CHEST

Liberation From Mechanical Ventilation in Critically Ill Adults

Executive Summary of an Official American College of Chest Physicians/American Thoracic Society Clinical Practice Guideline

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BACKGROUND: This clinical practice guideline addresses six questions related to liberation from mechanical ventilation in critically ill adults. It is the result of a collaborative effort between the American Thoracic Society (ATS) and the American College of Chest Physicians (CHEST).

METHODS: A multidisciplinary panel posed six clinical questions in a population, intervention, comparator, outcomes (PICO) format. A comprehensive literature search and evidence synthesis was performed for each question, which included appraising the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The Evidence-to-Decision framework was applied to each question, requiring the panel to evaluate and weigh the importance of the problem, confidence in the evidence, certainty about how much the public values the main outcomes, magnitude and balance of desirable and undesirable outcomes, resources and costs associated with the intervention, impact on health disparities, and acceptability and feasibility of the intervention.

RESULTS: Evidence-based recommendations were formulated and graded initially by subcommittees and then modified following full panel discussions. The recommendations were confirmed by confidential electronic voting; approval required that at least 80% of the panel members agree with the recommendation.

CONCLUSIONS: The panel provides recommendations regarding liberation from mechanical ventilation. The details regarding the evidence and rationale for each recommendation are presented in the *American Journal of Respiratory and Critical Care Medicine* and *CHEST*.

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KEY WORDS: evidence-based medicine; guidelines; mechanical ventilation

ABBREVIATIONS: ATS = American Thoracic Society; CHEST = American College of Chest Physicians; CLT = cuff leak test; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; NIV = noninvasive ventilation; PES = postextubation stridor; SBT = spontaneous breathing trial

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Mechanical ventilation is essential for many critically ill adults; however, it also is associated with numerous complications and patient discomfort. In an effort to facilitate liberation from mechanical ventilation, the American Thoracic Society (ATS) and the American College of Chest Physicians (CHEST) collaboratively developed evidence-based recommendations that address common clinical questions. The goal of the guidelines is to help clinicians safely and effectively liberate patients from mechanical ventilation and improve outcomes among critically ill patients.

Guidelines cannot take into account all the often compelling unique individual clinical circumstances. Clinicians are not expected to adhere to these recommendations blindly or universally. However, these unbiased evidence-based guidelines may provide support to clinicians who manage these vulnerable patients and have questioned the efficacy of selected methods for ventilator liberation.

Methods

Six cochairs were appointed, three each by the ATS and CHEST leadership, and reviewed for credentials and possible conflicts of interest. The six cochairs (T. D. G., P. E. M., J. D.T. from ATS and J. P. K., D. R. O., and G. A. S. from CHEST) suggested panelists to the ATS and CHEST staff, who then invited and reviewed them for potential conflicts of interest and finally approved them. The final panel consisted of the six cochairs, eight pulmonary/critical care physicians, four critical care physicians, one critical nurse, one physical therapist, and one critical care pharmacist. There were also two methodologists, one of whom is also a critical care physician. The panelists were divided among six topic groups as content experts for their particular area of expertise.

The six cochairs proposed six clinical questions, which were vetted and confirmed by the panel. Outcomes for each question were weighted following an approach outlined by the Grading Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group. After comprehensive evidence synthesis of published manuscripts, the panel used the GRADE approach to assess the overall certainty of the evidence for each question's associated outcomes. The Evidence-to-Decision framework facilitated panel deliberation and recommendation development.[1,2] Each recommendation was considered strong or conditional (Table 1) and required at least 80% panel consensus for approval. Any recommendation not meeting this threshold was revised based on panel feedback and resubmitted for vote.

Results

ATS and CHEST elected to share publication of the guideline, which consists of six questions and the related evidence syntheses and recommendations (Table 2). After appropriate review by the ATS and CHEST leadership, the guidelines are published as three manuscripts: an executive summary and two manuscripts that address three questions each. The panel made recommendations but did not support specific protocols for any of the six questions. One of two manuscripts is published in *CHEST*[3] and the other in the *American Journal of Respiratory and Critical Care Medicine*.[4] Both are accompanied by this executive summary.

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This Executive Summary is an overview of the official ATS/CHEST clinical practice guideline. It is being simultaneously published in *Chest* and the *American Journal of Respiratory and Critical Care Medicine*.

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TABLE 1] Implications of Recommendations by Stakeholders

Implications for	Strong Recommendation	Conditional Recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Clinicians should recognize that different choices will be appropriate for individual patients and that one must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Question 1: In acutely hospitalized patients ventilated more than 24 h, should the spontaneous breathing trial (SBT) be conducted with or without inspiratory pressure augmentation?

The evidence suggested that conducting the SBT with pressure augmentation was more likely to be successful, produced a higher rate of extubation success, and was associated with a trend toward lower ICU mortality than SBTs performed without pressure augmentation.

CHEST/ATS Recommendation

1. For acutely hospitalized patients ventilated more than 24 h, we suggest that the initial SBT be conducted with inspiratory pressure augmentation (5-8 cm H_2O) rather than without (T-piece or CPAP) (Conditional Recommendation, Moderate-Quality Evidence).

Remarks: This recommendation relates to how to conduct the initial SBT but does not inform how to ventilate patients between unsuccessful SBTs.

Values and Preferences

This recommendation places a high value on reducing the duration of mechanical ventilation and maximizing the probability of extubation success.

Question 2: In acutely hospitalized patients ventilated for more than 24 h, do protocols attempting to minimize sedation compared with approaches that do not attempt to minimize sedation impact duration of

TABLE 2] Summary of Recommendations

Recommendation	Strength of Recommendation	Certainty of Evidence (ie, Quality of Evidence)
1. For acutely hospitalized patients ventilated more than 24 h, we suggest that the initial SBT be conducted with inspiratory pressure augmentation (5-8 cm H_2O) rather than without (T-piece or CPAP)	Conditional	Moderate certainty in the evidence
2. For acutely hospitalized patients ventilated for more than 24 h, we suggest protocols attempting to minimize sedation	Conditional	Low certainty in the evidence
3. For patients at high risk for extubation failure who have been receiving mechanical ventilation for more than 24 h and who have passed am SBT, we recommend extubation to preventive NIV	Strong	Moderate certainty in the evidence
4. For acutely hospitalized patients who have been mechanically ventilated for > 24 h, we suggest protocolized rehabilitation directed toward early mobilization	Conditional	Low certainty in the evidence
5. We suggest managing acutely hospitalized patients who have been mechanically ventilated for > 24 h with a ventilator liberation protocol	Conditional	Low certainty in the evidence
6a. We suggest performing a CLT in mechanically ventilated adults who meet extubation criteria and are deemed at high risk for PES	Conditional	Very low certainty in the evidence
6b. For adults who have failed a CLT but are otherwise ready for extubation, we suggest administering systemic steroids at least 4 h before extubation; a repeated CLT is not required	Conditional	Moderate certainty in the evidence

More detailed discussions of questions 1-3 appear in Ouellette et al[3] and of questions 4-6 appear in Girard et al.[4] CLT = cuff leak test; NIV = noninvasive ventilation; PES = postextubation stridor; SBT = spontaneous breathing trial.

ventilation, duration of ICU stay, and short-term mortality (60 days)?

The evidence showed a trend toward a shorter duration of mechanical ventilation, a shorter ICU length of stay, and a trend toward lower short-term mortality in the protocolized sedation group.

CHEST/ATS Recommendation

2. For acutely hospitalized patients ventilated for more than 24 h, we suggest protocols attempting to minimize sedation (Conditional Recommendation, Low-Quality Evidence).

Remarks: There is insufficient evidence to recommend any protocol over another.

Values and Preferences

This recommendation places a high value on reducing mechanical ventilation duration, ICU length of stay, and short-term mortality and views the burden of protocolized sedation as very low.

Question 3: In high-risk patients receiving mechanical ventilation for more than 24 h who have passed an SBT, does extubation to preventive noninvasive ventilation (NIV) compared with no NIV have a favorable effect on duration of ventilation, ventilator-free days, extubation success (liberation > 48 h), duration of ICU stay, short-term mortality (60 days), or long-term mortality?

In studies of preventive NIV, there was heterogeneity in defining the high-risk patient. Risk factors included older age, comorbidities such as COPD or congestive heart failure, and hypercapnia during the SBT. The evidence synthesis indicated that preventive NIV was superior to no preventive NIV regarding extubation success, ICU length of stay, and both short- and long-term mortality.

CHEST/ATS Recommendation

3. For patients at high risk for extubation failure who have been receiving mechanical ventilation for more than 24 h and who have passed an SBT, we recommend extubation to preventive NIV (Strong Recommendation, Moderate Quality Evidence).

Remarks: Patients at high risk for failure of extubation may include those patients with hypercapnia, COPD, congestive heart failure, or other serious comorbidities. Physicians may choose to avoid extubation to NIV in selected patients for patient-specific factors including but not limited to the inability to receive ventilation through a mask or similar interface. Physicians who choose to use NIV should apply such treatment immediately after extubation to realize the outcome benefits.

Values and Preferences

This recommendation places a high value on early extubation and a lesser value on the burdens related to institution and maintenance of preventive NIV.

Question 4: Should acutely hospitalized adults who have been mechanically ventilated for >24 h be subjected to protocolized rehabilitation directed toward early mobilization or no protocolized attempts at early mobilization?

The evidence synthesis demonstrated that patients who received an intervention directed toward early mobilization had a shorter duration of mechanical ventilation and were more likely to be able to walk at hospital discharge. There were no differences in mortality, ICU length of stay, ability to walk at ICU discharge, 6-min walk distance, or ventilator-free days. Low rates of serious adverse events, including arrhythmias, have been reported.

ATS/CHEST Recommendation

4. For acutely hospitalized adults who have been mechanically ventilated for > 24 h, we suggest protocolized rehabilitation directed toward early mobilization (Conditional Recommendation, Low Quality Evidence).

Remarks: There is insufficient evidence to recommend any rehabilitation protocol over another.

Values and Preferences

This recommendation places a high value on reducing the duration of mechanical ventilation and maintenance of ambulation and a lower value on cost and resource use.

Question 5: Should acutely hospitalized adults who have been mechanically ventilated for > 24 h be managed with a ventilator liberation protocol or no protocol?

The guideline panel defined a "ventilator liberation protocol" as protocol-guided efforts to identify a patient's readiness for liberation (ie, extubation) from invasive mechanical ventilation. The evidence demonstrated that patients managed with a ventilator liberation protocol spent fewer hours on mechanical ventilation than did patients managed without a protocol. Additionally, management with a ventilator

liberation protocol led to patients being discharged from the ICU earlier than management without a protocol. However, ventilator liberation protocols had no significant effect on mortality or reintubation rates. Adverse events were rarely reported. Subgroup analyses found that compared with management without a ventilator liberation protocol, personnel-driven and computer-driven protocols had similar effects.

ATS/CHEST Recommendation

5. We suggest managing acutely hospitalized adults who have been mechanically ventilated for > 24 h with a ventilator liberation protocol (Conditional Recommendation, Low-Quality Evidence).

Remarks: The ventilator liberation protocol may be either personnel driven or computer driven.

Values and Preferences

This recommendation places a high value on reducing the duration of mechanical ventilation and ICU length of stay and a lower value on resource use.

Question 6: Should a cuff leak test (CLT) be performed prior to extubation of mechanically ventilated adults? Should systemic steroids be administered to adults who fail a CLT prior to extubation?

The evidence suggested that patients with an absent or insufficient cuff leak are at increased risk of postextubation stridor (PES) and unsuccessful extubation. Very low-quality evidence also suggested that the use of a CLT to guide management may decrease the reintubation and PES rate and delay extubation (due to a high false-positive rate). It has no effect on the duration of mechanical ventilation when considering the additional days associated with reintubation. Moderate-quality evidence suggested that administration of systemic steroids to patients failing a CLT may reduce both the reintubation and PES rates. Patients passing a CLT have a low risk of reintubation and PES, although these risks are also low among patients extubated without having a CLT performed.

ATS/CHEST Recommendations

6a. We suggest performing a CLT in mechanically ventilated adults who meet extubation criteria and are deemed high risk for PES (Conditional Recommendation, Very Low Certainty in the Evidence).

6b. For adults who have failed a CLT but are otherwise ready for extubation, we suggest administering systemic steroids at least 4 h before extubation; a repeated CLT is not required (Conditional Recommendation, Moderate-Quality Evidence).

Remarks: Risk factors for PES include traumatic intubation, intubation > 6 days, large endotracheal tube, female sex, and reintubation after unplanned extubation. A repeat CLT is not required following the administration of systemic steroids.

Values and Preferences

These recommendations place a high value on avoiding reintubation and delayed extubation and a lower value on PES, the burdens related to implementing the CLT, and the side effects of steroid use.

Summary

The recommendations in these guidelines are the result of our expert panel's interpretation of the existing evidence and how it may be applied in clinical practice. Only one recommendation, extubation to preventive noninvasive mechanical ventilation in high-risk patients, is strongly suggested. All others are considered conditional recommendations and include conducting SBTs with inspiratory pressure augmentation, using protocols to minimize sedation, using protocolized rehabilitation directed toward early mobilization, using ventilator liberation protocols, performing a CLT in mechanically ventilated patients who meet extubation criteria and are deemed at high risk for PES, and administering systemic steroids at least 4 h prior to extubation in patients who fail a CLT. A repeat CLT is not required.

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Response

To the Editor:

We would like to thank Dr Yaqoob et al for their interest in our study.[1] They performed an analysis to assess the association between sarcoidosis VTE using diagnostic codes from a large electronic medical record database. A significant association between the two conditions was observed at a magnitude similar to that in our report.

There are advantages and drawbacks to both coding-based studies and studies using individual medical record review. A coding-based study using a large database can take advantage of big data to produce more precise effect estimates and can detect small-sized associations. However, the completeness and accuracy of coding are generally limited.[2] A previous study demonstrated a positive predictive value of only 29% for International Classification of Diseases, Ninth Revision, Clinical Modification codes for VTE.[3] In fact, in our cohort, the initial search using diagnostic codes related to sarcoidosis identified 794 patients from the database, but only 345 patients (43%) were confirmed to have sarcoidosis after individual medical record review.[4] Conversely, studies using individual medical record review have limited practicality because of the time needed to access and interrogate the individual medical record. Consequently, the database is generally smaller than that of studies using large administrative data sets, resulting in lower precision and power but much higher diagnostic validation.

It is certainly useful to compare the results of both approaches in assessing associations of interest. If both yield similar results, as appears to be the case in these two studies of the association between sarcoidosis and VTE, it is reasonable to conclude that the observed association is the true association.

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Rethinking Inspiratory Pressure Augmentation in Spontaneous Breathing Trials

To the Editor:

In issuing a conditional recommendation in favor of inspiratory pressure augmentation during spontaneous breathing trials (SBTs) in a recent issue of *CHEST* (January 2017), Ouellete et al[1] noted that the available evidence informing the recommendation is at serious risk of bias. We highlight here some additional limitations and address other key issues to consider when evaluating the best technique for conducting SBTs.

Aside from the limitations identified by the authors,[1] all four trials ascertained outcomes only in patients who passed the SBT but reported these outcomes for the entire cohort. Because SBT pass rates are higher when using pressure support vs a T-piece, higher numbers of extubation success and failure will occur in patients randomized to a pressure support SBT. The impact of this bias is apparent because, paradoxically, both extubation success and extubation failure occurred more frequently in patients randomized to receive pressure support (70.5% vs 63.4% and 16.4% vs 14.8%, respectively). Notably, two of the four trials do not report extubation failure rates. None of these trials provide unbiased estimates of relevant outcomes for clinical decision-making.

The SBT is used as a diagnostic test to predict successful liberation from ventilation by assessing the patient's ability to tolerate the work of breathing after extubation. Given the impact of extubation failure on patient-centered outcomes, we believe clinicians should use the SBT technique that allows them to rule-in "successful extubation" with the greatest confidence; that is, a specific test with a high positive likelihood ratio for successful extubation.

The patient's work of breathing postextubation is best matched by SBTs conducted using T-piece or zero airway pressure on the ventilator.[2] Additional support reduces the work of breathing by 20% to 40%, potentially masking the risk of postextubation distress from cardiac failure or excess respiratory loading.[3] Compensating for the resistance of the endotracheal tube or the ventilator circuit is unnecessary because upper airway resistance is increased after extubation, and modern ventilators offer minimal loads.[4,5] Because T-piece testing best matches the postextubation respiratory load, it is likely more specific than pressure support ventilation for successful extubation.

Recommending a test that applies an unrealistically low work of breathing compared with that experienced postextubation puts fragile patients at risk of harm. Clinicians may take into account many parameters aside from the test alone when considering extubation, but SBTs using pressure support may misinform a complex decision. For these reasons, we advocate the use of T-piece or zero airway pressure when conducting SBTs.

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Response

To the Editor:

We thank Goligher et al for their interest in our manuscript.[1] They raise concerns about our conditional recommendation in favor of using pressure augmentation (PA) during a spontaneous breathing trial (SBT) compared with T-piece/CPAP.

Goligher et al are correct that because conducting the SBT with PA is more often successful, both the rates of extubation success and extubation failure could be higher (using the entire population as the denominator). However, if this were the only basis for higher extubation success rates, one would expect

patients extubated following a successful PA SBT to have higher rates of subsequent reintubation. In the two studies that we cited that contain relevant data,[2,3] when using a T-piece, SBT was successful in 216 patients, but extubation failed in 41 patients (19.0%), whereas with PA, SBT was successful in 259 patients and extubation failed in 49 patients (18.9%). Thus, conducting the SBT with PA does not appear to falsely predict extubation success and Goligher et al's hypothesis is, at least, incomplete. Because PA leads to more patients being successfully extubated with a shortened duration of mechanical ventilation, we stand by our recommendation.

A key to this debate involves the comparison of the burden of extubation failure and the risk of prolonging mechanical ventilation. It is well known that patients in whom extubation fails have worse outcomes than those in whom it is successful.[4] Reintubation in the ICU certainly is not risk free: however, death around the time of reintubation is extremely rare, particularly with modern intubation approaches.[5-7] It appears that in the majority of patients, reintubation identifies a cohort with a higher severity of illness or acquisition of new problems associated with ongoing mechanical ventilation. At the same time, not extubating also confers risk. As the declaration of SBT failure occurs more commonly with T-piece or CPAP than with PA, it follows that the population assessed with T-piece SBT will have prolonged mechanical ventilation and its attendant risks.[2,8] We believe that most clinicians and most patients favor strategies that lead to earlier extubation.

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Evaluation of Thoracentesis-Related Pneumothorax

A Community Clinician's Perspective

To the Editor:

The literature does not support routine practice of chest radiography following thoracentesis for evaluation of pneumothorax, yet this remains the standard of care amongst community pulmonary physicians.[1] The thoracentesis procedure has evolved such that ultrasound guidance is common practice for preprocedural identification and characterization of pleural effusion. With a nominal increase in time expenditure and training, the use of ultrasound can be further expanded to rule out pneumothorax. This is particularly valuable as ultrasound has

Liberation from Mechanical Ventilation: An Official American College of Chest Physicians/American Thoracic Society Clinical Practice Guideline

Inspiratory Pressure Augmentation during Spontaneous Breathing Trials, Protocols Minimizing Sedation, and Non-invasive Ventilation Immediately After Extubation

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ABSTRACT

Background: An update of evidence-based guidelines concerning liberation from mechanical ventilation is needed as new evidence has become available. The American College of Chest Physicians (CHEST) and the American Thoracic Society (ATS) have collaborated to provide recommendations to clinicians concerning ventilator liberation.

