.
Medical utilization: ICU length of stay					**Insufficient**
0 (0)	NA	NA	NA	NA	Not estimable.
Hospital-acquired pneumonia					**Insufficient**
0 (0)	NA	NA	NA	NA	Not estimable.

CI = confidence interval; ICU = intensive care unit; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

[a]Data are for larger studies with sufficient power to test for a 1-day difference in length of stay.

Twelve studies involving 1,519 patients met our inclusion criteria for KQ 3. All studies were conducted in ICU settings and used BPAP as the NPPV mode. Ten studies included a mixed population of patients with a variety of diagnoses causing respiratory failure. Two studies included only patients with a diagnosis of COPD. The included studies described three general strategies for using NPPV in the management of ventilator weaning: five studies investigated the use of NPPV in facilitating early extubation (i.e., comparing "usual" weaning strategy with extubation prior to meeting extubation criteria but with the application of NPPV as a bridge to liberation from invasive mechanical ventilation); five studies described the use of NPPV versus supportive care in preventing recurrent acute respiratory failure postextubation; and two studies examined the use of NPPV versus supportive care in the treatment of recurrent acute respiratory failure postextubation. Eleven studies reported effects on reintubation, and 11 reported mortality; no study reported myocardial infarction rates. One study was conducted in Canada and one multicenter study included sites in the United States; all others were carried out in Europe or Asia. Of the 12 studies, 6 were of good methodological quality, 5 were of fair quality, and 1 was of poor quality.

Tables D, E, and F summarize the findings and strength of evidence for each major strategy. In mixed populations of patients intubated for acute respiratory failure, current evidence shows a nonstatistically significant reduction in mortality but no effects on reintubation rates when BPAP is used to facilitate early extubation versus usual care (low strength of evidence). However, early extubation to BPAP is associated with lower rates of hospital-acquired pneumonia (low strength of evidence). Effects did not differ significantly for patients at high risk for reintubation who received anticipatory (presymptomatic) BPAP postextubation compared with those with recurrent respiratory failure when NPPV was used postextubation only among symptomatic patients. There is insufficient evidence to determine whether use of BPAP postextubation is associated with lower hospital or ICU length of stay or myocardial infarction compared with supportive care. No included studies used CPAP in the NPPV mode.

When compared with conventional weaning, we found lower mortality in patients with COPD, and a nonstatistically significant reduction in mortality in studies enrolling patients with mixed etiologies of acute respiratory failure. Results were similar for hospital-acquired pneumonia rates. NPPV did not affect reintubation rates, an effect that was consistent across diagnostic subgroups. When used to prevent acute respiratory failure postextubation, NPPV decreased mortality and reintubation only for patients at high-risk of recurrent respiratory failure. Only two studies evaluated NPPV to treat recurrent acute respiratory failure postextubation. These studies did not show a benefit for NPPV on any outcome.

Table D. Summary of the strength of evidence for KQ 3—NPPV-assisted ventilator weaning versus conventional weaning

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality—COPD					**Low**
2 (140)	RCT/Fair	Consistent	Direct	Imprecise	OR = 0.17 (0.05 to 0.65) RD = 129 fewer per 1,000 (50 to 151)
Hospital mortality—mixed etiologies					**Insufficient**
3 (214)	RCT/Fair	Inconsistent	Direct	Imprecise	OR = 0.46 (0.06 to 3.59) RD = NA
Reintubation rate					**Low**
4 (303)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.83 (0.48 to 1.44) RD = NA
Myocardial infarction					**Insufficient**
0 (none)	NA	NA	NA	NA	OR = not estimated
Medical utilization: hospital length of stay					**Insufficient**
2 (229)	RCT/	Consistent	Indirect	Imprecise	Not estimable; no study found a statistically significant difference in LOS.
Medical utilization: ICU length of stay					**Insufficient**
3 (279)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; 2 of 3 studies found a statistically significant decrease in LOS.
Hospital-acquired pneumonia—COPD					**Low**
2 (140)	RCT/Fair	Consistent	Direct	Imprecise	OR = 0.14 (0.04 to 0.48) RD = 167 fewer per 1,000 (33 to 233)
Hospital-acquired pneumonia—mixed etiologies					**Low**
3 (214)	RCT/Fair	Inconsistent	Direct	Imprecise	OR = 0.53 (0.19 to 1.46) RD = NA

CI = confidence interval; LOS = length of stay; NA = Not applicable; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

[a]Data are for larger studies with sufficient power to test for a 1-day difference in LOS.

Table E. Summary of the strength of evidence for KQ 3—NPPV versus supportive care to prevent respiratory failure postextubation					
	Domains Pertaining to SOE				Strength of Evidence
Number of Studies (Subjects)	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality—high-risk group					**Low**
3 (365)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.60 (0.34 to 1.04) RD = NA
Hospital mortality—average-risk group					**Insufficient**
1 (406)	RCT/Fair	NA	Direct	Imprecise	OR = 1.52 (0.25 to 9.21) RD = NA
Reintubation rate—high-risk group					**Low**
3 (365)	RCT/Good	Consistent	Direct	Imprecise	0.43 (0.24 to 0.77)
Reintubation rate—average-risk group					**Low**
2 (499)	RCT/Fair	Consistent	Direct	Imprecise	OR = 1.56 (0.89 to 2.76) RD = NA
Myocardial infarction					**Insufficient**
0 (none)	NA	NA	NA	NA	OR = not estimated
Medical utilization: hospital length of stay					**Insufficient**
3 (365)	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; no study found a statistically significant difference in LOS.
Medical utilization: ICU length of stay					**Insufficient**
3 (365)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; no study found a statistically significant difference in LOS.
Hospital-acquired pneumonia					**Low**
2 (268)[a]	RCT/Fair	Consistent	Direct	Imprecise	OR = 0.52 (0.28 to 0.97) RD = 102 fewer per 1,000 (6 to 164)

CI = confidence interval; LOS = length of stay; NA = Not applicable; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

[a]Data are for larger studies with sufficient power to test for a 1-day difference in LOS.

Table F. Summary of the strength of evidence for KQ 3—NPPV versus supportive care to treat respiratory failure postextubation					
Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**Low**
2 (302)	RCT/Good	Consistent	Direct	Imprecise	OR = 1.52 (0.78 to 2.97) RD = NA
Reintubation rate					**Low**
2 (302)	RCT/Good	Consistent	Direct	Imprecise	OR = 1.05 (0.66 to 1.67) RD = NA
Myocardial infarction					**Insufficient**
0 (none)	NA	NA	NA	NA	OR = not estimated
Medical utilization: hospital length of stay					**Insufficient**
1 (81)[a]	RCT/Good	NA	Indirect	Imprecise	Not estimable.
Medical utilization: ICU length of stay					**Insufficient**
2 (302)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; no study found a statistically significant difference in LOS.
Hospital-acquired pneumonia					**Insufficient**
1 (81)	RCT/Good	NA	Direct	Imprecise	OR = 1.02 (0.42 to 2.48)

CI = confidence interval; LOS = length of stay; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

[a]Data are for larger studies with sufficient power to test for a 1-day difference in LOS.

Key Question 4. Variation by Subgroups

Key points from the Results chapter are:

- The effects of NPPV on intubation rates are stronger when NPPV is initiated in the ICU than when it is initiated in the ED, but these findings are based on indirect comparisons.
- Few studies reported details about clinical setting and associated resources, experience and training of clinicians, or the use of clinical protocols. With the exception of diagnosis at study entry, no studies reported results by patient characteristics.
- The pooled OR associated with NPPV for both mortality and intubation shows a stronger effect for efficacy trials compared with effectiveness trials, but only two effectiveness trials were included in the analysis, and the 95% CIs overlapped.
- The treatment effects for NPPV on mortality and intubation rates are consistent across studies conducted in the United States or Canada versus European countries versus other countries.
- With the exception of the clinical setting in studies that compared NPPV with usual supportive care or invasive ventilator support (KQ 1), too few studies reported sufficient data to evaluate whether effectiveness or risks of NPPV vary by setting or patient characteristics.

Of the 69 studies included in this report overall, 65 included information about the clinical setting in which NPPV was initiated, 3 provided specific information about the experience or training of study clinicians, 2 reported patients' mean body mass index, 16 reported data on patients' neurological or mental status, 17 reported a measure of disease burden, and 67 reported mean baseline acute physiology scores for predicted ICU mortality. We conducted subgroup analysis for: the clinical setting, the geographical world region and efficacy-effectiveness category. Of the 49 studies that pertain to KQ 1, NPPV was initiated in the ED setting in 10 studies and in the ICU setting in 23 studies. In the remaining 16 studies, clinical setting was either not reported, or NPPV was initiated in another setting such as a general medicine ward or ambulance. The majority

of studies were conducted in Europe. Most studies were classified as mixed efficacy-effectiveness studies; only two were classified as effectiveness studies.