Methods: Comprehensive evidence syntheses, including meta-analyses, were performed to summarize all available evidence relevant to the guideline panel's questions. The evidence was appraised using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach and the results were summarized in evidence profiles. The evidence syntheses were discussed and recommendations developed and approved by a multi-disciplinary committee of experts in mechanical ventilation.

Results: Recommendations for three PICO (population, intervention, comparator, outcome) questions concerning ventilator liberation are presented in this document. The guideline panel considered the balance of desirable (benefits) and undesirable consequences (burdens, adverse effects, costs), quality of evidence, feasibility, and acceptability of various interventions with

respect to the selected questions. Conditional (weak) recommendations were made to use inspiratory pressure augmentation in the initial spontaneous breathing trial (SBT), and to use protocols to minimize sedation, for patients ventilated for more than 24 hours. A strong recommendation was made to use preventative non-invasive ventilation (NIV) for high-risk patients ventilated for more than 24 hours immediately after extubation to improve selected outcomes. The recommendations were limited by the quality of the available evidence.

Conclusion: The guideline panel provided recommendations for inspiratory pressure augmentation during an initial SBT, protocols minimizing sedation, and preventative NIV, in relation to ventilator liberation.

SUMMARY OF RECOMMENDATIONS

1. **For acutely hospitalized patients ventilated more than 24 hours, we suggest that the initial SBT be conducted with inspiratory pressure augmentation (5-8 cm H_2O) rather than without (T-piece or CPAP).** (Conditional recommendation, Moderate quality evidence)
   Remarks: This recommendation relates to how to conduct the initial SBT, but does not inform how to ventilate prolonged weaning patients between SBTs.

2. **For acutely hospitalized patients ventilated for more than 24 hours, we suggest protocols attempting to minimize sedation.** (Conditional recommendation, Low quality of evidence)
   Remarks: There is insufficient evidence to recommend any protocol over another.

3. **For patients at high risk for extubation failure who have been receiving mechanical ventilation for more than 24 hours, and who have passed an SBT, we recommend extubation to preventative NIV** (Strong recommendation, moderate quality of evidence).
   Remarks: Patients at high risk for failure of extubation may include those patients with hypercapnia, COPD, CHF, or other serious co-morbidities. Physicians may choose to

avoid extubation to NIV in selected patients for patient-specific factors including but not limited to the inability to receive ventilation through a mask or similar interface. Physicians who choose to use NIV should apply such treatment immediately after extubation to realize the outcome benefits.

INTRODUCTION

Mechanical ventilation is a life-saving intervention, but it is also associated with complications. Therefore, it is desirable to liberate patients from mechanical ventilation as soon as the underlying cause that led to the mechanical ventilation has sufficiently improved and the patient is able to sustain spontaneous breathing and adequate gas exchange. This clinical practice guideline provides evidence-based recommendations on 3 specific ventilator liberation techniques. The guidelines were a collaborative effort between the American Thoracic Society (ATS) and the American College of Chest Physicians (CHEST). Development of the guidelines followed systematic reviews of the literature and use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to develop recommendations. The guidelines address the following questions:

Question #1: In acutely hospitalized patients ventilated more than 24 hours, should the spontaneous breathing trial (SBT) be conducted with or without inspiratory pressure augmentation?

Question #2: In acutely hospitalized patients ventilated for more than 24 hours, do protocols attempting to minimize sedation compared to approaches that do not attempt to minimize sedation impact duration of ventilation, duration of ICU stay and short-term mortality (60 days)?

Question #3: In high-risk patients receiving mechanical ventilation for more than 24 hours who have passed an SBT, does extubation to preventative non-invasive ventilation (NIV) compared to no NIV have a favorable effect on duration of ventilation, ventilator-free days, extubation

success (liberation > 48 hours), duration of intensive care unit (ICU) stay, short-term mortality (60 days), or long-term mortality?

This guideline is the companion to another guideline that is being published separately and addresses questions related to physical rehabilitation protocols, ventilator liberation protocols, and cuff leak test.[1] Neither guideline is intended to impose a standard of care. They provide the basis for rational decisions in the liberation of patients from mechanical ventilation. Clinicians, patients, third-party payers, stakeholders, or the courts should not view the recommendations contained in these guidelines as dictates. Guidelines cannot take into account all of the often compelling unique individual clinical circumstances. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines by rote or in a blanket fashion.

METHODS

Expert Panel Composition

CHEST's Professional Standards Committee (PSC), Guidelines Oversight Committee (GOC), and the ATS's Document Development and Implementation Committee (DDIC) selected and approved the co-chairs of the panel. Prospective panelists were selected by the co-chairs based on their expertise relative to the proposed guideline questions. The panelists were reviewed by representatives from both the American Thoracic Society and CHEST for possible conflicts of interest and credentials. The GOC then reviewed all panelists for final approval. The final panel consisted of the six co-chairs and fourteen panelists, who were then divided among 6 topic groups as content experts for their particular area of expertise.

Conflicts of Interest

All panel nominees were reviewed and vetted by a joint conflict of interest (COI) review committee composed of members from the ATS and CHEST. After review, nominees who were found to have no substantial COI were approved, while nominees with potential intellectual and financial conflicts of interest that were considered to be manageable were "approved with

management." Panelists who were approved with management were prohibited from participating in discussions or voting on recommendations in which they had substantial conflicts of interest. We created a grid associating panelists' COI with relevant PICO questions for use during voting. The COI grid can be found in the supplemental materials on the CHEST journal website [provide link].

The final panel consisted of the 6 co-chairs (TDG, JPK, PEM, DRO, GAS, and JDT), 7 pulmonary/critical care physicians, 4 critical care physicians, 1 critical care nurse, 1 physical therapist, and 1 critical care pharmacist. The panel worked with two methodologists (WA, SP), one of whom is also a critical care physician.

Formulation of Key Questions and Outcome Prioritization

The six co-chairs drafted a total of 6 key clinical questions in a PICO (Population, Intervention, Comparator, Outcome) format (Table 1). The co-chairs were asked to rate the outcomes to be used for all six questions numerically on a scale of 1-9, according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group's three categories of outcomes for decision-making (1-3 – not important; 4-6 – important; 7-9 – critical). We used the co-chairs' average score for each outcome to determine the outcome category, and we only assessed the outcomes rated as "critical" or "important".

Systematic Literature Searches

All panelists reviewed the PICO questions and with the help of the methodologist, finalized the search terms, inclusion and exclusion criteria, and databases that would be searched.

The methodologist performed a systematic search of the literature for relevant systematic reviews and individual studies in December 2014 using the following databases: MEDLINE via PubMed, the Cochrane Library, and CINAHL. Searches were conducted using a combination of the National Library of Medicine's Medical Subject Headings (MeSH) and other key words specific to each topic. Reference lists from relevant retrievals were also searched, and additional papers were manually added to the search results. To account for all of the literature pertaining to each topic, searches were not limited by language, study design, or publication date.

Additional details on literature searches and the selection of studies can be found in the supplemental materials on the CHEST website [provide link].

Study Selection and Data Extraction

Studies retrieved from the completed literature searches were then reviewed for relevance through two rounds of screening. Two reviewers excluded studies that did not meet the inclusion criteria based on title or abstract. We retrieved studies that met the inclusion criteria for full text review to determine their final inclusion. In both rounds of screening, studies were reviewed independently by two reviewers. Disagreements were resolved through discussion or by a third reviewer if required.

We extracted relevant data from each eligible study into structured data tables. One panelist performed the data extraction and another panelist independently reviewed the extracted data. Discrepancies were resolved by discussion. A discrepancy resolution plan employing a third reviewer was in place but never invoked.

Risk of Bias Assessment

The methodologist assessed the risk of bias of all included studies. We used the Cochrane Risk of Bias tool to assess risk of bias for randomized controlled trials (RCTs).[2] We used the Documentation and Appraisal Review Tool (DART) to assess the quality of systematic reviews when applicable.[3]

Meta-Analyses

When individual studies were available or a meta-analysis needed to be updated, we used the Cochrane Collaboration Review Manager, version 5.2[4] to pool the results across individual studies. We used a random-effects model and the method of DerSimonian and Laird to pool the individual estimates.[5] Relative risk (RR) was used to report the results for dichotomous outcomes and mean difference (MD) for continuous outcomes with accompanying 95% confidence intervals (CI). Statistical heterogeneity of the pooled results was assessed using the Higgins' I^2 and the Chi-square tests. A Higgins'I^2 value of $\geq$50% or Chi-square $p<0.05$ was considered to represent significant heterogeneity.

Assessing the Certainty of Evidence

We assessed the overall certainty of the evidence for each outcome of interest using the GRADE approach.[6] Evidence profiles were created using the Guideline Development Tool (GDT), which categorized the overall quality of the body of evidence into one of four levels: high, moderate, low, or very low. Each level represents the confidence in the estimated effects for a specific question (Table 2). Panel members in each group reviewed the evidence profiles and provided input and feedback.

Recommendations

The panel developed recommendations for each of the PICO questions based on the GRADE evidence profiles. We used the Evidence to Decision (EtD) framework to guide the discussions that ultimately led to the development of a recommendation. Panel members made decisions regarding the balance between benefits and harm, impact of patients' values and preferences, cost, health equity, feasibility, and acceptability of the intervention. Pertinent points were recorded during the discussion process. The advantage of using the EtD framework was to facilitate the discussion and to ensure that all important categories were discussed before formulating the recommendation.

Recommendations were graded using the GRADE approach.[7] The recommendations were either "strong" or "conditional" (weak) according to this approach. Strong recommendations use the wording "we recommend" and conditional recommendations are worded using "we suggest". The implications of the strength of recommendation are summarized in Table 3.

Consensus Development

The guideline panel met through online webinars multiple times to work through the EtD and develop recommendations for each PICO question. Because all panel members were not able to attend every webinar, all drafted recommendations were presented again to the full panel in an

online anonymous voting survey in order to reach consensus and gather feedback from those unable to participate. Panelists were requested to indicate their level of agreement on each recommendation based on a 5-point Likert scale derived from the GRADE grid.[8,9] Panelists were also invited to provide feedback on each recommendation with suggestions for rewording. Conflicted panelists (per the terms of management) were not permitted to vote on the related recommendation. No panelists had conflicts that required exclusion from voting. Approval of each recommendation required, by CHEST policy, a 75% voting participation rate and an 80% consensus. Any recommendation that did not meet these criteria was revised by the panel based on the feedback and a new survey that incorporated those revisions was completed.

Peer Review Process

Reviewers from the GOC, the CHEST Board of Regents (BOR) and the *CHEST* journal reviewed the content and methods, including consistency, accuracy and completeness. The manuscript was revised after consideration by the panel of the feedback received from the peer reviewers.

RESULTS

Question #1: In acutely hospitalized patients ventilated more than 24 hours, should the spontaneous breathing trial (SBT) be conducted with or without inspiratory pressure augmentation?

Background: Clinicians tend to underestimate the capacity of patients to breathe successfully when disconnected from the ventilator, as shown by two large weaning trials.[10,11] Moreover, weaning predictors such as maximal inspiratory pressure, static respiratory system compliance, and rapid-shallow breathing index, lack sufficient positive and negative predictive value to make them routinely useful for judging patients' ability to wean. Once patients meet several readiness

criteria, a preferred approach is to conduct a spontaneous breathing trial (SBT) involving little or no ventilator support. If the SBT provokes signs of respiratory failure, ventilation is resumed but, if it does not, the clinician may move towards extubation.

The SBT can be conducted using no inspiratory pressure augmentation (T-piece or CPAP) or with modest inspiratory pressure augmentation (pressure support, generally limited to 5-8 cm H_2O, or automatic tube compensation [ATC]). On the one hand, it could be argued that the patient demonstrating ability to breathe while receiving no inspiratory pressure augmentation has convincingly shown weaning readiness (i.e., this result may be very specific, but may not be sensitive). On the other hand, some patients failing an SBT without pressure augmentation might pass with pressure support, and some of these may be safely extubated (i.e., this result may be more sensitive, but less specific). There is no consensus as to how to conduct the SBT, leading to differing approaches across ICUs.

Summary of the evidence: We conducted a systematic review that identified four relevant trials and these formed the evidence base that served to guide the panel's recommendations.[12-15] All were prospective and randomized, and three were single-center trials. Three of the trials enrolled patients from mixed medical-surgical ICUs, whereas one trial enrolled from a medical ICU.[13] In all trials, patients had to be judged clinically stable and ready for weaning to be considered for study participation. For the spontaneous breathing trial (SBT), subjects were allocated to T-piece breathing (no pressure augmentation) or to a modest level of pressure support (pressure augmentation) for a period of 30 minutes to 2 hours. The amount of pressure support provided was 5, 7, or 8 cm H_2O or via automatic tube compensation (which provides inspiratory pressure support to overcome with work of breathing imposed by the artificial airway).

The SBT was terminated if the patient exhibited signs of poor tolerance; otherwise, the SBT was considered successful ("successful SBT"). When the SBT was successful, the patient was extubated at the end of the time period and provided supplemental oxygen. "Extubation success" was defined as not requiring reintubation or non-invasive ventilation in the next 48 hours.

Three trials provided information regarding the frequency of successful SBTs.[12-14] Extubation success could be assessed in all four trials whereas only two trials reported ICU mortality.[12-14] When the trials were pooled via meta-analysis, conducting the SBT with pressure augmentation was more likely to be successful (84.6% vs 76.7%; RR 1.11, 95% CI 1.02-1.18); produced a

higher rate of extubation success (75.4% vs 68.9%; RR 1.09, 95% CI 1.02-1.18); and was associated with a trend towards lower ICU mortality (8.6% vs 11.6%; RR 0.74, 95% CI 0.45-1.24) (Table 4).

There are several limitations to the studies used for analysis. The clinicians in the studies were unblinded to SBT technique. In addition, the total number of subjects in the trials was small and three of the four trials were performed in a single center. The mixed ICU populations from which study subjects were drawn limit our confidence when applying these results to individual patients. This is especially the case in subsets that accounted for only a small minority of all patients studied (e.g., those with respiratory failure due to neuromuscular disease). Finally, study patients were those undergoing their first SBT thus limiting generalizations to those who have failed one or more previous SBTs.

The evidence used to guide this recommendation was of moderate confidence for SBT and extubation success, but of low certainty for ICU mortality (Table 4). We considered but did not include for meta-analysis, one additional trial that conducted the SBT initially using T-piece and, if that failed, extended the duration using pressure support of 7 cm H_2O for 30 minutes.[16] If the SBT with pressure augmentation was successful, patients were extubated. Of all enrolled subjects (n=118), 31 failed the SBT without pressure augmentation but 21 of these were successful following pressure augmentation and were extubated. The rates of extubation success were similar in those who passed the SBT without pressure augmentation and those who failed initially but passed when pressure augmentation was added, further supporting our recommendation.

The panel judged that the desirable consequences of conducting the SBT with pressure augmentation outweighed any potential undesirable consequences. This judgment was based on the success of the SBT conducted with pressure augmentation as well as the high rate of extubation success associated with the intervention.

CHEST/ATS Recommendation: For acutely hospitalized patients ventilated more than 24 hours, we suggest that the initial SBT be conducted with inspiratory pressure augmentation (5-8 cm H_2O) rather than without (T-piece or CPAP). (Conditional recommendation, Moderate quality evidence).

Remarks: This recommendation relates to how to conduct the initial SBT, but does not inform how to ventilate prolonged weaning patients between SBTs.

Values and Preferences: This recommendation places a high value on reducing the duration of mechanical ventilation and maximizing the probability of extubation success.

Question #2: In acutely hospitalized patients ventilated for more than 24 hours, do protocols attempting to minimize sedation compared to approaches that do not attempt to minimize sedation impact duration of ventilation, duration of ICU stay, and short-term mortality (60 days)?

Background: Mechanically ventilated patients often receive sedative and analgesic drugs for a variety of reasons. These drugs have the potential to alter mental status and suppress respiratory drive. Accordingly, it is conceivable that these pharmacological effects may impede liberation from mechanical ventilation. Strategies to minimize the effects of these drugs (e.g. bedside nursing sedation algorithms, daily sedative interruption) have been used for several decades. We sought to review the published evidence evaluating the utility of sedation minimization strategies on duration of ventilation, duration of ICU stay and short-term mortality (60 days).

Summary of the evidence: We performed a systematic review that included six relevant trials.[17-22] These six trials formed the evidence base that was used to inform the guideline panel's judgment. All were unblinded, randomized trials that compared protocols that minimized sedation to cohorts of patients that were not managed with such protocols. Three studies used nursing sedation algorithms and three used protocols for daily sedative interruption. The studies included patients from both medical and surgical ICUs. For the outcomes of duration of ventilation and duration of ICU stay, all six trials had relevant data. For the outcome of short-term mortality, only three of the studies had relevant data.[17,19,20]

The outcome of duration of mechanical ventilation was assessed by the group to be of critical importance. Six trials were pooled via meta-analysis for the outcome of duration of mechanical ventilation (695 patients received protocolized sedation, 699 patients received no protocolized sedation). The six studies were judged to have serious risk of bias. The majority of studies did not blind patients, personnel or outcome assessors. Additionally, protocol adherence was not

measured or reported in the majority of studies. They were also noted to have serious levels of inconsistency and imprecision (i.e. wide confidence intervals around the absolute effect). Accordingly, the evidence was noted to be of very low quality.

Six trials were pooled via meta-analysis for the outcome of ICU length of stay (695 patients received protocolized sedation, 699 patients received no protocolized sedation). This outcome was noted by the group to be of critical importance. The six studies were noted to have serious risk of bias. They were also noted to have serious levels of inconsistency and imprecision. Accordingly, the evidence was noted to be of very low quality.

Six trials were pooled via meta-analysis for the outcome of short-term mortality (203/695 mortality with protocolized sedation, 217/699 mortality with no protocolized sedation). This outcome was noted by the group to be of critical importance. The six studies were noted to have serious risk of bias. In contrast to the previous two PICO outcome questions, the levels of inconsistency and imprecision were not noted to be serious. Accordingly, the evidence was noted to be of moderate quality.

The summary of the pooled evidence showed no significant difference in the duration of mechanical ventilation in the protocolized sedation group (mean difference 1.00 day shorter; 95% CI-2.14 to 0.14)(Table 5). The summary of the pooled evidence showed a shorter ICU length of stay in the protocolized sedation group (mean difference 1.78 days shorter; 95% confidence intervals -3.41 to -0.14). The summary of the pooled evidence showed no significant difference in short-term mortality in the protocolized sedation group (RR 0.93; 95% confidence intervals 0.77 to 1.11; p = 0.42).

An important limitation of the evidence subjected to meta-analysis was the wide variation in management of the control groups across the six studies. Those studies demonstrating no benefit of protocolized sedation strategies tended to have lighter levels of sedation in the control groups compared to those that did demonstrate a benefit.

Two studies that may inform practitioners concerning sedation strategies were not included in the analysis. One study that randomized 430 patients receiving mechanical ventilation to either a sedation protocol or to a sedation protocol plus daily sedation interruption demonstrated no difference in the duration of mechanical ventilation or in ICU length of stay.[23] In a different

approach, Strom and colleagues enrolled 140 patients receiving mechanical ventilation in a study that assigned patients to receive no sedation as the study intervention, compared with a sedation protocol with daily sedation interruption.[24] Of the patients who were alive and receiving mechanical ventilation after 48 hours, patients in the "no sedation" group had more ventilator free days, and a shorter ICU stay, than did those receiving daily sedation interruption. These studies were not included in the analysis because their intervention and comparator treatments did not match those stipulated by the PICO question.

Despite the limitations of the evidence, the panel judged the desirable effects of sedation protocols aimed at minimizing sedation (shorter duration of ICU stay and possible trend of reduced duration of ventilation) to outweigh the undesirable effects associated with not minimizing sedation in ventilated patients.

CHEST/ATS Recommendation: For acutely hospitalized patients ventilated for more than 24 hours, we suggest protocols attempting to minimize sedation. (Conditional recommendation, Low quality of evidence).

Remarks: There is insufficient evidence to recommend any protocol over another.

Values and Preferences: This recommendation places a high value on reducing mechanical ventilation duration and ICU length of stay, and views the burden of protocolized sedation as very low.

Question #3: In high-risk patients receiving mechanical ventilation for more than 24 hours who have passed an SBT, does extubation to preventative NIV compared to no NIV have a favorable effect on duration of ventilation, ventilator-free days, extubation success (liberation > 48 hours), duration of intensive care unit (ICU) stay, short-term mortality (60 days), or long-term mortality?

Background: Patients intubated for acute respiratory failure are at increased risk for complications including infection and multi-system organ failure.[25] The risk for complications and mortality rises with increasing duration of mechanical ventilation, as do the associated health care costs.[26] Delaying endotracheal tube removal in patients who otherwise appear ready for extubation adversely affects outcome by increasing the risk for pneumonia and the length of ICU and hospital stay when compared to patients extubated in a timely manner.[27] Conversely, studies

have found that patients requiring re-intubation (extubation failure) after satisfactorily tolerating an SBT have increased risk for complications, prolonged hospital stay and significantly increased mortality.[28]

NIV improves outcomes in patients with acute respiratory failure. Application of NIV to patients suffering from respiratory failure due to acute exacerbations of chronic obstructive pulmonary disease (COPD) reduces the need for intubation, the frequency of complications, the hospital length of stay, and the mortality rate compared to standard therapy.[29] Patients with acute cardiogenic pulmonary edema and respiratory failure have a more rapid improvement in respiratory distress, hypercapnia, metabolic acidosis, and reduction in intubation rate when NIV is employed compared with oxygen therapy alone.[30] The use of NIV in immunocompromised hosts with diffuse pulmonary infiltrates reduces the intubation rate as well as ICU and hospital mortality.[31]

While there has been considerable support for the use of NIV in selected groups of patients presenting with respiratory failure, the results have been less well defined for the application of NIV to patients following extubation. In one randomized trial in 221 patients who developed respiratory failure a mean of 9 hours after extubation, NIV was not effective in reducing the need for re-intubation and was associated with a higher ICU mortality rate in comparison with standard medical therapy (including supplemental oxygen and bronchodilators) in at-risk patients who had been extubated following a successful spontaneous breathing trial but subsequently developed respiratory failure.[32] In contrast, other trials show that NIV applied immediately after extubation may reduce re-intubation rates in critically ill patients, with meta-analyses of these studies indicating that duration of MV, ventilator-associated pneumonia, ICU length of stay, hospital length of stay, and mortality may also be improved.[33,34] We examined available data on the use of NIV immediately after extubation for ventilated patients who had passed an SBT and were at high risk of extubation failure to determine the effect of this treatment on the need for re-intubation, ICU length of stay, and short- and long-term mortality.

Summary of the evidence: Five randomized, controlled trials (RCT) met criteria for our assessment of the data. Nava and colleagues randomized 97 high-risk patients who were extubated following successful SBT to receive either NIV or standard care one hour after extubation.[35] High-risk patients were those who failed more than one SBT, had a $PaCO_2$>45 mm

Hg after extubation, more than one co-morbid condition, a weak cough, or upper airway stridor that did not require immediate re-intubation. The NIV group had a reduced need for re-intubation (4/48 v 12/49, p=0.027) and a reduction in ICU mortality (3/48 v 9/49, p<0.01).

Ferrer and colleagues randomized 162 patients to non-invasive ventilation or standard care after extubation.[36] Patients were selected following a successful SBT if they had risk factors for re-intubation defined as: age>65 years, cardiac failure as a cause for respiratory failure, or an APACHE II score greater than 12 on the day of extubation. Patients receiving NIV had reduced re-intubation rates (13/79 v 27/83, p=0.029) and ICU mortality (2/79 v 12/83, p=0.015), but not ICU length of stay or long-term mortality. Of interest, those patients who were hypercapnic during the SBT had reduced ICU mortality if they received NIV compared with standard care post-extubation (0/27 v 4/22, p=0.035). In follow-up, Ferrer and colleagues randomized 106 mechanically ventilated patients who had hypercapnia with a PaCO2>45 mm Hg during a successful SBT to post-extubation NIV or conventional oxygen treatment.[37] Respiratory failure defined by predetermined criteria was more frequent in the conventional oxygen group than in the NIV group (25/52 v 8/54, p<0.0001). Re-intubation rates, ICU length of stay, and ICU mortality rates were not statistically different between the groups, which was attributed to the fact that NIV was used as a "rescue strategy" in those patients developing respiratory failure. Mortality at 90 days, a secondary endpoint for this study, was lower in the patients receiving NIV than in the patients receiving conventional oxygen treatment (6/54 v 16/52, p=0.0244).

Khilnani et al. studied 40 patients with an acute exacerbation of COPD requiring mechanical ventilation.[38] After passing a weaning assessment, patients were randomized to receive NIV immediately following extubation versus conventional therapy, with no significant difference found between groups in terms of re-intubation or ICI length of stay. Mohamed and Abdalla examined outcomes in 120 patients randomized to NIV or an oxygen mask.[39] They found that patients treated with NIV had reduced ICU mortality (6.6% v16.6%, p<0.035) and re-intubation rates (15% v 25%, p=0.04) when compared with controls.

In assessing the aggregate data, all 5 studies noted above addressed extubation success. NIV was favored over standard care in high-risk patients following extubation (RR=1.14; 95% CI: 1.05-1.23) (Table 6). Four studies[35-37,39] examined the outcomes of ICU length of stay and short-term mortality, with the finding that NIV was significantly better than conventional therapy for each

outcome (ICU LOS: mean difference -2.48 days, 95% CI -4.03 to -0.93; short-term mortality: RR=0.37, 95% CI 0.19-0.70). Two studies[36,37] demonstrated significantly lower long-term mortality with NIV as compared with standard care in high-risk patients following extubation (RR=0.58, 95% CI 0.27-1.22). There was heterogeneity between studies in defining the high risk patient. Risk factors included a variety of co-morbidities to include COPD, CHF, hypercapnia, older age, and a higher severity of illness. Patients under 65 years of age, who pass their first SBT, have a normal pCO_2, have no significant respiratory or cardiac co-morbidities, and can protect their airway, would be considered to be at low risk for re-intubation in all of the included studies.

Two studies suggest that high-flow nasal cannula may improve patient outcomes after extubation in patients receiving mechanical ventilation. Maggiore and colleagues assigned 105 patients mechanically ventilated for more than 24 hours to either a Venturi mask or nasal high-flow therapy after extubation.[40] Patients receiving high-flow nasal therapy were less likely to be re-intubated than those patients receiving treatment by Venturi mask (4% v 21%, p=0.01). Hernandez and colleagues treated 264 patients receiving mechanical ventilation at low risk for re-intubation after extubation with a high-flow nasal cannula, and compared this group with 263 patients receiving conventional oxygen therapy.[41] Patients receiving high-flow nasal cannula treatment had less respiratory failure (22/264 v 38/263, p=0.03) and a lower rate of re-intubation at 72 hours (13/264 v 32/263, p=0.004). These studies became available after the literature search was conducted, but may inform clinicians about post-extubation strategies similar to preventative NIV.

The panel judged the desirable consequences of extubation to preventative NIV to clearly outweigh the undesirable consequences. The desirable consequences considered by the panel included improved extubation success as well as a 2-day reduction of ICU length of stay. The panel noted that potential undesirable consequences of NIV include nasal bridge damage, conjunctivitis, and nasal ulceration. However, the desirable consequences outweigh these potential harms.

CHEST/ATS Recommendation: For patients at high risk for extubation failure who have been receiving mechanical ventilation for more than 24 hours, and who have passed a spontaneous

breathing trial, we recommend extubation to preventative NIV (Strong recommendation, moderate grade of evidence).

Remarks: Patients at high risk for failure of extubation may include those patients with hypercapnia, COPD, CHF, or other serious co-morbidities. Physicians may choose to avoid extubation to NIV in selected patients for patient-specific factors including but not limited to the inability to receive ventilation through a mask or similar interface. Physicians who choose to use NIV should apply such treatment immediately after extubation to realize the outcome benefits.

Values and Preferences: This recommendation places a high value on early extubation which will lead to substantial benefits including a reduction in ventilator-related and ICU-related complications, and to reductions in health care costs accruing from reduction in ICU stay.

SUMMARY

These clinical practice guidelines include a strong recommendation that patients who are at high risk for extubation failure and who have passed a spontaneous breathing trial be extubated to preventative NIV. Moderate quality evidence exists that clinically important outcomes are improved by this strategy. Conditional recommendations are to use inspiratory pressure augmentation during the initial SBT, and to employ protocols to minimize sedation, in patients ventilated for more than 24 hours. The latter two recommendations are limited by the quality of the available evidence. As further research becomes available, these recommendations will be readdressed and updated.

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Table 1. PICO Questions

Study Characteristic	Inclusion Criteria	Exclusion Criteria
KQ 1: Spontaneous Breathing Trial		
Populations	• Acutely hospitalized patients ventilated for >24 hours	Patients who didn't pass first SBT
Interventions	• SBT conducted with inspiratory pressure augmentation (i.e. pressure support ventilation, automatic tube compensation)	None
Comparators	• SBT conducted without inspiratory pressure augmentation	None
Outcomes	• Duration of ventilation • Ventilator-free days • Extubation Success • Successful SBT • Duration of ICU stay • Short-term mortality (<60 days) • Long-term mortality	None
Study Design	• Systematic Reviews, RCT, Observational	None
KQ 2: Sedation Protocols		
Populations	• Acutely hospitalized patients ventilated for >24 hours	None
Interventions	• Protocolized attempts to seek minimum sedation required	None
Comparators	• An approach that does not seek to minimize sedation	None
Outcomes	• Duration of ventilation • Ventilator-free days • Extubation Success • Duration of ICU stay • Short-term mortality (<60 days) • Long-term mortality	None
Study Design	• Systematic Reviews, RCT	None
KQ 3: Extubation to non-invasive ventilation		
Populations	• Patients ventilated for >24 hours, who have passed an SBT, but are at high risk for extubation failure	None
Interventions	• Extubation to preventative non-invasive ventilation	None
Comparators	• Extubation without preventative non-invasive ventilation	None
Outcomes	• Duration of ventilation • Ventilator-free days • Extubation Success • Duration of ICU stay • Short-term mortality (<60 days) • Long-term mortality	None
Study Design	• Systematic Reviews, RCT, Observational	None

Table 2. Quality of Evidence Grades

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 3. Implications of strong and weak (conditional) recommendations for different users of guidelines

	Strong Recommendation	**Weak (conditional) Recommendation**
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Table 4. Evidence Profile for conducting the spontaneous breathing trial with or without inspiratory pressure augmentation

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SBT conducted with pressure augmentation**	**without pressure augmentation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Extubation Success												
4	randomised trials	serious [1]	not serious	not serious	not serious	none	312/423 (73.8%)	303/452 (67.0%)	**RR 1.09** (1.02 to 1.18)	60 more per 1000 (from 13 more to 121 more)	MODERATE [1]	CRITICAL
Successful SBT												
3	randomised trials	serious [1]	not serious	not serious	not serious	none	388/488 (79.5%)	331/452 (73.2%)	**RR 1.11** (1.03 to 1.18)	81 more per 1000 (from 22 more to 132 more)	MODERATE [1]	IMPORTANT
Short term Mortality (assessed with: ICU Mortality)												
2	randomised trials	serious [1]	not serious	not serious	serious [2]	none	26/300 (8.7%)	36/307 (11.7%)	**RR 0.74** (0.45 to 1.24)	30 fewer per 1000 (from 28 more to 64 fewer)	LOW [1,2]	IMPORTANT
ICU LOS												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SBT conducted with pressure augmentation	without pressure augmentation	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [3]	not serious	not serious	not serious	none	-/267	not pooled	ICU LOS was reported in 2 trials (Esteban 1997 and Matić 2004) Estimated effects were reported as median values: 270 (235-290) and 331 (292-396) hours observed in SBT with pressure and without pressure, respectively in Matić 2004; Esteban 1997 showed an estimated effect favoring the SBT without pressure (t-tube) with median values of 288 hours and 240 hours for SBT with pressure and t-tube		MODERATE [3]	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

1. One study with unclear randomization methods, one study with unclear allocation concealment methods, and two studies with unclear report on outcome assessment
2. Low number of events; 95% CI crosses line of no effect
3. Unclear randomization methods and unclear if outcome assessors were blinded in Matic 2004 study

Table 5. Evidence Profile for protocols attempting to minimize sedation compared to no attempt to minimize sedation

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Protocolized sedation**	**no sedation minimization**	**Relative (95% CI)**	**Absolute (95% CI)**		
Duration of Ventilation (assessed with: days)												
6	randomised trials	serious [1]	serious [2]	not serious	serious [3]	none	528	531	-	MD **1 days lower** (2.14 lower to 0.14 higher)	VERY LOW	IMPORTANT
ICU Length of Stay												
6	randomised trials	serious [1]	serious [4]	not serious	serious [3]	none	695	699	-	MD **1.78 days fewer** (3.41 fewer to 0.14 fewer)	VERY LOW	IMPORTANT
Short-term Mortality												
6	randomised trials	serious [1]	not serious	not serious	not serious	none	203/695 (29.2%)	217/699 (31.0%)	**RR 0.93** (0.77 to 1.11)	**22 fewer per 1000** (from 34 more to 71 fewer)	MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

1. Majority of studies did not blind patients, personnel or outcome assessors. Additionally, compliance to protocol (intervention) was not reported or measured in a majority of studies, which could possibly effect reported differences between groups
2. I-squared value of 62%
3. Fairly wide confidence intervals around absolute effect
4. I-squared value of 71%

Table 6. Evidence Profile for extubation to non-invasive ventilation compared to extubation without non-invasive ventilation

Bibliography: 1) Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Critical care medicine. 2005;33(11):2465-2470. 2) Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006;173(2):164-170. 3) Ferrer M, Sellares J, Valencia M, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. Lancet. 2009;374(9695):1082-1088. 4) Khilnani GC, Galle AD, Hadda V, Sharma SK. Non-invasive ventilation after extubation in patients with chronic obstructive pulmonary disease: a randomized controlled trial. Anaesth Intensive Care. 2011;39:217-223. 5) Mohamed KAE, Abdalla MH. Role of non invasive ventilation in limiting re-intubation after planned extubation. Egyptian Journal of Chest Diseases and Tuberculosis. 2013;62(4):669-674.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Extubation to noninvasive ventilation**	**extubation without noninvasive ventilation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Extubation Success												
5	randomised trials	serious [1]	not serious	not serious	not serious	none	230/261 (88.1%)	204/264 (77.3%)	**RR 1.14** (1.05 to 1.23)	**11 fewer per 100** (from 4 fewer to 18 fewer)	MODERATE	CRITICAL
ICU LOS												
4	randomised trials	serious [1]	not serious	not serious	not serious	none	241	244	-	MD **2.48 days fewer** (4.03 fewer to 0.93 fewer)	MODERATE	IMPORTANT
Short-term Mortality (ICU Mortality)												
4	randomised trials	serious [1]	not serious	not serious	serious [2]	none	12/241 (5.0%)	35/244 (14.3%)	**RR 0.37** (0.19 to 0.70)	**9 fewer per 100** (from 4 fewer to 12 fewer)	LOW	IMPORTANT
Long-term Mortality (follow up: 90 days)												
2	randomised trials	not serious	serious [3]	not serious	serious [4]	none	24/133 (18.0%)	40/135 (29.6%)	**RR 0.58** (0.27 to 1.22)	**12 fewer per 100** (from 7 more to 22 fewer)	LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. Unclear randomization methods and allocation concealment in studies. Many studies did not blind outcome assessors or research personnel
2. Low number of events
3. I-squared value of 57%

CHEST® Online Supplement

e-Table 1. COI Grid

Panelist's Name	PICO 1: In acutely hospitalized patients who have been ventilated >24 hours (P), should the spontaneous breathing trial (SBT) be conducted with inspiratory pressure augmentation (I) or no inspiratory pressure augmentation (C)?	PICO 2: Should acutely hospitalized patients who have been ventilated >24 hours (P) receive protocolized attempts to minimize sedation (I) or an approach that does not seek to minimize sedation (C)?	PICO 3: Should patients who have been ventilated >24 hours and passed an SBT, but are at high risk for extubation failure (P), be extubated with immediate non-invasive ventilation (I) or without immediate non-invasive ventilation (C)?	PICO 4: Should mechanically ventilated patients being considered for extubation (P) receive cuff leak test-based management (I) or not (C)?	PICO 5: Should acutely hospitalized patients who have been ventilated >24 hours (P) be managed with physical therapy protocols directed toward early mobilization (I) or be managed without protocolized attempts at early mobilization (C)?	PICO 6: Should acutely hospitalized patients who have been ventilated >24 hours (P) be managed with protocolized liberation (I) or non-protocolized liberation (C)?	All disclosures
Burns, Suzanne, RN, MSN, ACNP, RRT	Copyright for BWAP (Burns Wean Assessment Program);	Copyright for BWAP (Burns Wean Assessment Program);.	Copyright for BWAP (Burns Wean Assessment Program);	Copyright for BWAP (Burns Wean Assessment Program);.	Copyright for BWAP (Burns Wean Assessment Program);	Copyright for BWAP (Burns Wean Assessment Program);	Copyright for BWAP (Burns Wean Assessment Program)
Epstein, Scott, MD, FCCP	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	Royalties or In-kind Benefits – from the following: UpToDate, Kluwers, Author of several chapters

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Esteban, Andres, MD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No COI's to disclose
Fan, Eddy, MD	PSI Foundation Grant Mechanical Ventilation; Nihon Khoden Grant HFOV	No relevant COIs	No relevant COIs	No relevant COIs	CIHR Grant Early Rehabilitation to Institution	PSI Foundation Grant Mechanical Ventilation to Institution; Nihon Khoden Grant HFOV;	PSI Foundation Grant Mechanical Ventilation to Institution; PSI Foundation Grant ECMO to Institution; Nihon Khoden Grant HFOV to Institution; CIHR Grant Early Rehabilitation to Institution; Alung Technologies Inc Speaking Activity; ATS MV in ARDS Guideline Chair; SCCM Scientific Review Committee Chair
Ferrer, Miguel, MD, PhD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No COI's to disclose
Fraser, Giles, PharmD, MCCM	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No COI's to disclose