Table G summarizes the findings and strength of evidence for each of these analyses. Because these subgroup comparisons were made across studies, and thus were indirect comparisons, the study design was classified as an observational approach. Effects on mortality were lower for effectiveness studies but did not differ for intubation rates. These analyses were limited by the paucity of effectiveness trials. The pooled estimate of effect did not differ significantly across different settings or different countries.

Discussion

Key Findings

In this review, we included 69 trials that that compared NPPV with other common treatment strategies (supportive care and conventional mechanical ventilation). We also included trials that compared different types of NPPV with one another (CPAP vs. BPAP). We included common outcomes of interest such as mortality and adverse events, but also examined more difficult to measure issues such as resource utilization and efforts to shorten the duration of mechanical ventilation (by facilitating weaning from invasive ventilation, preventing extubation failure, and for treating recurrent respiratory failure).

Table G. Summary of the strength of evidence for KQ 4—variability in treatment effect by study characteristics

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Different treatment effects by study effectiveness characteristics					**Low**
43 (4,467)[a]	Observational	Inconsistent	Direct	Imprecise	OR (95% CI) for mortality: Efficacy trial: 0.56 (0.31 to 1.02) Mixed trial: 0.52 (0.41 to 0.66) Effectiveness trial: 0.99 (0.66 to 1.49) OR (95% CI) for intubation: Efficacy trial: 0.29 (0.19 to 0.46) Mixed trial: 0.29 (0.21 to 0.41) Effectiveness trial: 0.58 (0.16 to 2.13)
Different treatment effects across clinical settings					**Low**
43 (4,467)[a]	Observational	Consistent	Direct	Imprecise	OR (95% CI) for mortality: ED: 0.72 (0.49 to 1.05) ICU: 0.48 (0.35 to 0.66) OR (95% CI) for intubation: ED: 0.50 (0.26 to 0.95) ICU: 0.23 (0.15 to 0.34)
Different treatment effects across geographical regions[b]					**Low**
43 (4,467)[a]	Observational	Consistent	Direct	Imprecise	OR (95% CI) for mortality: Europe: 0.58 (0.46 to 0.73) U.S./Canada: 0.58 (0.25 to 1.33) OR (95% CI) for intubation: Europe: 0.33 (0.22 to 0.48) U.S./Canada: 0.36 (0.20 to 0.66)

KQ = Key Question; OR = odds ratio; SOE = strength of evidence; ED = emergency department; ICU = intensive care unit

[a]39 studies and 3,792 patients for analyses of intubation rates.

[b]Geographical regions used were: U.S./Canada, Europe, and other.

Key findings with a high strength of evidence were decreased mortality and intubation rates for NPPV versus supportive care. This effect was established most strongly for patients with ACPE, or severe exacerbations of COPD, but more limited evidence showed a consistent effect across different populations including those with postoperative acute respiratory failure and acute respiratory failure in post-transplant patients. We found moderate strength of evidence for: a lack of treatment effect on myocardial infarction rates, reduced hospital-acquired pneumonia, and comparable effects for CPAP and BPAP. We found the evidence insufficient to estimate the effects of NPPV on utilization of medical resources due to inconsistent effects across studies, indirectness of the outcomes reported (length of stay), and imprecise results. Few studies reported effects beyond the duration of hospitalization and no studies reported effects on functional status or quality of life.

NPPV was compared with invasive ventilation in only 405 subjects, a finding itself likely related to widespread contemporary clinician belief that avoiding invasive ventilation is strongly desired. Compared with invasive ventilation, NPPV lowered hospital-acquired pneumonia but did not reduce mortality or length of stay.

Compared with studies evaluating NPPV for initial treatment of acute respiratory failure, fewer studies examined the effects of NPPV to assist in weaning from invasive ventilation or to prevent or treat recurrent acute respiratory failure postextubation. When compared with conventional weaning, we found low SOE for lower mortality in patients with COPD and a nonstatistically significant reduction in mortality in studies enrolling patient with mixed etiologies of acute respiratory failure. Results were similar for hospital-acquired pneumonia rates. NPPV did not affect reintubation rates, an effect that was consistent across diagnostic subgroups. Evidence was insufficient to estimate effects for other outcomes. When used to prevent acute respiratory failure postextubation, NPPV decreased mortality and reintubation (low SOE) only for patients at high-risk of recurrent respiratory failure. Only two studies evaluated NPPV to treat recurrent acute respiratory failure postextubation. These studies did not show a benefit for NPPV on any outcome. Evidence was insufficient to estimate effects for other outcomes.