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Girard, Timothy, MD	No relevant COIs	Speaking Activity Hospira, Inc.; DSMB data and safety monitoring board; activites occurred within past 3 years but have ended	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	Speaking Activity Hospira, Inc.; DSMB data and safety monitoring board; activites occurred within past 3 years but have ended
Gong, Michelle, MD	NHLBI Grant Lung Injury Prevention; CMS Grant Electronic Interface for acute care; NHLBI Grant Low cost pragmatic trials to institution	NIA Grant Delirium; NHLBI Grant Lung Injury Prevention; CMS Grant Electronic Interface for acute care; NHLBI Grant Low cost pragmatic trials to institution	NHLBI Grant Lung Injury Prevention; CMS Grant Electronic Interface for acute care; NHLBI Grant Low cost pragmatic trials to institution	NHLBI Grant Lung Injury Prevention; CMS Grant Electronic Interface for acute care; NHLBI Grant Low cost pragmatic trials to institution	NHLBI Grant Lung Injury; CMS Grant Electronic Interface for acute care; NHLBI Grant Low cost pragmatic trials to institution	NHLBI Grant Lung Injury Prevention; CMS Grant Electronic Interface for acute care; NHLBI Grant Low cost pragmatic trials to institution	NHLBI Grant Lung Injury Prevention in salary support; CMS Grant Electronic Interface for acute care; NIA Grant Delirium; NHLBI Grant Low cost pragmatic trials to institution

Hough, Catherine, MD	NIH/NHLBI Grant Clinical Research Network for the Treatment of ALI and ARDS; NIH/NBLBI Improving decision making for patients with prolonged mechanical ventilation to institution; University of Washington Grant Insomnia and functional recovery after acute lung injury; PCORI Grant Improving psychological distress among critical illness survivors and their informal; NIH/INI Grant "The Mind USA Study"; NIH/NHLBI Grant "Identifying Effective Strategies to Disclose Prognosis in Patients with ARDS"	NIH/NHLBI Grant Clinical Research Network for the Treatment of ALI and ARDS; NIH/NBLBI Improving decision making for patients with prolonged mechanical ventilation to institution; University of Washington Grant Insomnia and functional recovery after acute lung injury; PCORI Grant Improving psychological distress among critical illness survivors and their informal; NIH/INI Grant "The Mind USA Study"; NIH/NHLBI Grant "Identifying Effective Strategies to Disclose Prognosis in Patients with ARDS"	NIH/NHLBI Grant Clinical Research Network for the Treatment of ALI and ARDS; NIH/NBLBI Improving decision making for patients with prolonged mechanical ventilation to institution; University of Washington Grant Insomnia and functional recovery after acute lung injury; PCORI Grant Improving psychological distress among critical illness survivors and their informal; NIH/INI Grant "The Mind USA Study"; NIH/NHLBI Grant "Identifying Effective Strategies to Disclose Prognosis in Patients with ARDS"	NIH/NHLBI Grant Clinical Research Network for the Treatment of ALI and ARDS; NIH/NBLBI Improving decision making for patients with prolonged mechanical ventilation to institution; University of Washington Grant Insomnia and functional recovery after acute lung injury; PCORI Grant Improving psychological distress among critical illness survivors and their informal; NIH/INI Grant "The Mind USA Study"; NIH/NHLBI Grant "Identifying Effective Strategies to Disclose Prognosis in Patients with ARDS"	NIH/NHLBI Grant Clinical Research Network for the Treatment of ALI and ARDS; NIH/NBLBI Improving decision making for patients with prolonged mechanical ventilation to institution; University of Washington Grant Insomnia and functional recovery after acute lung injury; PCORI Grant Improving psychological distress among critical illness survivors and their informal; NIH/INI Grant "The Mind USA Study"; NIH/NHLBI Grant "Identifying Effective Strategies to Disclose Prognosis in Patients with ARDS"	NIH/NHLBI Grant Clinical Research Network for the Treatment of ALI and ARDS; NIH/NBLBI Improving decision making for patients with prolonged mechanical ventilation to institution; University of Washington Grant Insomnia and functional recovery after acute lung injury; PCORI Grant Improving psychological distress among critical illness survivors and their informal; NIH/INI Grant "The Mind USA Study"; NIH/NHLBI Grant "Identifying Effective Strategies to Disclose Prognosis in Patients with ARDS"	NIH/NHLBI Grant Clinical Research Network for the Treatment of ALI and ARDS; NIH/NBLBI Improving decision making for patients with prolonged mechanical ventilation to institution; University of Washington Grant Insomnia and functional recovery after acute lung injury; PCORI Grant Improving psychological distress among critical illness survivors and their informal; NIH/INI Grant "The Mind USA Study"; NIH/NHLBI Grant "Identifying Effective Strategies to Disclose Prognosis in Patients with ARDS"
Kress, John, MD, FCCP	No relevant COIs	Speaking Activity Hospira	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	Speaking Activity Hospira

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Mehta, Sangeeta, MD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No COIs to disclose
Morris, Peter, MD, FCCP	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	NIH Grant Early ICU Rehablilitation in Mechanically Ventilated; Department of Defense Grant Early ICU Rehabilitation of Burn Patients requiring mechanical ventilation	No relevant COIs	NIH Grant Early ICU Rehablilitation in Mechanically Ventilated Patients; NIH Grant ARDS network; Department of Defense Grant Early ICU Rehabilitation of Burn Patients requiring mechanical ventilation; involved in many industry studies that have contracts with Wake Forest. Committee membership - SCCM committee on the institution of ABC guidelines.
Nanchal, Rahul, MD, FCCP	Clinical and Translational Science Institute (CTSI) Grant Biomarkers of Aspiration and Risk of Ventilator Associated Events	Clinical and Translational Science Institute (CTSI) Grant Biomarkers of Aspiration and Risk of Ventilator Associated Events	Clinical and Translational Science Institute (CTSI) Grant Biomarkers of Aspiration and Risk of Ventilator Associated Events	Clinical and Translational Science Institute (CTSI) Grant Biomarkers of Aspiration and Risk of Ventilator Associated Events	No relevant COIs	Clinical and Translational Science Institute (CTSI) Grant Biomarkers of Aspiration and Risk of Ventilator Associated Events	Clinical and Translational Science Institute (CTSI) Grant Biomarkers of Aspiration and Risk of Ventilator Associated Events

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Ouellette, Daniel, MD, FCCP	Cardeas Pharmaceutical Grant $32,000 per year for two years to institution. Ventilator Associated Pneumonia -	Cardeas Pharmaceutical Grant $32,000 per year for two years to institution. Ventilator Associated Pneumonia -	Cardeas Pharmaceutical Grant $32,000 per year for two years to institution. Ventilator Associated Pneumonia -	Cardeas Pharmaceutical Grant $32,000 per year for two years to institution. Ventilator Associated Pneumonia -	Cardeas Pharmaceutical Grant $32,000 per year for two years to institution. Ventilator Associated Pneumonia -	Cardeas Pharmaceutical Grant $32,000 per year for two years to institution. Ventilator Associated Pneumonia -	Cardeas Pharmaceutical Grant $32,000 per year for two years to institution. Ventilator Associated Pneumonia – Chair, Guideline Oversight Committee
Pawlik, Amy, DPT	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No COI's to disclose

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Schmidt, Gregory, MD, FCCP	No relevant COIs	NIH Grant ICU delrium	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	NIH Grant ICU delrium; Spectral Diagnositics Grant Septic shock; Author Royalty UpToDate 9/10/2013
Schweickert, William, MD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	Hill Rom Grant Epidemiology of Early Mobilization	No relevant COIs	Hill Rom Grant Epidemiology of Early Mobilization
Sessler, Curtis, MD, FCCP	No relevant COIs	Speaking Activity Hospira payment from AACN	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	Speaking Activity Hospira payment from AACN Copywrite holder for RASS is Virginia Commonwealth University: Sessler, C.N., Grap, M.J., Brophy, G., Elswick, R.K. "Richmond Agitation-Sedation Scale (RASS)". Copyright. Registration number TX 7-616-498.

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Stroem, Thomas, MD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	Danish Strategic Research Council Grant Intensive Care to Professor Palle Toft - no salary support
Truwit, Jonathon, MD, FCCP	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	Research Support Astra Zeneca - Ticagrelor for Community Acquired Pneumonia; Advisory Board Spiration Data and Safety monitoring Advisory Board

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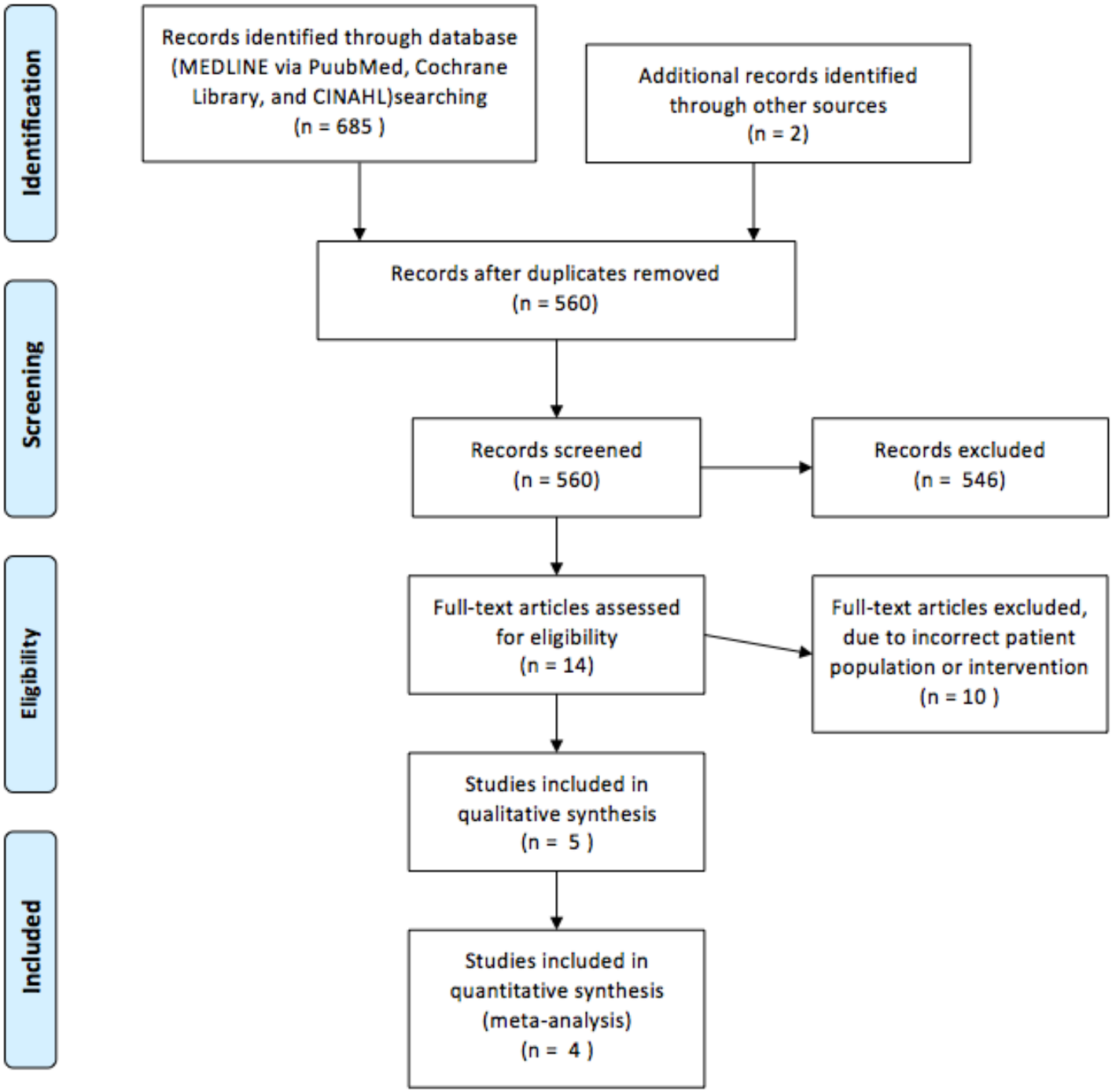
e-Figure 1 – PRISMA Flow Diagram for PICO Question 1 – "In patients ventilated for 24 hours or more, should the spontaneous breathing trial be conducted with pressure augmentation or without pressure augmentation?"



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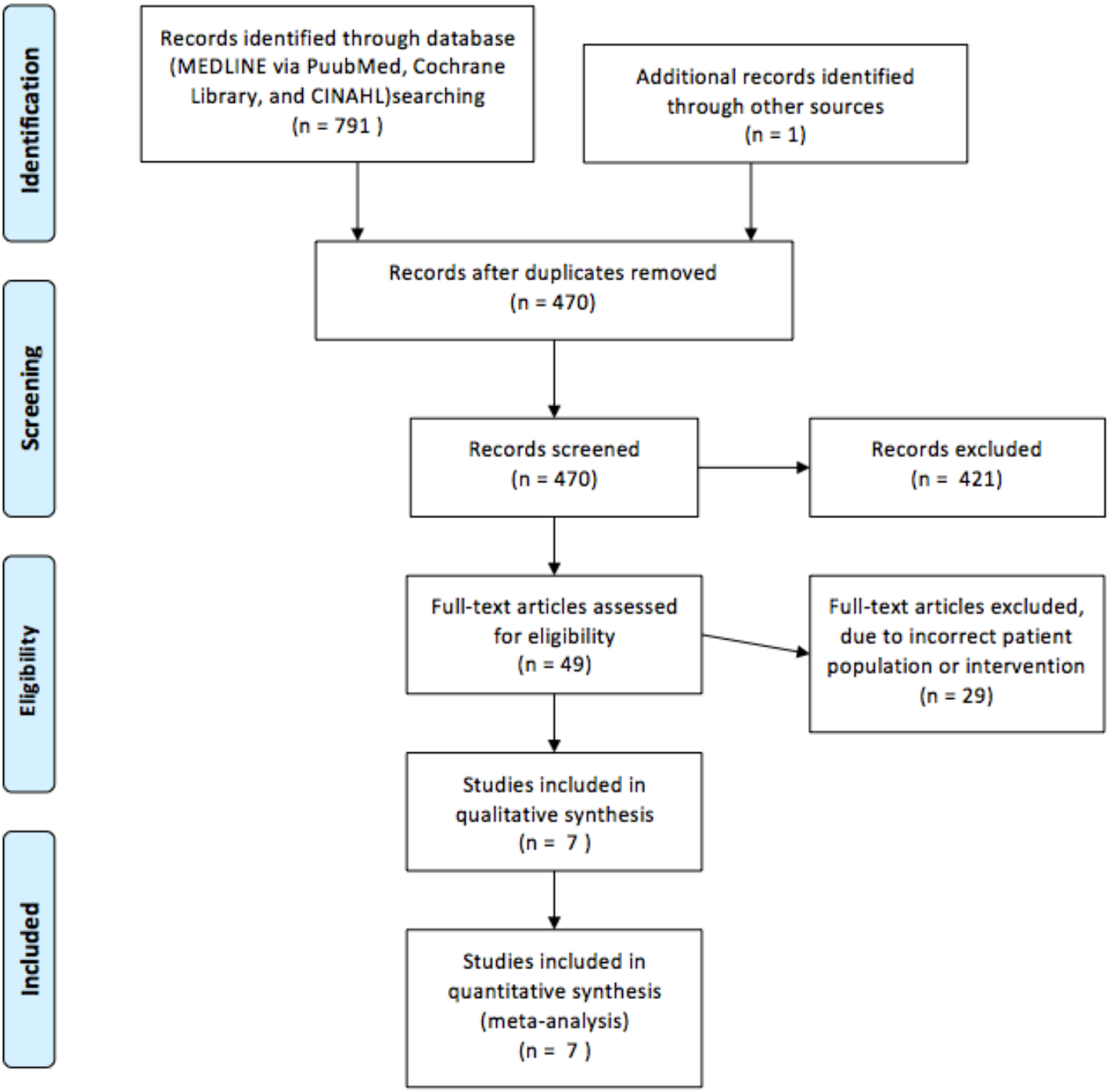
e-Figure 2. PRISMA Flow Diagram for PICO Question 2: "In acutely hospitalized patients ventilated for more than 24 hours, do protocols attempting to minimize sedation compared to an approach that does not attempt to minimize sedation impact duration of ventilation, duration of ICU stay and short-term mortality (60 days)?"



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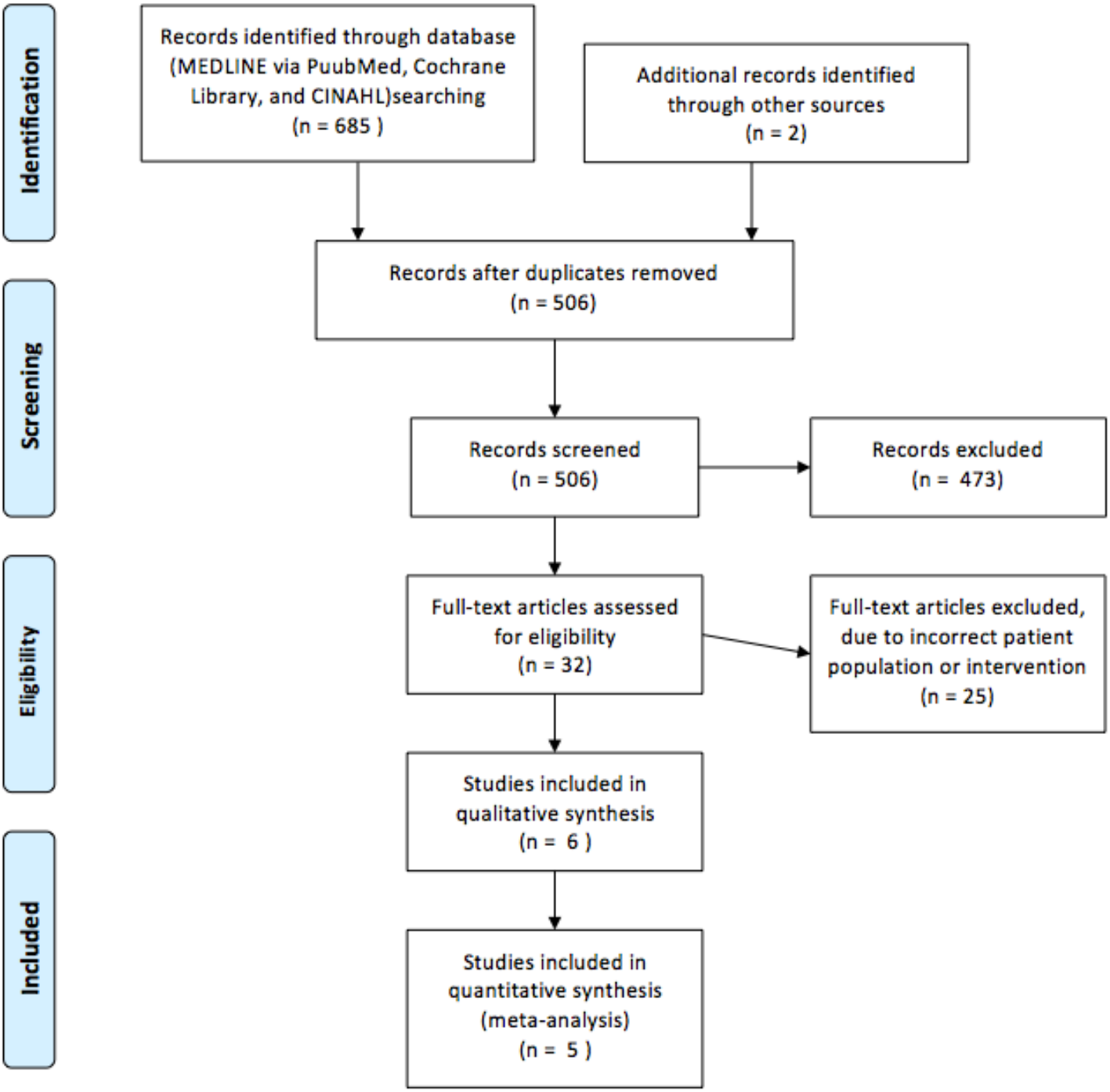
e-Figure 3. PRISMA Flow Diagram for PICO Question 3: "In acutely hospitalized patients ventilated for more than 24 hours, do protocols attempting to minimize sedation compared to protocols that do not attempt to minimize sedation impact duration of ventilation, duration of ICU stay and short-term mortality (60 days)?"



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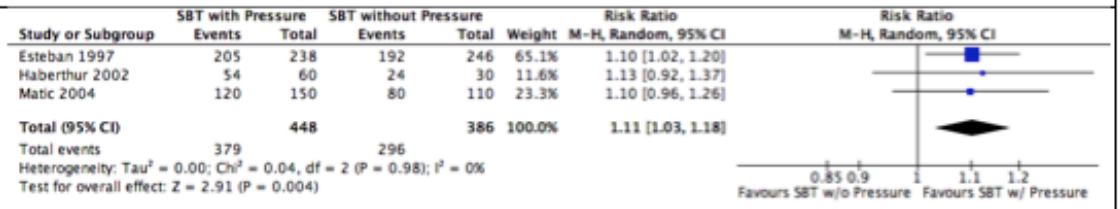
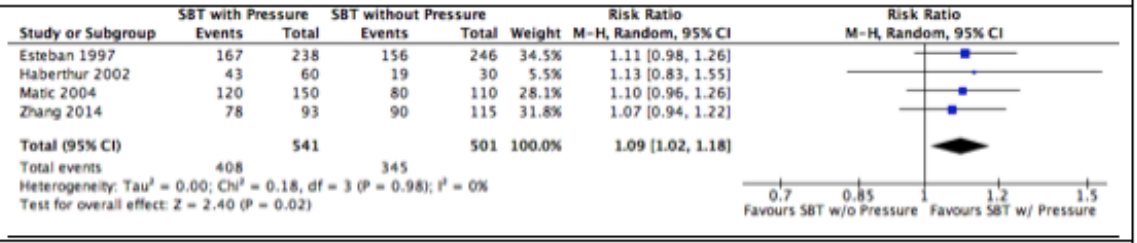
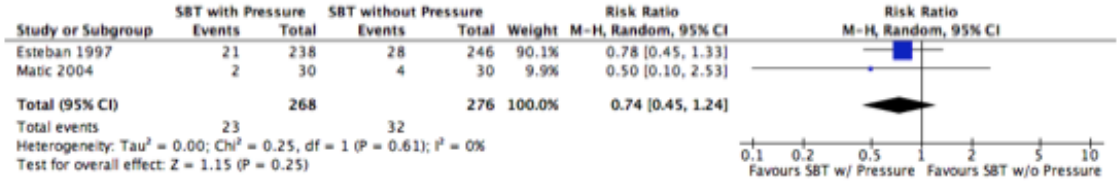
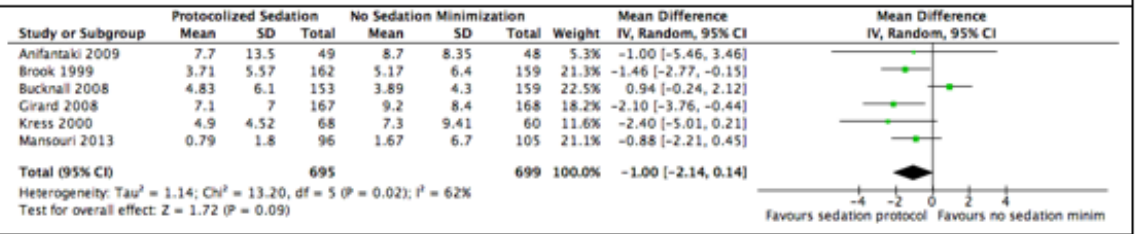
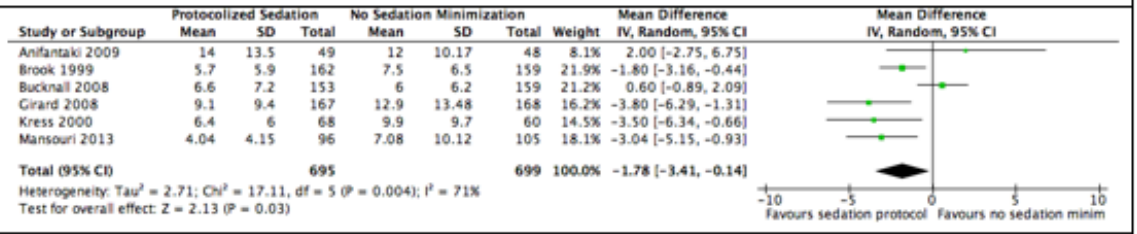
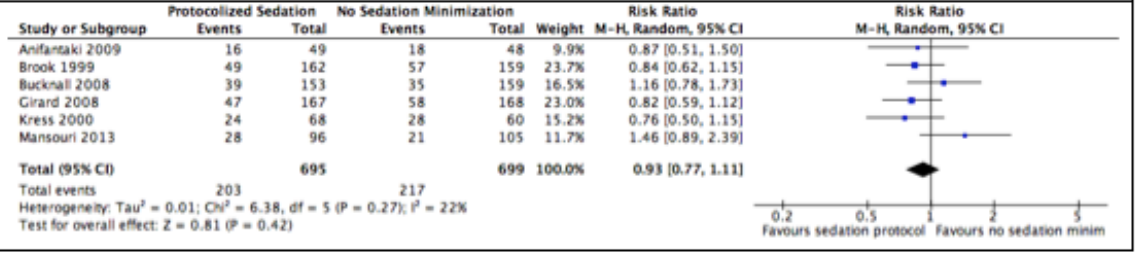
e-Table 2. Forest Plots by Recommendation and Outcome

Topic and Recommendation #	Outcome	Forest Plot
SBT, 1	Successful SBT	
SBT, 1	Extubation Success	
SBT, 1	Short-Term Mortality	
Sedation, 2	Duration of Ventilation	
Sedation, 2	ICU LOS	
Sedation, 2	Short-Term Mortality	

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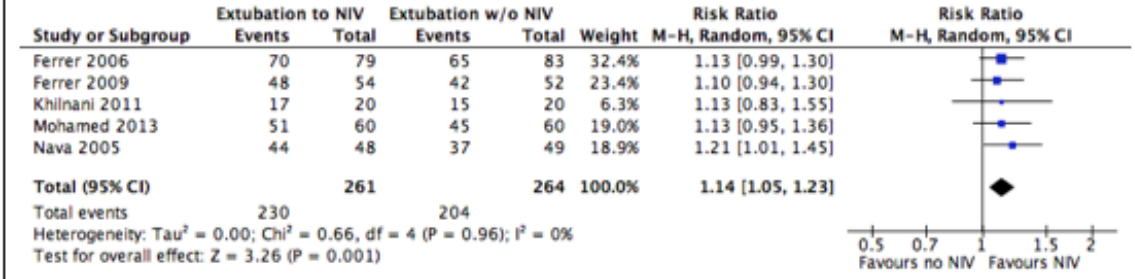
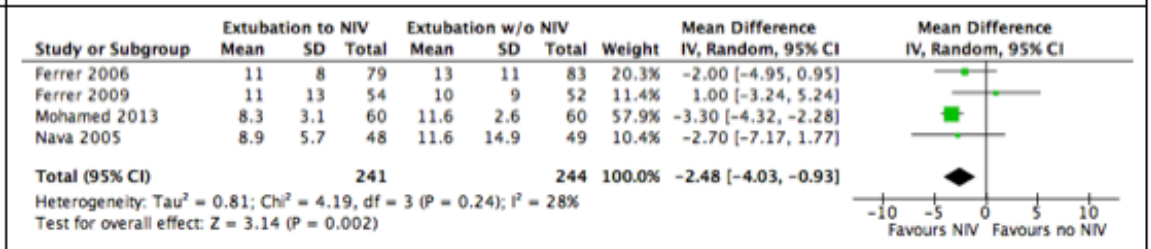
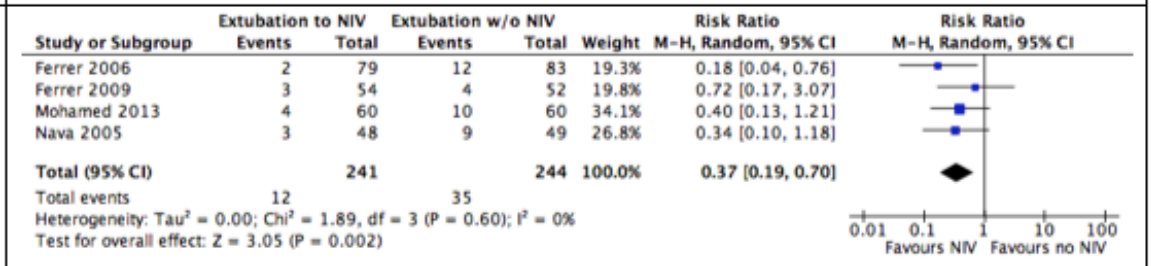
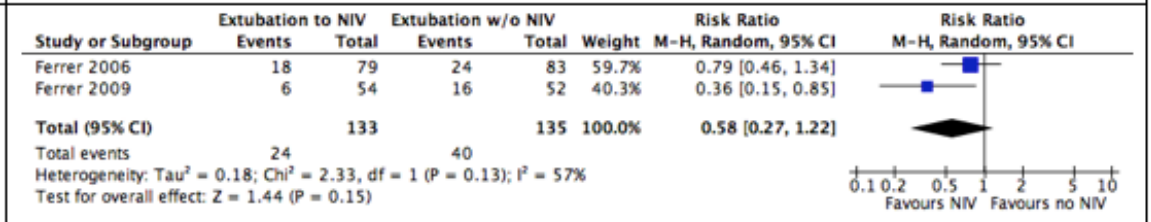
NIV, 3	Extubation Success	
NIV, 3	ICU LOS	
NIV, 3	Short-term Mortality	
NIV, 3	Long-term Mortality	

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e-Table 3. Evidence to Decision Framework for PICO 1

<table>
<tr><th></th><th>Criteria</th><th>Judgements</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is there a problem priority?</td><td>○ No
○ Probably no
○ Uncertain
○ Probably yes
● Yes
○ Varies</td><td>Several studies have demonstrated that about 75% of mechanically ventilated patients can be successfully extubated after passing a trial of spontaneous breathing. However, controversy still exists on the best technique used to conduct the SBT.</td><td></td></tr>
<tr><td rowspan="3">Benefits & harms of the options</td><td>What is the overall certainty of this evidence?</td><td>○ No included studies
○ Very low
○ Low
● Moderate
○ High</td><td rowspan="3">The relative importance or values of the main outcomes of interest:
<table>
<tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence (GRADE)</th></tr>
<tr><td>Extubation Success</td><td>CRITICAL</td><td>⨁⨁⨁◯ MODERATE</td></tr>
<tr><td>Successful SBT</td><td>IMPORTANT</td><td>⨁⨁⨁◯ MODERATE</td></tr>
<tr><td>Short term Mortality</td><td>IMPORTANT</td><td>⨁⨁◯◯ LOW</td></tr>
<tr><td>ICU LOS</td><td>IMPORTANT</td><td>⨁⨁⨁◯ MODERATE</td></tr>
</table></td><td rowspan="3"></td></tr>
<tr><td>Is there important uncertainty about how much people value the main outcomes?</td><td>○ Important uncertainty or variability
○ Possibly important uncertainty or variability
○ Probably no important uncertainty or variability
● No important uncertainty or variability
○ No known undesirable outcomes</td></tr>
<tr><td>Are the desirable anticipated effects large?</td><td>○ No
○ Probably no
○ Uncertain
● Probably yes
○ Yes
○ Varies</td></tr>
</table>

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	Criteria	Judgements	Research evidence	Additional considerations
	Are the undesirable anticipated effects small?	○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies		
	Are the desirable effects large relative to undesirable effects?	○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies		
Resource use	**Are the resources required small?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies		
	Is the incremental cost small relative to the net benefits?	○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies	No data was found on costs of the intervention, however, mean incremental charges of mechanical ventilation in ICU patients has been found to be on average $1,522 per day	
Equity	**What would be the impact on health inequities?**	○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ○ Varies		Not relevant.

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	Criteria	Judgements	Research evidence	Additional considerations
Acceptability	**Is the option acceptable to key stakeholders?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies		
Feasibility	**Is the option feasible to implement?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies		

Recommendation

Should SBT be conducted with pressure augmentation vs. without pressure augmentation be used in patients ventilated for more than 24hrs?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	○	○	○	●	○

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	○	○	●	○

Recommendation	In patients ventilated for 24 hours or more, we suggest that the initial SBT be conducted with pressure augmentation (5-8cm H2O)
Justification	
Subgroup considerations	This does not take into account the patients who failed the initial SBT. This also does not take into account patients with severe neuromuscular weakness
Implementation considerations	
Monitoring and evaluation	
Research possibilities	

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e-Table 4. Evidence to Decision Framework for PICO 2

<table>
<tr><th colspan="5">Assessment</th></tr>
<tr><th></th><th>Criteria</th><th>Judgements</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is there a problem priority?</td><td>○ No
○ Probably no
○ Uncertain
○ Probably yes
● Yes
○ Varies</td><td>Patients undergoing mechanical ventilation frequently require sedation and analgesia. There is growing evidence that suggests that over-sedation has been linked to both short-term (longer duration of ventilation, longer ICU and hospital lengths of stay) and long-term (psychological recovery) outcomes.</td><td></td></tr>
<tr><td>Benefits & harms of the options</td><td>What is the overall certainty of this evidence?</td><td>○ No included studies
○ Very low
● Low
○ Moderate
○ High</td><td>The relative importance or values of the main outcomes of interest:<table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence (GRADE)</th></tr></table></td><td></td></tr>
</table>

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Assessment				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
	Is there important uncertainty about how much people value the main outcomes?	○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	Duration of Ventilation — IMPORTANT — ⨁◯◯◯ VERY LOW ICU Length of Stay — IMPORTANT — ⨁◯◯◯ VERY LOW Short-term Mortality — IMPORTANT — ⨁⨁⨁◯ MODERATE	
	Are the desirable anticipated effects large?	○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies		
	Are the undesirable anticipated effects small?	○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies		

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Assessment				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
	Are the desirable effects large relative to undesirable effects?	○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies		
Resource use	**Are the resources required small?**	○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies		Workload.
	Is the incremental cost small relative to the net benefits?	○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	A systematic review of seven studies reported the impact of sedation protocols on the costs of sedative agents used; all found a reduction in the costs of sedative agents with protocolised sedation, which was reported as significant in four studies with values ranging from 22% to 94% of the cost for non-protocol managed sedation	

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Assessment				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
Equity	**What would be the impact on health inequities?**	○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ○ Varies		
Acceptability	**Is the option acceptable to key stakeholders?**	○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies		
Feasibility	**Is the option feasible to implement?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ● Varies		Practical issues - culture, staffing, etc.

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Recommendation

Should Protocolized sedation vs. no attempt to minimize sedation be used for patients mechanically ventilated for 24 hours or more?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	○	○	○	●	○

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	○	○	●	○

Recommendation	For acutely hospitalized patients ventilated for more than 24 hours, we suggest protocols attempting to minimize sedation. (Weak recommendation, Low quality of evidence)
Justification	
Subgroup considerations	
Implementation considerations	
Monitoring and evaluation	
Research possibilities	

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e-Table 5. Evidence to Decision Framework for PICO 3

<table>
<tr><th colspan="5">Assessment</th></tr>
<tr><th></th><th>Criteria</th><th>Judgements</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is there a problem priority?</td><td>○ No
○ Probably no
○ Uncertain
○ Probably yes
● Yes
○ Varies</td><td>Reintubation occurs in 4-23% of mechanically ventilated patients within 48-72 hours of planned extubation. Extubating patients to noninvasive ventilation (NIV) could provide a means of avoiding reintubation in high risk patients.</td><td>Harms associated with the need of reintubation</td></tr>
<tr><td>Benefits & harms of the options</td><td>What is the overall certainty of this evidence?</td><td>○ No included studies
○ Very low
○ Low
● Moderate
○ High</td><td>The relative importance or values of the main outcomes of interest:<table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence (GRADE)</th></tr></table></td><td>There is not much concern from patients or physicians in identifying important variability in these outcomes. These outcomes are universally important.</td></tr>
</table>

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<table>
<tr><th colspan="5">Assessment</th></tr>
<tr><th></th><th>Criteria</th><th>Judgements</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr>
<td></td>
<td>Is there important uncertainty about how much people value the main outcomes?</td>
<td>○ Important uncertainty or variability
○ Possibly important uncertainty or variability
○ Probably no important uncertainty or variability
● No important uncertainty or variability
○ No known undesirable outcomes</td>
<td rowspan="4">
<table>
<tr><td>Extubation Success</td><td>CRITICAL</td><td>⨁⨁⨁◯ MODERATE</td></tr>
<tr><td>ICU LOS</td><td>IMPORTANT</td><td>⨁⨁⨁◯ MODERATE</td></tr>
<tr><td>Short-term Mortality (ICU Mortality)</td><td>IMPORTANT</td><td>⨁⨁◯◯ LOW</td></tr>
<tr><td>Long-term Mortality</td><td>IMPORTANT</td><td>⨁⨁◯◯ LOW</td></tr>
</table>
</td>
<td rowspan="4">physicians.

Patients on NIV could deteriorate and develop organ failure, so they get reintubated. Studied local complications seem to be unlikely but more serious effects of organ failure that have yet to be studied may occur

Possible harms/complications associated with NIV - nasal bridge damage, conjunctivitis, nasal ulceration</td>
</tr>
<tr>
<td></td>
<td>Are the desirable anticipated effects large?</td>
<td>○ No
○ Probably no
○ Uncertain
○ Probably yes
● Yes
○ Varies</td>
</tr>
<tr>
<td></td>
<td>Are the undesirable anticipated effects small?</td>
<td>○ No
○ Probably no
○ Uncertain
● Probably yes
○ Yes
○ Varies</td>
</tr>
</table>

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Assessment				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
	Are the desirable effects large relative to undesirable effects?	○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies		
Resource use	**Are the resources required small?**	○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	No data was found on the cost of the intervention	
	Is the incremental cost small relative to the net benefits?	○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies	Mean incremental charges of mechanical ventilation in ICU patients has been found to be on average $1,522 per day. Total ICU costs have been found to be approximately $3,000/day	Reduced ICU LOS, and reduced ventilation may offer a cost benefit.