We also sought to determine whether the effects of NPPV varied by clinical setting, the experience and composition of the treating clinicians, by patient characteristics, and by whether each individual study was primarily an efficacy or an effectiveness trial. In an exploratory analysis, treatment effects for death or intubation did not differ significantly if NPPV was initiated in an ICU versus in an ED. We used global geographical region as a proxy for experience with NPPV and found no significant difference in treatment effects across regions. Most studies were classified as mixed efficacy-effectiveness studies; only two were classified as predominately effectiveness studies. Effects on mortality were lower for effectiveness studies but did not differ for intubation rates. These analyses were limited by the paucity of effectiveness trials.

Findings in Relation to What Is Already Known

Our results are generally consistent with previous systematic reviews[42,44,45] and clinical guidelines.[38,53,54] Previous reviews have found similar benefits on mortality and intubation rates in patients with respiratory failure due to ACPE[33,36,39,44,45] and severe exacerbations of COPD.[42,43] Our review spanned multiple conditions, finding consistent treatment effects across conditions, whereas prior reviews tend to be focused on a single cause of acute respiratory failure. Like others, we found few studies addressing acute respiratory failure in patients who are postoperative, post-transplant, or who have acute respiratory failure in the context of obesity-hypoventilation syndrome, acute respiratory distress syndrome, asthma or interstitial lung disease. As in other reviews, our study found comparable effects for CPAP and BPAP, but by incorporating indirect comparisons, we were able to strengthen this conclusion. Also of note, our review is the first to classify trials by efficacy and effectiveness characteristics, an analysis that highlights the paucity of effectiveness studies.

Mortality is increased with the duration of invasive mechanical ventilation and in patients who have recurrent respiratory failure following extubation from mechanical ventilation. This additional mortality risk is likely due to higher rates of delirium, lower mobility, and higher infection rates due to longer exposure to intravascular catheters and endotracheal tubes. Therefore, there is a potential role for NPPV in these clinical scenarios.[10,55-57] Our review has limitations when evaluating the role of NPPV as a method to facilitate weaning from invasive ventilation or to prevent or treat acute respiratory failure following extubation. We identified a relatively small number of trials that were analyzed in three subgroups depending on the specific clinical application of NPPV. For each clinical scenario, we conducted exploratory analysis by diagnostic group or risk of recurrent acute respiratory failure, indirect comparisons that are subject to confounding.

Our review also highlights the limited data for patients with acute respiratory failure not due to COPD or

congestive heart failure, and the poor reporting of factors that may be related to treatment effects such as the experience of the treating clinicians and patient characteristics.

Applicability

Relatively few studies were conducted in the United States or Canada (n = 8), with most studies (57%) conducted in Europe. There is a longer clinical experience with NPPV in Europe compared with the U.S., leading us to hypothesize that outcomes may be better in European countries. However, our analyses showed treatment effects for NPPV that were consistent across studies conducted in the U.S. or Canada compared with European or other countries. Other study reporting issues also affect applicability. The study interventions were not well-described in the majority of the studies, a limitation that could impede dissemination and contribute to the knowledge deficits described in surveys of clinicians. Twelve of the 69 studies poorly described the patient population, and 9 reported only outcomes that occurred 72 hours or less after initiating NPPV or a control intervention. More consistent reporting of patient characteristics, including overall medical comorbidity, race, and body mass index, would facilitate evaluations of differential effects in these important subgroups.

Limitations of the Comparative Effectiveness Review Process

Our findings have limitations related to the literature and our approach. Important limitations of the literature include few studies in certain populations of high interest, incomplete reporting of outcomes related to resource utilization, and descriptions of the interventions that were often inadequate to permit replication. In addition, the limited reporting of adverse effects and myocardial infarction suggest the possibility of selective outcomes reporting. Limitations in reporting precluded any analyses of variability in treatment effects by patient characteristics. A patient-level meta-analysis was not possible in the current study, but would be useful approach to examine this issue. Our review methods also had limitations. Our study was limited to English-language publications, which may have contributed to different conclusions about the effects of NPPV on ventilator weaning compared with Burns et al.[31] Although we attempted to evaluate the impact of effectiveness versus efficacy studies, our approach consisted of indirect comparisons without adjustment for potential confounders. The approach was further limited by a simple rules-based approach to classifying certain items in the efficacy-effectiveness scale (e.g., university affiliation = highly trained) and few effectiveness studies.