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Assessment				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
Equity	**What would be the impact on health inequities?**	○ Increased ○ Probably increased ● Uncertain ○ Probably reduced ○ Reduced ○ Varies		ICU access?
Acceptability	**Is the option acceptable to key stakeholders?**	○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies		Some practitioners may not choose to extubate
Feasibility	**Is the option feasible to implement?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies		

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Recommendation

Should Extubation to noninvasive ventilation vs. extubation without noninvasive ventilation be used for pts ventilated for >24hrs who have passed an SBT and who are at high risk for extubation failure?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	○	○	○	○	●

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	○	○	○	●

Recommendation	In patients who have been ventilated for 24 or more hours who have passed a spontaneous breathing trial and who are at high risk for extubation failure, we recommend that patients be treated with noninvasive ventilation immediately after extubation.
Justification	Reduced LOS, reduced mortality, extubation success outcomes
Subgroup considerations	The majority (80-90%) of ventilated patients are successfully extubated and do not need reintubation. This recommendation specifically addresses the high risk subset of patients.
Implementation considerations	
Monitoring and evaluation	
Research possibilities	

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AMERICAN THORACIC SOCIETY DOCUMENTS

Official Executive Summary of an American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: Liberation from Mechanical Ventilation in Critically Ill Adults

Gregory A. Schmidt, Timothy D. Girard, John P. Kress, Peter E. Morris, Daniel R. Ouellette, Waleed Alhazzani, Suzanne M. Burns, Scott K. Epstein, Andres Esteban, Eddy Fan, Miguel Ferrer, Gilles L. Fraser, Michelle Gong, Catherine Hough, Sangeeta Mehta, Rahul Nanchal, Sheena Patel, Amy J. Pawlik, Curtis N. Sessler, Thomas Strøm, William Schweickert, Kevin C. Wilson, and Jonathon D. Truwit

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE EXECUTIVE SUMMARY WAS APPROVED BY THE AMERICAN THORACIC SOCIETY BOARD OF DIRECTORS AND BY THE AMERICAN COLLEGE OF CHEST PHYSICIANS BOARD OF REGENTS

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ABSTRACT

Background: This clinical practice guideline addresses six questions related to liberation from mechanical ventilation in critically ill adults. It is the result of a collaborative effort between the American Thoracic Society (ATS) and American College of Chest Physicians (CHEST).

Methods: A multi-disciplinary panel posed six clinical questions in a Population, Intervention, Comparator and Outcomes (PICO) format. A comprehensive literature search and evidence synthesis was performed for each question, which included appraising the certainty in the evidence (i.e., the quality of evidence) using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. The Evidence-to-Decision Framework was applied to each question, requiring the panel to evaluate and weigh the: importance of the problem, confidence in the evidence, certainty about how much the public value the main outcomes, magnitude and balance of desirable and undesirable outcomes, resources and costs associated with the intervention, impact on health disparities, and acceptability and feasibility of the intervention.

Results: Evidence-based recommendations were formulated and graded, initially by subcommittees and then modified following full panel discussions. The recommendations were confirmed by confidential electronic voting; approval required that at least 80% of the panel members agree with the recommendation.

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Conclusion: The panel provides recommendations regarding liberation from mechanical ventilation. The details regarding the evidence and rationale for each recommendation are presented in the American Journal of Respiratory and Critical Care Medicine and CHEST.

Introduction

Methods

Results

Question 1: In Acutely Hospitalized Patients Ventilated More Than 24 Hours, Should the Spontaneous Breathing Trial (SBT) Be Conducted with Or without Inspiratory Pressure Augmentation?

ATS/CHEST recommendation

Remarks

Values and preferences

Question 2: In Acutely Hospitalized Patients Ventilated for More Than 24 Hours, Do Protocols Attempting to Minimize Sedation Compared to Approaches That do not Attempt to Minimize Sedation Impact Duration of Ventilation, Duration of ICU Stay, and Short-Term Mortality (60 Days)?

ATS/CHEST recommendation

Remarks

Values and preferences

Question 3: In High-Risk Patients Receiving Mechanical Ventilation for More Than 24 Hours Who Have Passed A Spontaneous Breathing Trial (SBT), Does Extubation to Preventive Noninvasive Ventilation Compared to no Noninvasive Ventilation Have a Favorable Effect on Duration of Ventilation, Ventilator-Free Days, Extubation Success (Liberation > 48 Hours), Duration of Intensive Care Unit (ICU) Stay, Short-Term Mortality (60 Days), or Long-Term Mortality?

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INTRODUCTION

Mechanical ventilation is essential for many critically ill adults; however, it also is associated with numerous complications and patient discomfort. In an effort to facilitate liberation from mechanical ventilation the American Thoracic Society (ATS) and American College of Chest Physicians (CHEST) collaboratively developed evidence-based recommendations that address common clinical questions. The goal of the guidelines is to help clinicians safely and effectively liberate patients from mechanical ventilation and improve outcomes among critically ill patients.

Guidelines cannot take into account all of the often compelling unique individual clinical circumstances. Clinicians are not expected to adhere to these recommendations blindly or universally. However, these unbiased, evidence-based guidelines may provide support to clinicians who manage these vulnerable patients and have questioned the efficacy of selected methods for ventilator liberation.

METHODS

Six co-chairs were appointed, three each by the American Thoracic Society (ATS) and CHEST leadership, and reviewed for credentials and possible conflicts of interest. The six co-chairs (ATS: TDG, PEM, JDT and CHEST: JPK, DRO, GAS) suggested panelists to the ATS and CHEST staff, who invited, reviewed for potential conflicts of interest, then finally approved them. The final panel consisted of the six co-chairs, eight pulmonary/critical care physicians, four critical care physicians, one critical nurse, one physical therapist, and one critical care pharmacist. There were also two

methodologists, one of whom is also a critical care physician. The panelists were divided among six topic groups as content experts for their particular area of expertise.

The six co-chairs proposed six clinical questions, which were vetted and confirmed by the panel. Outcomes for each question were weighted following an approach outlined by the Grading Recommendations, Assessment, Development and Evaluation (GRADE) Working Group. After comprehensive evidence synthesis of published manuscripts, the panel used the GRADE approach to assess the overall certainty of the evidence for each question's associated outcomes. The Evidence-to-Decision framework facilitated panel deliberation and recommendation development. Each recommendation was considered strong or conditional (Table 1) and required at least 80% panel consensus for approval. Any recommendation not meeting this threshold was revised based on panel feedback and resubmitted for vote.

RESULTS

ATS and CHEST elected to share publication of the guideline, which consists of six questions and the related evidence syntheses and recommendations (Table 2). After appropriate review by ATS and CHEST leadership, the guidelines are published as three manuscripts; an executive summary and two manuscripts that address three questions each. The panel made recommendations but did not support specific protocols for any of the six questions. One of two manuscripts is

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published in CHEST (1) and the other in the American Journal of Respiratory and Critical Care Medicine (2). Both are accompanied by this executive summary.

Question 1: In Acutely Hospitalized Patients Ventilated More Than 24 Hours, Should the Spontaneous Breathing Trial (SBT) Be Conducted with Or without Inspiratory Pressure Augmentation?

The evidence suggested that conducting the SBT with pressure augmentation was more likely to be successful; produced a higher rate of extubation success; and was associated with a trend towards lower ICU mortality than SBTs performed without pressure augmentation.

ATS/CHEST recommendation

For acutely hospitalized patients ventilated more than 24 hours, we suggest that the initial SBT be conducted with inspiratory pressure augmentation (5-8 cm H_2O) rather than without (T-piece or CPAP). (Conditional recommendation, Moderate certainty in the evidence)

Remarks: This recommendation relates to how to conduct the initial SBT, but does not inform how to ventilate prolonged weaning patients between SBTs.

Values and Preferences

This recommendation places a high value on reducing the duration of mechanical ventilation and maximizing the probability of extubation success.

Question 2: In Acutely Hospitalized Patients Ventilated for More Than 24 Hours, Do Protocols Attempting to Minimize Sedation Compared to Approaches That do not Attempt to Minimize Sedation Impact Duration of Ventilation, Duration of ICU Stay, and Short-Term Mortality (60 Days)?

The evidence showed a trend towards a shorter duration of mechanical ventilation, a shorter ICU length of stay, and a trend towards lower short-term mortality in the protocolized sedation group.

ATS/CHEST recommendation

For acutely hospitalized patients ventilated for more than 24 hours, we suggest protocols attempting to minimize sedation. (Conditional recommendation, Low certainty in the evidence).

Remarks

There is insufficient evidence to recommend any protocol over another.

Values and preferences

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This recommendation places a high value on reducing mechanical ventilation duration, ICU length of stay, and short-term survival, and views the burden of protocolized sedation as very low.

Question 3: In High-Risk Patients Receiving Mechanical Ventilation for More Than 24 Hours Who Have Passed A Spontaneous Breathing Trial (SBT), Does Extubation to Preventive Noninvasive Ventilation Compared to no Noninvasive Ventilation Have a Favorable Effect on Duration of Ventilation, Ventilator-Free Days, Extubation Success (Liberation > 48 Hours), Duration of Intensive Care Unit (ICU) Stay, Short-Term Mortality (60 Days), or Long-Term Mortality?

In studies of preventive NIV, there was heterogeneity in defining the high-risk patient. Risk factors included older age, comorbidities such as chronic obstructive pulmonary disease or congestive heart failure, and hypercapnia during the SBT. The evidence synthesis indicated that preventive NIV was superior to no preventive NIV with regards to extubation success; ICU length of stay; and both short- and long-term mortality.

ATS/CHEST recommendation

For patients at high risk for extubation failure who have been receiving mechanical ventilation for more than 24 hours, and who have passed a spontaneous breathing trial, we recommend extubation to preventative NIV (Strong recommendation, moderate certainty in the evidence).

Remarks

Patients at high risk for failure of extubation may include those patients with hypercapnia, COPD, CHF, or other serious co-morbidities. Physicians may choose to avoid extubation to NIV in selected patients for patient-specific factors including but not limited to the inability to receive ventilation through a mask or similar interface. Physicians who choose to use NIV should apply such treatment immediately after extubation to realize the outcome benefits.

Values and preferences

This recommendation places a high value on early extubation and a lesser value on the burdens related to institution and maintenance of preventive NIV.

Question 4: Should Acutely Hospitalized Adults Who Have Been Mechanically Ventilated for >24 Hours Be Subjected to Protocolized Rehabilitation Directed toward Early Mobilization or no Protocolized Attempts at Early Mobilization?

The evidence synthesis demonstrated that patients who received an intervention directed toward early mobilization had a shorter duration of mechanical ventilation and were more likely to be able to walk at hospital discharge. There were no differences in mortality, ICU length of stay, ability to walk at ICU discharge, six minute walk distance, or ventilator-free days. Low rates of serious adverse events, including arrhythmias, have been reported.

ATS/CHEST recommendation

For acutely hospitalized adults who have been mechanically ventilated for >24 hours, we suggest protocolized rehabilitation directed toward early mobilization (Conditional recommendation, low certainty in the evidence).

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Remarks

There is insufficient evidence to recommend any rehabilitation protocol over another.

Values and preferences

This recommendation places a high value on reducing the duration of mechanical ventilation and maintenance of ambulation, and a lower value on cost and resource utilization.

Question 5: Should Acutely Hospitalized Adults Who Have Been Mechanically Ventilated for >24 Hours Be Managed with a Ventilator Liberation Protocol or no Protocol?

The guideline panel defined a "ventilator liberation protocol" as protocol-guided efforts to identify a patient's readiness for liberation (i.e., extubation) from invasive mechanical ventilation. The evidence demonstrated that patients managed with a ventilator liberation protocol spent fewer hours on mechanical ventilation than did patients managed without a protocol. Additionally, management with a ventilator liberation protocol led to being discharged from the ICU earlier than management without a protocol. However, ventilator liberation protocols had no significant effect on mortality or reintubation rates. Adverse events were rarely reported. Subgroup analyses found that, compared to management without a ventilator liberation protocol, personnel-driven and computer-driven protocols had similar effects.

ATS/CHEST recommendation

We suggest managing acutely hospitalized adults who have been mechanically ventilated for >24 hours with a ventilator liberation protocol (Conditional recommendation, low certainty in the evidence).

Remarks

The ventilator liberation protocol may be either personnel-driven or computer-driven.

Values and preferences

This recommendation places a high value on reducing the duration of mechanical ventilation and ICU length of stay and a lower value on resource utilization.

Question 6: Should a Cuff Leak Test (CLT) Be Performed prior to Extubation of Mechanically Ventilated Adults? Should Systemic Steroids Be Administered to Adults Who Fail a CLT prior to Extubation?

The evidence suggested that patients with an absent or insufficient cuff leak are at increased risk of post-extubation stridor (PES) and unsuccessful extubation. Very low quality evidence also suggested that the use of a CLT to guide management may decrease the reintubation and PES rate, and delay extubation (due to high false positive rate). It has no effect on the duration of mechanical ventilation when considering the additional days associated with reintubation. Moderate quality

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evidence suggested that administration of systemic steroids to patients failing a CLT may reduce both the reintubation and PES rates. Patients passing a CLT have a low risk of reintubation and PES, although these risks are also low among patients extubated without having a CLT performed.

ATS/CHEST recommendations

1. We suggest performing a CLT in mechanically ventilated adults who meet extubation criteria and are deemed high risk for PES (Conditional recommendation, very low certainty in the evidence).
2. For adults who have failed a cuff leak test but are otherwise ready for extubation, we suggest administering systemic steroids at least 4 hours before extubation (Conditional recommendation, moderate certainty in the evidence).

Remarks

Risk factors for PES include: traumatic intubation, intubation > 6 days, large endotracheal tube, female sex, and reintubation after unplanned extubation. A repeat cuff leak test is not required following the administration of systemic steroids.

Values and preferences

These recommendations place a high value on avoiding reintubation and delayed extubation and a lower value on PES, the burdens related to implementing the cuff leak test, and the side effects of steroid use.

SUMMARY

The recommendations in these guidelines are the result of our expert panel's interpretation of the existing evidence and how it may be applied in clinical practice. Only one recommendation, extubation to preventive non-invasive mechanical ventilation in high risk patients, is strongly suggested. All others are considered conditional recommendations and include: conducting spontaneous breathing trials with inspiratory pressure augmentation, using protocols to minimize sedation, using protocolized physical therapy directed toward early mobilization, using ventilator liberation protocols, performing a CLT in mechanically ventilated patients who meet extubation criteria and are deemed high risk for post-extubation stridor, and administering systemic steroids at least 4 hours prior to extubation in patients who fail a CLT.

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Table 1

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at\ a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Table 2

RECOMMENDATION	STRENGTH OF RECOMMENDATION	CERTAINTY IN THE EVIDENCE (i.e., Quality of Evidence)
1. For acutely hospitalized patients ventilated more than 24 hours, we suggest that the initial SBT be conducted with inspiratory pressure augmentation (5-8 cm H2O) rather than without (T-piece or CPAP).	Conditional	Moderate certainty in the evidence
2. For acutely hospitalized patients ventilated for more than 24 hours, we suggest protocols attempting to minimize sedation.	Conditional	Low certainty in the evidence
3. For patients at high risk for extubation failure who have been receiving mechanical ventilation for more than 24 hours, and who have passed a spontaneous breathing trial, we recommend extubation to preventive NIV.	Strong	Moderate certainty in the evidence

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4. For acutely hospitalized patients who have been mechanically ventilated for >24 hours, we suggest protocolized physical therapy directed toward early mobilization.	Conditional	Low certainty in the evidence
5. We suggest managing acutely hospitalized patients who have been mechanically ventilated for >24 hours with a ventilator liberation protocol.	Conditional	Low certainty in the evidence
6a. We suggest performing cuff leak test in mechanically ventilated patients who meet extubation criteria and deemed high risk for PES.	Conditional	Very low certainty in the evidence
6b. For adults who have failed a cuff leak test but are otherwise ready for extubation, we suggest administering systemic steroids at least 4 hours before extubation. A repeat cuff leak test is not required.	Conditional	Moderate certainty in the evidence

[*] *More detailed discussions of questions 1-3 appear in CHEST (1) and of questions 4-6 appear in American Journal of Respiratory and Critical Care Medicine (2)* http://www.atsjournals.org/doi/abs/10.1164/rccm.201610-2075ST

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AMERICAN THORACIC SOCIETY DOCUMENT

An Official American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: Liberation from Mechanical Ventilation in Critically Ill Adults.

Rehabilitation Protocols, Ventilator Liberation Protocols, and Cuff Leak Tests

Timothy D. Girard, Waleed Alhazzani, John P. Kress, Daniel R. Ouellette, Gregory A. Schmidt, Jonathon D. Truwit, Suzanne M. Burns, Scott Epstein, Andres Esteban, Eddy Fan, Miguel Ferrer, Gilles L. Fraser, Michelle Ng Gong, Catherine Hough, Sangeeta Mehta, Rahul Nanchal, Sheena Patel, Amy Pawlik, Curtis N. Sessler, Thomas Strom, William Schweickert, Kevin C. Wilson, and Peter E. Morris

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY (ATS) AND THE AMERICAN COLLEGE OF CHEST PHYSICIANS (CHEST) WAS APPROVED BY THE ATS BOARD OF DIRECTORS AND BY THE CHEST BOARD OF REGENTS

This article is one component of the official ATS/CHEST clinical practice guideline; it is being simultaneously published in the American Journal of Respiratory and Critical Care Medicine and in Chest. Recommendations 1-3 in detail are being published as a separate article in CHEST.

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ABSTRACT

Background: Interventions that lead to earlier liberation from mechanical ventilation can improve patient outcomes. This guideline, a collaborative effort between the American Thoracic Society (ATS) and the American College of Chest Physicians (CHEST), provides evidence-based recommendations to optimize liberation from mechanical ventilation in critically ill adults.

Methods: Two methodologists performed evidence syntheses to summarize available evidence relevant to key questions about liberation from mechanical ventilation. The methodologists appraised the certainty in the evidence (i.e., the quality of evidence) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach and summarized the results in evidence profiles. The guideline panel then formulated recommendations after considering the balance of desirable consequences (benefits) versus undesirable consequences (burdens, adverse effects, and costs), the certainty in the evidence, and the feasibility and acceptability of various interventions. Recommendations were rated as strong or conditional.

Results: The guideline panel made four conditional recommendations related to rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. The recommendations were for acutely hospitalized adults mechanically ventilated for >24 hours to receive protocolized rehabilitation directed toward early mobilization; be managed with a ventilator liberation protocol; be assessed with a cuff leak test if they meet extubation criteria but are deemed high risk for post-extubation stridor; and be administered systemic steroids for at least 4 hours before extubation if they fail the cuff leak test.

Conclusion: The ATS/CHEST recommendations are intended to support healthcare professionals in their decisions related to liberating critically ill adults from mechanical ventilation.

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SUMMARY OF RECOMMENDATIONS

1. **For acutely hospitalized adults who have been mechanically ventilated for >24 hours, we suggest protocolized rehabilitation directed toward early mobilization** (conditional recommendation, low certainty in the evidence).
2. **We suggest managing acutely hospitalized adults who have been mechanically ventilated for >24 hours with a ventilator liberation protocol** (conditional recommendation, low certainty in the evidence).
3. **We suggest performing a cuff leak test in mechanically ventilated adults who meet extubation criteria and are deemed high risk for post-extubation stridor** (conditional recommendation, very low certainty in the evidence).
4. **For adults who have failed a cuff leak test but are otherwise ready for extubation, we suggest administering systemic steroids for at least 4 hours before extubation** (conditional recommendation, moderate certainty in the evidence).

INTRODUCTION

Mechanical ventilation is a life-saving intervention. Since it is associated with complications, patients should be liberated from the ventilator as soon as the underlying cause that led to mechanical ventilation has sufficiently improved and the patient is able to sustain unassisted spontaneous breathing. In this clinical practice guideline, we provide evidence-based recommendations on the liberation of adults from invasive mechanical ventilation. In a collaborative effort between the American Thoracic Society (ATS) and the American College of Chest Physicians (CHEST), we conducted systematic reviews of the literature and used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to develop recommendations that answer the following questions:

Question 1: Should acutely hospitalized adults who have been mechanically ventilated for >24 hours be subjected to protocolized rehabilitation directed toward early mobilization or no protocolized attempts at early mobilization?

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Question 2: Should acutely hospitalized adults who have been mechanically ventilated for >24 hours be managed with a ventilator liberation protocol or no protocol?

Question 3a: Should a cuff leak test be performed prior to extubation of mechanically ventilated adults?
Question 3b: Should systemic steroids be administered to adults who fail a cuff leak test prior to extubation?

The recommendations provided in this manuscript – and others published separately related to inspiratory pressure augmentation during spontaneous breathing trials, sedation protocols, and extubation to preventative non-invasive ventilation – form the ATS/CHEST clinical practice guidelines on liberation from mechanical ventilation in critically ill adults (1). An executive summary outlining all recommendations is also available (2).

These guidelines provide the basis for rational decisions in the liberation of intensive care unit (ICU) patients from mechanical ventilation. Neither clinicians treating mechanically ventilated patients (e.g., critical care physicians and nurses, respiratory therapists) nor other stakeholders (e.g., patients, third-party payers, courts) should view the recommendations contained in these guidelines as dictates. Though evidence-based guidelines can summarize the best available evidence regarding the effects of an intervention in a given patient population, they cannot take into account all of the unique clinical circumstances that may arise during intensive care. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines by rote or in a blanket fashion.

METHODS

Expert Panel Composition and Conflicts of Interest Management

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ATS' Document Development and Implementation Committee (DDIC), CHEST's Professional Standards Committee (PSC), and CHEST's Guidelines Oversight Committee (GOC) selected and approved the co-chairs of the guideline panel. The co-chairs identified potential panelists based upon their expertise in critical care medicine, particularly mechanical ventilation, sedation, or rehabilitation.

A committee of representatives from ATS and CHEST reviewed the invited panelists' conflict of interest disclosures, statements of interest, and curricula vitae. Panelists determined to have no substantial conflicts of interest were approved, while those with potential intellectual and financial conflicts of interest that were considered manageable were "approved with management", meaning that they were prohibited from participating in discussions or voting on recommendations in which they had substantial conflicts of interest. Three invited panelists were disqualified due to conflicts of interest deemed not manageable. A conflict of interest grid is included in the online supplement.

ATS' DDIC and CHEST's GOC approved the composition of the final panel, which consisted of 20 voting members: 6 co-chairs, 7 pulmonary/critical care physicians, 4 critical care physicians, 1 critical care nurse / respiratory therapist, 1 critical care pharmacist, and 1 physical therapist. The panel worked with two methodologists, one of whom is also a critical care physician, who assessed the quality of the evidence and participated in discussions, but did not vote on recommendations. Panelists were divided into six working groups. Each group addressed one question and each methodologist worked with three working groups.

Formulation of Key Questions and Outcome Prioritization

The co-chairs drafted key clinical questions in a PICO (Population, Intervention, Comparator, and Outcome) format. These PICO questions are intentionally presented in a sequence that reflects the order of their application when managing a mechanically ventilated patient in the ICU. They identified outcomes that might be affected by each of the interventions and rated the relative importance of the outcomes numerically (from 1 to 9), according to the GRADE

approach's three categories of outcomes for decision-making: 1 through 3 indicate the outcome is not important for decision-making; 4 through 6 indicate that the outcome is important for decision-making; 7 through 9 indicate that the outcome is critical for decision-making. We only assessed the evidence for outcomes whose average rating fell into the "critical" or "important" categories.

Systematic Literature Searches

After all panelists reviewed and approved the PICO questions, the panelists and methodologists finalized inclusion and exclusion criteria for studies to be selected, as well as search terms to identify studies. The methodologists divided the PICO questions, and each systematically identified the relevant literature for their questions by searching Medline plus one or more of the following databases to: Cochrane Library, EMBASE, or CINAHL. We did not mandate duplicate search or screening. We conducted literature searches using a combination of the National Library of Medicine's medical subject headings (MeSH) and other keywords specific to each question. To capture as much of the literature pertaining to each topic as possible, we did not limit searches by language or publication date. We initially sought published systematic reviews relevant to the question and, if none were identified, sought randomized trials. If no randomized trials were found, we sought observational studies. If no observational studies were found, we sought large case series. Reference lists from selected studies were also searched and additional papers were manually added to the search results. Searches were first performed in December 2014 and then updated periodically, most recently in May 2015. Additional details on the literature searches and the selection of studies can be found in the online supplement.

Study Selection and Data Extraction

The methodologists reviewed all publications retrieved from the literature searches for relevance, initially excluding some based on their title and/or abstract. They then reviewed the full texts of publications that were not excluded by title or abstract, either including or

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excluding each. Finally, they extracted relevant data from each selected study and entered the data in structured data tables. We did not mandate duplicate data abstraction.

Meta-Analyses

When data from individual studies were amenable to pooling or a previously published meta-analysis needed to be updated, we used the Cochrane Collaboration Review Manager, version 5.3 to pool the results across individual studies (3). We used a random-effects model and the method of DerSimonian and Laird to pool the individual estimates (4). We used relative risk (RR) to report the results for dichotomous outcomes and mean difference (MD) to report the results for continuous outcomes, each with an accompanying 95% confidence interval (CI). We assessed statistical heterogeneity of the pooled results using the I^2 and Chi^2 tests, considering an I^2 value of ≥50% or a Chi^2 $p<0.05$ to indicate significant heterogeneity. Results from the meta-analyses are provided in the evidence tables and online supplement.

Assessing Certainty in the Evidence

We used the GRADE approach to assess certainty in the estimated effects of each intervention on each outcome of interest (5). The methodologists assessed the risk of bias in all included studies, using the Cochrane Risk of Bias tool to assess risk of bias for randomized trials (6) and the Documentation and Appraisal Review Tool (DART) to assess the quality of systematic reviews (7). The methodologists created evidence profiles using the Guideline Development Tool (8), which categorized overall certainty in the evidence into one of four levels: high, moderate, low, or very low. Each level represents our certainty in the accuracy of the estimated effects for a specific intervention (Table 1). The panelists reviewed the evidence profiles and provided input and feedback.

Recommendations

Based upon the evidence profiles, the panel developed recommendations to answer each PICO question. We used the Evidence-to-Decision (EtD) framework to guide the discussions that led to each recommendation (8). In the EtD framework, panel members made decisions regarding

the balance between desirable consequences (benefits) and undesirable consequences (burdens, adverse effects, and costs), patient values and preferences, cost and cost-effectiveness, health equity, feasibility, and acceptability of the intervention. Pertinent points were recorded during the discussion process. Using the GRADE approach (9), we rated each recommendation as either "strong" or "conditional." Strong recommendations use the wording "we recommend", whereas conditional recommendations are worded using "we suggest". The implications of the strength of the recommendation are summarized in Table 2.

Consensus Development

The guideline panel met during multiple online webinars to discuss the evidence profiles and EtD framework, and to develop recommendations for each PICO question. Because all panel members were not able to attend every webinar, all panel members reviewed and voted to approve or modify preliminary recommendations using an online anonymous voting survey conducted after the online webinars were completed. This process allowed us to gather feedback from all panel members, including those unable to participate by webinars, and ultimately reach consensus regarding each recommendation. In the online surveys, panelists indicated their level of agreement on each recommendation using a 5-point Likert scale derived from the GRADE grid (10), and they could provide feedback on each preliminary recommendation. Panelists with potential conflicts of interest requiring management were not allowed to vote on the preliminary recommendation(s) for which they had a potential conflict of interest. A recommendation was made only after at least 75% of panel members voted on that recommendation and at least 80% of those voting selected "pass." Any recommendations that did not pass these standards were revised by the panel based on the feedback, and a new survey that incorporated those revisions was distributed.

Manuscript preparation

Per prior agreement by ATS and CHEST, we prepared three manuscripts: An executive summary that describes the guideline development process and provides the recommendations for all six PICO questions (2) and two manuscripts that each provides the evidence syntheses, rationale,

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and recommendations for three of the six PICO questions (1). All members of the panel reviewed each of the three manuscripts; comments were addressed by the co-chairs and the revised manuscripts were redistributed to the full panel for further review. Once the manuscripts were approved by the full panel, they were submitted simultaneously to ATS and CHEST for independent peer review.

Peer Review Process

For ATS, the document was reviewed by four content experts and a guideline methodology expert who did not participate in the preparation of the guidelines. For CHEST, the document was reviewed by individuals from the GOC, the Board of Reagents (BOR), and peer reviewers assigned by the *CHEST* journal. All reviewers assessed both the content and methods, including consistency, accuracy, and completeness. Comments from the ATS and CHEST reviewers were collated into a single decision letter and sent to the co-chairs. The manuscripts were subsequently revised by the panel according to feedback received from the peer reviewers. Following several cycles of review and revisions, the manuscripts were deemed satisfactory and sent to the ATS leadership (Executive Committee and Board of Directors) and CHEST leadership (GOC and BOR) for further review and final approval.

RESULTS

Question 1: Should Acutely Hospitalized Adults Who Have Been Mechanically Ventilated For >24 Hours Be Subjected to Protocolized Rehabilitation Directed toward Early Mobilization Or no Protocolized Attempts at Early Mobilization?

Background: In these guidelines, we use the term “rehabilitation” to describe any program directed toward mobilization, regardless of whether the program is implemented by a nurse, physical therapist, or other clinician. Studies examining ICU-initiated early rehabilitation have become increasingly prominent in the literature. Conceptually, early rehabilitation efforts in the ICU are supported by three observations. First, bedrest during critical illness negatively affects

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the musculoskeletal, cardiovascular, respiratory, and immune systems, thereby slowing recovery (11,12). Second, immobility-related complications (e.g., pressure ulcers, venous thromboembolism) are common in ICU patients (13,14). Finally, profound weakness is common among ICU survivors (15,16). ICU-acquired weakness often persists after hospital discharge and can remain disruptive to normal life function for months to years (17-22). Indeed, weakness is associated with reduced post-ICU survival (23,24).

Evidence regarding ICU-initiated early rehabilitation has progressed during the past 15 years from quality improvement projects and case reports to observational studies and randomized trials, leading to professional society recommendations (17-19). Clinical discussions have similarly progressed from whether it is safe for mechanically ventilated patients to receive early rehabilitation to the feasibility, approaches, benefits, and safety of ICU-initiated early rehabilitation. New practice paradigms suggest that there might be an optimal window during which to deliver ICU-initiated early rehabilitation, since muscle loss is rapid and early in the ICU setting (25) and mobility programs beginning after discharge from the ICU appear to have limited impact on mitigating weakness and functional decline (26). Despite accumulating evidence and growing acceptance, there remains great equipoise regarding ICU-initiated early rehabilitation (27-30), with controversy as to whether there is sufficient patient-level efficacy to justify the in-hospital costs and burdens of ICU early rehabilitation programs.

Summary of evidence: Our search identified three systematic reviews (31-33), which included four trials (34-37) that enrolled adults who were mechanically ventilated in the ICU for more than 24 hours and compared any intervention directed toward early mobilization with usual care. No additional relevant trials were identified that had not been included in the systematic reviews. Among the trials, the duration of mechanical ventilation prior to enrollment and the intervention varied. Durations of mechanical ventilation included less than 72 hours (37), 72 hours or longer (35), five days or longer (36), and seven days or longer (34). Interventions included cycling exercise five days per week (34); sitting in a chair for 30 to 120 minutes three days per week (35); marching in place, moving from a sitting to standing position, extremity

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activity, and active resistance movements (36); and, daily sedative interruption followed by range of motion exercises, bed mobility, functional activities, and sitting, standing, or walking (37). These four randomized trials informed the guideline panel's judgments.

The guideline panel identified *a priori* nine outcomes as "critical" to guide the formulation of treatment recommendations. The critical outcomes included mortality, ICU length of stay, ability to walk at ICU discharge, ability to walk at hospital discharge, six-minute walk distance at hospital discharge, duration of mechanical ventilation, ventilator-free days, serious adverse events, and arrhythmias.

When the data were pooled via meta-analysis, patients who had received an intervention directed toward early mobilization had a shorter duration of mechanical ventilation (mean difference 2.7 fewer days, 95% CI 1.19 to 4.21) and were more likely to be able to walk at hospital discharge (64.0% versus 41.4%; relative risk 1.56, 95% CI 1.15 to 2.10) (Table 3). There were no meaningful differences in mortality, ICU length of stay, ability to walk at ICU discharge, six-minute walk distance, or ventilator-free days. The trials did not report sufficient details to assess adverse events. However, a large case series reported serious adverse event rates, which were low for all adverse events (6.5 events per 1,000 physical therapy sessions) and for arrhythmias (1.9 events per 1,000 physical therapy sessions) (38).

The evidence has several important limitations. It was not possible to blind patients or clinicians to treatment allocation. For all outcomes, the number of patients and events were small, leading to imprecise estimates of treatment effects. The estimated effect on ICU length of stay was inconsistent across studies. And, we were not able to estimate the risk of serious adverse events per patient during their ICU stay due to insufficient reporting in the randomized trials. As a result, the overall certainty in the evidence was low.

Panel judgments: Despite the limitations of the evidence, the guideline panel judged the desirable consequences of rehabilitation directed toward early mobilization to outweigh the

undesirable consequences. The desirable consequences considered by the panel included a shorter duration of mechanical ventilation and increased likelihood of being able to walk at hospital discharge. The panel considered the 2.7-day reduction in the duration of mechanical ventilation to be particularly large relative to the 8-day average duration of mechanical ventilation in the four trials. The primary undesirable consequence considered by the guideline panel was altered resource requirements, since implementation may require that human resources be allocated to rehabilitation. A cost analysis using assumptions based upon published literature estimated that protocolized rehabilitation in the ICU can result in a cost saving per patient (39). Two randomized trials published after our evidence synthesis found no difference in outcomes among patients who received intensive rehabilitation compared to those who received standard rehabilitation (40-41).

The panel's votes are summarized in Table e1 and judgments are summarized in Table e2.

ATS/CHEST recommendation

For acutely hospitalized adults who have been mechanically ventilated for >24 hours, we suggest protocolized rehabilitation directed toward early mobilization (conditional recommendation, low certainty in the evidence).

Remarks

There is insufficient evidence to recommend any rehabilitation protocol over another.

Values and preferences

This recommendation places a high value on reducing the duration of mechanical ventilation and increasing the likelihood of being able to walk at discharge and a lower value on cost and resource utilization.

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Question 2: Should Acutely Hospitalized Adults Who Have Been Mechanically Ventilated For >24 Hours Be Managed with a Ventilator Liberation Protocol Or no Protocol?

Background: As the underlying cause of respiratory failure is treated and improves, ICU practitioners can hasten successful liberation from the ventilator by offering the patient opportunities to demonstrate sustainable ventilation and oxygenation without support from the mechanical ventilator. Indeed, multiple randomized trials have shown that daily use of spontaneous breathing trials (SBTs) to identify patients ready for liberation is safe and reduces time to extubation compared with approaches that gradually wean ventilator support (e.g., systematically reducing inspiratory pressure in pressure support ventilation [PSV] or the mandatory ventilator rate in synchronized intermittent mandatory ventilation [SIMV]). Ventilator liberation protocols have been designed to systematically apply such evidence to practice. These protocols, which are usually implemented by respiratory care providers and/or nurses but have also been computer-driven in some cases, are designed to reduce variability in the assessment of readiness for liberation.

Summary of evidence: Prior to searching for relevant evidence, the guideline panel defined a "ventilator liberation protocol" as protocol-guided efforts to identify a patient's readiness for liberation from invasive mechanical ventilation. We also defined the patient population of interest to be acutely hospitalized adults mechanically ventilated for more than 24 hours; our rationale was that we thought that the potential benefit of ventilator liberation protocols would be greatest among this population. Our literature search identified a recent Cochrane Database systematic review (42), which included 17 trials comparing ventilator liberation protocols with no protocol (i.e., physician judgment) among critically ill adults receiving invasive mechanical ventilation; 15 were randomized trials (43-57) and 2 were quasi-randomized trials (i.e., allocation by odd/even hospital number) (58,59). In most trials, the protocols were conducted by respiratory therapists or nurses and extubation was approved by a physician. Our literature search did not identify any additional relevant trials not included in the Cochrane review.

Seven trials required that participants be mechanically ventilated >24 hours prior to enrollment (48,52-54,57-59), whereas one required >48 hours (55), two required >12 hours (51,56), and 7 trials did not describe a specific duration of ventilation prior to enrollment (43-47,49,50). Most trials enrolled patients in mixed ICUs (45,46,48,50,52,57), though five included only medical ICU patients (43,44,55,56,58), three included only surgical ICU patients (49,53,54), and three enrolled only neurological ICU patients (47,51,57). The protocols studied were computer-driven protocols in 4 trials (43,52,53,55) and personnel-driven in 13 trials. Among the latter, 8 were SBT-based protocols (44,47,48,50,51,54,58,59), 4 were stepwise-reduction protocols (45,46,49,56), and one used both SBTs and stepwise reductions in ventilator support (57).

The guideline panel identified *a priori* five outcomes as "critical" and one outcome as "important" for guiding the formulation of treatment recommendations. The critical outcomes included overall mortality, hospital mortality, duration of mechanical ventilation, reintubation, and ICU length of stay. The important outcome was ICU mortality.

We used the estimated treatment effects derived from the Cochrane review to inform our recommendation (Table 4). On average, patients managed with a ventilator liberation protocol spent 25 fewer hours on mechanical ventilation (95% CI 12.5 to 35.5 fewer hours) than did patients managed without a protocol. Additionally, management with a ventilator liberation protocol led to being discharged from the ICU 0.96 days earlier (95% CI 0.24 to 1.7 days) than management without a protocol. Ventilator liberation protocols, however, had no significant effect on overall mortality (22.3% vs. 22.2%; OR 1.02, 95% CI 0.82 to 1.26) or reintubation rates (10.6% vs. 11.9%; OR 0.74, 95% CI 0.44 to 1.23). Apart from reintubation, which was reported in 11 of 17 trials, adverse events were rarely reported. Three trials reported accidental self-extubation rates (44,47,55), which were not significantly affected by ventilator liberation protocols (OR 0.43, 95% CI 0.14 to 1.34). In subgroup analyses, personnel-driven and computer-driven protocols had similar effects compared with management without a ventilator liberation protocol.