Research Gaps and Recommendations for Future Research

We used the framework recommended by Robinson et al.[58] to identify gaps in evidence and classify why these gaps exist (Table H). Although we recommend multicenter RCTs to address some evidence gaps, we are aware that there are some particular challenges to conducting these RCTs. It is difficult to blind patients or treating clinicians to the treatment group. While lack of blinding is unlikely to bias ascertainment of mortality outcomes, it could introduce bias in the assessment of more subjective outcomes and a subtle bias into patient care. Therefore it is critical that supportive treatments be specified carefully and that outcomes be assessed by individuals who are blind to treatment assignment. Some studies included in our review reported effects on length of stay for the sample overall and the subgroup of survivors. In clinical applications where NPPV has a mortality advantage, length-of-stay analyses could be biased if analyses use all patients randomized. Studies should report length of stay for the sample overall and for the subgroup of survivors. Additionally, the application of NPPV among patients at the end of life needs further study. Many providers do not conceptualize NPPV as a form of life support, and this constitutes a potential threat to the patient-centeredness of care among those with do not attempt resuscitation orders. Finally, we recommend that authors provide more careful descriptions of the patient population, details of randomization and allocation concealment, and detailed intervention protocols to facilitate dissemination of effective treatments. An additional area of research that could facilitate the implementation of NPPV would be study of evidence-based treatment algorithms such as decision support aids or in-time electronic screening tools that could help identify patients early who could benefit from NPPV.

Conclusions

In summary, for patients with acute respiratory failure due to severe exacerbations of COPD or congestive heart failure, NPPV plus supportive care shows important reductions in mortality and intubation rates compared with supportive care alone. BPAP has been studied more rigorously, but direct comparisons of CPAP and BPAP in patients with ACPE show similar efficacy. Current evidence suggests potential benefit for patients with acute respiratory failure who are postoperative or post-transplant

and as a method to facilitate weaning from invasive ventilation or prevent recurrent postextubation respiratory failure in those at high risk. However, the evidence for these indications is much weaker. Limited evidence shows similar treatment effects across different settings and the possibility of less benefit in trials designed to replicate usual clinical practice. There is a clear need for further studies in patient populations where NPPV has not been rigorously studied and to understand the role of training and effectiveness when used as part of routine clinical care.

Table H. Evidence gaps and future research

Evidence Gap	Reason	Type of Studies To Consider
Patients		
Effects vs. supportive care in patients with asthma, interstitial lung disease, pneumonia, acute decompensated, obesity-hypoventilation syndrome and those who are postoperative or post-transplant	Insufficient or imprecise information	Multicenter RCTs
Uncertain benefit of NPPV to assist weaning	Imprecise information	Multicenter RCTs
Uncertain benefit of NPPV to prevent recurrent acute respiratory failure postextubation	Imprecise information	Multicenter RCTs
Whether NPPV treatment effects vary by patient characteristics	Insufficient information	Patient level meta-analyses Subgroup analyses from large, multicenter RCTs Improved reporting in trial publications
Outcomes		
Effects on resource utilization NPPV compared with supportive care for acute respiratory failure	Insufficient information; not the right information	Analyze effects on resource utilization from large trials Model effects on resource utilization
Effects on psychological response, functional status, or health-related quality of life	Insufficient information	Multicenter RCTs
Settings		
Effectiveness of NPPV as implemented in usual care (outside of RCTs)	Insufficient information	Observational studies
Uncertainty about the effects of training, staffing composition/ratios and use of algorithms on NPPV effectiveness	Insufficient information	Observational studies

NPPV = noninvasive positive-pressure ventilation; RCT = randomized controlled trial

Glossary

ACPE	acute cardiogenic pulmonary edema
AHRQ	Agency for Healthcare Research and Quality
APACHE	Acute Physiology And Chronic Health Evaluation
BPAP	bilevel positive airway pressure
CER	comparative effectiveness review
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
ED	emergency department
ICU	intensive care unit
KQ	Key Question
MeSH	medical subject headings
NPPV	noninvasive positive-pressure ventilation
OR	odds ratio
$PaCO_2$	partial pressure of carbon dioxide in blood
PaO_2	partial pressure of oxygen in arterial blood
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
SAPS	Simplified Acute Physiology Score
TEP	Technical Expert Panel
TOO	Task Order Officer

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