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Overall, the panel's confidence in the estimated treatment effects was low, primarily due to risk of bias and inconsistency in results. The most important limitation that may have biased results was the unblinded nature of the trials, which was uniform across trials since the nature of the intervention and control strategies makes blinding impossible. The number of patients and events was small in most studies, leading to imprecise estimates of treatment effects on most outcomes. Finally, the estimated effect on ICU length of stay was inconsistent across studies.

Panel judgements: Despite the limitations of the evidence, the guideline panel considered the desirable effects of ventilator liberation protocols to outweigh the undesirable effects. Specifically, the panel considered desirable effects—which included a 25-hour reduction in duration of mechanical ventilation and a 1-day reduction in ICU length of stay—to be large relative to the median duration of mechanical ventilation in most ICUs (5 days) (60). Though trials reported few, if any, undesirable effects of ventilator liberation protocols, the guideline panel noted that the trials did not assess some potentially important undesirable effects, such as diminished weaning expertise among ICU practitioners (e.g., physicians, nurses, and respiratory therapists), especially trainees. When discussing this limitation of the evidence, however, the panel noted that one recent observational study examined the relationship between training with ventilator protocols and subsequent knowledge about ventilator management and found no evidence of diminished knowledge among critical care physicians who trained in a high-intensity ventilator protocol environment (61).

The panel's votes are summarized in Table e1 and judgments are summarized in Table e3.

ATS/CHEST recommendation

We suggest managing acutely hospitalized adults who have been mechanically ventilated for >24 hours with a ventilator liberation protocol (conditional recommendation, low certainty in the evidence).

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Remarks

The ventilator liberation protocol may be either personnel-driven or computer-driven. There is insufficient evidence to recommend any ventilator liberation protocol over another.

Values and preferences

This recommendation places a high value on reducing the duration of mechanical ventilation and ICU length of stay and a lower value on resource utilization.

Question 3a: Should a Cuff Leak Test Be Performed Prior to Extubation of Mechanically Ventilated Adults?

Question 3b: Should Systemic Steroids Be Administered to Adults Who Fail a Cuff Leak Test Prior to Extubation?

Background: Endotracheal intubation can lead to laryngeal edema, which is more common among patients who are intubated >36 hours (62) and has been associated with an incidence of post-extubation stridor of 6% to 37% (63). Patients with post-extubation stridor are likely at increased risk of reintubation, though the published frequency of this outcome has varied from zero to 80%. Reintubation itself is associated with increased morbidity and mortality (63-68). Thus, identifying laryngeal edema prior to extubation might be useful, as extubation could be delayed and systemic steroids administered to minimize post-extubation risks. A delay in extubation, however, leads to ongoing risk of complications associated with mechanical ventilation, such as barotrauma and ventilator-associated pneumonia. Direct visualization of the vocal cords is difficult with an endotracheal tube in position; thus, the cuff leak test is frequently used as a surrogate indicator of laryngeal edema.

Summary of evidence: We identified 14 relevant observational studies (62,69-81): 11 studies measured the reintubation rate among patients who had undergone a cuff leak test and 13 measured the post-extubation stridor rate among patients who had undergone a cuff leak test.

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We also identified three randomized trials that compared the effects of systemic steroids to placebo among patients who failed a cuff leak test (82-84). The studies varied in their definition of a failed cuff leak test (i.e., an absent or insufficient cuff leak): four studies used a bedside assessment, five studies used the percent of tidal volume not exhaled (range: 10%-24%), and eight studies used lost tidal volume on exhalation (range: 88 to 283 mL).

The guideline panel identified *a priori* three outcomes as "critical" to guide the formulation of treatment recommendations; rates of re-intubation, post-extubation stridor, and delayed extubation. We did not pool the observational data for analysis because two meta-analyses were recently published that included 12 of the 14 studies that we identified (63,85). One meta-analysis reported that a failed cuff leak test was an insensitive but specific predictor of upper airway obstruction (i.e., post-extubation stridor or laryngeal edema visualized by laryngoscopy), with a pooled sensitivity and specificity of 0.56 (95% CI 0.48-0.63) and 0.92 (95% CI 0.90-0.93), respectively (85). The pooled likelihood ratio (LR) for upper airway obstruction after failing a cuff leak test was 5.90 (95% CI 4.00-8.69) and after passing a cuff leak test was 0.48 (95% CI 0.33-0.72). The area under the curve for the Receiver Operating Characteristic (ROC) for upper airway obstruction was 0.92 (95% CI 0.89-0.94). Three of the studies permitted analysis for reintubation; failing a cuff leak test predicted reintubation with a pooled sensitivity and specificity of 0.63 (95% CI 0.38-0.84) and 0.86 (95% CI 0.81-0.90), respectively. The pooled likelihood ratio for reintubation after failing a cuff leak test was 4.04 (95% CI 2.21-7.40) and after passing a cuff leak test was 0.46 (95% CI 0.26-0.82). The other meta-analysis included 16 studies and demonstrated that the area under the curve for the ROC for laryngeal edema and reintubation were 0.89 and 0.82, respectively (63).

Most of the studies in these two meta-analyses were observational, which may have resulted in biased estimates and did not directly answer the question of interest. We therefore used the data from these observational studies to simulate a trial comparing cuff leak test-guided management with management without a cuff leak test; this required assumptions that all patients in the intervention group who failed a cuff leak test had extubation delayed by one day

and all patients in the control group and those passing a cuff leak test in the intervention group were extubated without delay. The results of this simulation showed that cuff leak test-guided management decreased both the reintubation rate (2.4% versus 4.2%; RR 0.58, 95% CI 0.40-0.83) and post-extubation stridor rate (4.0% versus 6.7%; RR 0.60, 95% CI 0.47-0.77) but also resulted in more unnecessarily delayed extubations (9.2% absolute increase) (Table 5). The estimated number of additional days of mechanical ventilation were similar among patients receiving care informed by a cuff leak test and those not receiving a cuff leak test (491 days per 1000 patients versus 504 days per 1000 patients, respectively) when we assumed that reintubation resulted in an additional 12 days of mechanical ventilation. Though this assumption is evidence-based (64,67), we recognize that reintubation due to post-extubation stridor may result in fewer than 12 additional days of mechanical ventilation. Therefore, we performed a sensitivity analysis to assess when cuff leak test guidance would be advantageous. If reintubation results in 11 or fewer additional days of mechanical ventilation, guidance by the cuff leak test is unlikely to be of benefit and may be harmful. Whereas the added days per patient are small, the added patient-ICU days for 1000 patients managed with the cuff leak test is not small, and this could impact ICU bed availability. The panel had very low certainty in the estimates because the analysis was based upon simulated data from observational studies and most of the primary studies had serious risk of bias.

We estimated the effect of systemic steroid therapy in patients who failed a cuff leak test by pooling the estimates from three randomized trials (81-83) (Table 6). Systemic steroid therapy reduced both the reintubation rate (5.8% versus 17.0%; RR 0.32, 95% CI 0.14-0.76) and post-extubation stridor rate (10.8% versus 31.9%; RR 0.35, 95% CI 0.20-0.63). The panel had moderate certainty in these estimates because they were derived from randomized trials but the confidence intervals were wide and the number of patients was small.

In summary, the evidence suggests that patients who have an absent cuff leak have an increased incidence of both post-extubation stridor and unsuccessful extubation. Use of a cuff leak test to guide management has the following effects: decreases the reintubation rate and

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post-extubation stridor rate, delays extubation, and has no effect on the duration of mechanical ventilation. The administration of systemic steroids to patients who fail a cuff leak test reduces both the reintubation and post-extubation stridor rates. Patients passing a cuff leak test have a low risk of reintubation and post-extubation stridor, although the risks are also low among patients extubated without having a cuff leak test. These findings informed the guideline panel's recommendations.

Panel judgments: The panel debated the advantages of cuff leak test-guided management (small absolute decreases in both the reintubation rate [1.8%] and post-extubation stridor rate [2.7%]) versus the downsides of cuff leak test-guided management (a large absolute increase in the delayed extubation rate [9.2%]). The panel was particularly concerned about the large proportion of patients whose extubation will be unnecessarily delayed by cuff leak test-based management due to a false positive test result (i.e., the absence of a cuff leak when there is no laryngeal edema), even though the additional days of mechanical ventilation were similar among those receiving care informed by a cuff leak test and those not receiving a cuff leak test. We assumed a one-day delay in extubation following a failed cuff leak test, but two trials of administering systemic steroids found that extubation was delayed by only by 4-12 hours (86,87). The panel also considered that delays in extubation may extend beyond one day for some patients. The panel's heightened concern was driven by recognition that most patients whose management is not guided by a cuff leak test are successfully extubated. The panel also considered that the cuff leak test is easy to perform, inexpensive, safe (as long as effective oral care is performed prior to the test), and improves clinician comfort with the extubation decision when a patient passes a cuff leak test.

The panel discussed the possibility that the cuff leak test could be reserved for patients at high risk for post-extubation stridor, such as patients who experienced a traumatic intubation, were intubated > 6 days, have a large endotracheal tube, are female, or were reintubated after an unplanned extubation (62,76,88). Similar to previous recommendations on the use of the cuff leak test and steroids to prevent post-extubation stridor and reintubation (89), the panel

concluded that the cuff leak test should be reserved for high-risk patients, i.e., best practice is to assess each patient individually for risk factors for failed extubation.

With respect to systemic steroid therapy following a failed a cuff leak test, the balance of the benefits (decreased reintubation and post-extubation stridor rates) versus the downsides (adverse effects) of systemic steroid therapy was much clearer since the frequency and severity of adverse effects are relatively small given the short duration of systemic steroid administration. In addition to our analysis above, systemic steroid use was further supported by a randomized, double-blind trial of methylprednisolone (four 20mg doses administered over 12 hours) versus placebo prior to extubation in all patients (a cuff leak test was not performed), which found that steroids reduced post-extubation stridor, reintubations, and reintubations due to post-extubation stridor (90).

The panel's votes are summarized in Table e1 and judgments are summarized in Table e4.

ATS/CHEST recommendations

- We suggest performing a cuff leak test in mechanically ventilated adults who meet extubation criteria and are deemed high risk for post-extubation stridor (conditional recommendation, very low certainty in the evidence).
- For adults who have failed a cuff leak test but are otherwise ready for extubation, we suggest administering systemic steroids at least 4 hours before extubation, (conditional recommendation, moderate certainty in the evidence).

Remarks

Risk factors for post-extubation stridor include traumatic intubation, intubation > 6 days, large endotracheal tube, female sex, and reintubation after unplanned extubation. A repeat cuff leak test is not required following the administration of systemic steroids.

Values and preferences

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These recommendations place a high value on avoiding reintubation, post-extubation stridor, and delayed extubation, and a lower value on the burdens related to implementing the cuff leak test and the side effects of steroid use.

SUMMARY

The recommendations in these guidelines are the result of our panel's systematic review of the existing evidence and our interpretation of how the evidence should be applied in clinical practice. They include conditional recommendations for protocolized rehabilitation directed toward early mobilization, for a ventilator liberation protocol, for performing a cuff leak test in mechanically ventilated patients who meet extubation criteria and are deemed high risk for post-extubation stridor, and for administering systemic steroids for <24 hours prior to extubation in patients who failed a cuff leak test. A conditional recommendation indicates that the desirable consequences probably outweigh the undesirable consequences of the intervention and well-informed patients or substitute decision-makers may make different choices regarding whether or not they are managed with the intervention. As new studies are conducted and evidence accumulates, these recommendations should be reassessed and modified as-needed.

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Table 1: Certainty in the Evidence

Rating	Definition
High	High confidence that the true effect lies close to that of the estimated effect.
Moderate	Moderate confidence in the estimated effect. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Low confidence in the estimated effect. The true effect may be substantially different from the estimated effect.
Very Low	Very low confidence in the estimated effect. The true effect is likely to be substantially different from the estimated effect

Table 2: Implications of strong and conditional recommendations

	Strong Recommendation	**Conditional Recommendation**
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

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Table 3: Evidence profile for the comparison of protocolized rehabilitation aimed at early mobilization versus no protocolized rehabilitation.

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Protocols for early mobilization	usual care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	randomized trials	not serious [1]	not serious	not serious	serious [2]	none	26/168 (15.5%)	27/176 (15.3%)	**RR 1.02** (0.62 to 1.67)	3 more per 1000 (from 58 fewer to 103 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ICU Length of Stay												
4	randomized trials	not serious	serious [3]	not serious	serious [2]	none [4]	172	183	-	MD **0.56 fewer** (2.76 fewer to 1.63 more)	⊕⊕◯◯ LOW	CRITICAL
Ability to walk at ICU Discharge (independent at ICU discharge)												
1	randomized trials	not serious	not serious	not serious	very serious [5]	none	3/31 (9.7%)	5/36 (13.9%)	**RR 0.70** (0.18 to 2.68)	42 fewer per 1000 (from 114 fewer to 233 more)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Protocols for early mobilization	usual care	Relative (95% CI)	Absolute (95% CI)		
Ability to walk at Hospital Discharge (independent at Hospital discharge)												
2	randomized trials	not serious	not serious	not serious	serious [6]	none	48/75 (64.0%)	36/87 (41.4%)	**RR 1.56** (1.15 to 2.10)	232 more per 1000 (from 62 more to 455 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Six Minute Walk Distance at discharge (meters)												
1	randomized trials	not serious	not serious	not serious	very serious [5]	none	31	36	-	MD **53 more** (16.96 fewer to 122.96 more)	⊕⊕◯◯ LOW	CRITICAL
Duration of Mechanical Ventilation (days)												
1	randomized trials	serious [7]	not serious	not serious	serious [6]	none	49	55	-	MD **2.7 fewer** (4.21 fewer to 1.19 fewer)	⊕⊕◯◯ LOW	CRITICAL
Ventilator Free Days												
1	randomized trials	not serious	not serious	not serious	very serious [5]	none	49	55	-	MD **2.4 more** (3.59 fewer to 8.39 more)	⊕⊕◯◯ LOW	CRITICAL
Serious Adverse Events												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Protocols for early mobilization	usual care	Relative (95% CI)	Absolute (95% CI)		
1	case series	N/A	N/A	N/A	N/A	N/A	34/5267 (0.6%)	N/A	not estimable	6.5 events per 1000 PT treatment sessions	⊕⊕◯◯ LOW	CRITICAL
Serious Adverse Event (Arrhythmia)												
1	case series	N/A	N/A	N/A	N/A	N/A	10/5267 (0.2%)	N/A	not estimable	1.9 events per 1000 PT treatment sessions	⊕⊕◯◯ LOW	CRITICAL

MD – mean difference, RR – relative risk

1. Although studies were unblinded, we did not lower the quality if evidence for risk of bias because all studies used proper randomization, and mortality is unlikely to be affected by lack of blinding
2. We downgraded by one level for imprecision because the ends of the confidence interval lead to opposite courses of action.
3. We downgraded by one level for inconsistency, I^2= 52%
4. Although we could not reliably assess for publication bias due to small number of studies, we did not downgrade.
5. We downgraded by two levels for imprecision because the ends of the confidence interval lead to opposite courses of action and the number of events was small.
6. We downgraded by one level for imprecision due to small number of events
7. We downgraded for risk of bias due to lack of blinding.

Table 4: Evidence profile for the comparison of ventilator liberation protocols versus no ventilator liberation protocols.

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Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Protocolized weaning**	**non-protocolized weaning**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
15	randomized trials	not serious	not serious [1]	not serious	serious [2]	none	249/1119 (22.3%)	247/1115 (22.2%)	**OR 1.02** (0.82 to 1.26)	3 more per 1000 (from 32 fewer to 42 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital Mortality												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Protocolized weaning	non-protocolized weaning	Relative (95% CI)	Absolute (95% CI)		
8	randomized trials	not serious [3]	not serious [4]	not serious	serious [5]	none	204/760 (26.8%)	198/763 (26.0%)	**OR 1.04** (0.82 to 1.32)	8 more per 1000 (from 36 fewer to 57 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ICU Mortality (assessed with: Death during ICU stay)												
7	randomized trials	serious [6]	not serious [7]	not serious	very serious [8]	none	45/359 (12.5%)	49/352 (13.9%)	**OR 0.93** (0.58 to 1.48)	8 fewer per 1000 (from 53 fewer to 54 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Duration of Mechanical Ventilation (hours)												
14	randomized trials	serious [9]	serious [10]	not serious	not serious	none	1107	1098	-	MD **25 hours fewer** (35.5 fewer to 12.5 fewer)	⊕⊕◯◯ LOW	CRITICAL
Duration of Mechanical Ventilation (Professional lead)												
12	randomized trials	serious [9]	not serious [11]	not serious	not serious	none	1030	1021	-	MD **23 hours fewer** (47 fewer to 11.5 fewer)	⊕⊕⊕◯ MODERATE	

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Protocolized weaning	non-protocolized weaning	Relative (95% CI)	Absolute (95% CI)		
Failed Extubation (assessed with: reintubation within 48 hours after extubation)												
11	randomized trials	not serious [12]	serious [13]	not serious	serious [14]	none	79/747 (10.6%)	88/740 (11.9%)	**OR 0.74** (0.44 to 1.23)	28 fewer per 1000 (from 23 more to 63 fewer)	⊕⊕◯◯ LOW	CRITICAL
ICU Length of Stay												
8	randomized trials	serious [9]	not serious	not serious	serious [15]	none	697	681	-	MD **0.96 days fewer** (1.7 fewer to 0.24 fewer)	⊕⊕◯◯ LOW	CRITICAL

MD – mean difference, RR – relative risk

1. We did not downgrade for inconsistency, I squared is 18%
2. We downgraded by one level for imprecision, the CI included significant benefit and harm (0.82, 1.26)
3. We did not down grade for risk of bias, although, two trials (Krishnan 2004 and Namen 2001) were at high risk of bias due to improper randomization and lack of allocation concealment, we believe that most of the information is derived from low risk of boas trials.
4. No statistical heterogeneity, I^2= 0%
5. We downgraded by one level due to imprecision, the confidence interval include both significant benefit and significant harm (0.82, 1.32)
6. We downgraded by one level for risk of bias. Three studies (De Carvalho 2002, Ogica 2007, and Piotto 2011) had unclear or in appropriate randomization and allocation concealment
7. Although I^2 = 40% w did not downgrade for inconsistency.
8. We downgraded by two levels for imprecision, the confidence intervals are very wide (0.58, 1.48) and the number of events is small (94 events)
9. We downgraded by one level for risk of bias, the original data distribution is skewed, the data was transformed to log scales and geometric mean was used.
10. We downgraded by one level for heterogeneity, I squared is 67%
11. Although I^2 = 48% we did not downgrade for inconsistency
12. Although non of the trials were blinded we did not downgrade for risk of bias because we believe that the effect of lack of blinding on reintubation is minimal.
13. We downgraded by one level for inconsistency, the Chi squared test P = 0.06, and the I squared = 48%, the heterogeneity was not explained by subgroup analysis
14. We downgraded by one level for imprecision, the CI included significant benefit and harm (0.44, 1.23)
15. We downgraded for imprecision, the upper limit of the CI crossed the minimally important difference threshold.

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Table 5: Evidence profile for a simulated randomized trial comparing management based upon a cuff leak test versus management without a cuff leak test.

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CLT	No CLT	Relative (95% CI)	Absolute (95% CI)		
Failed Extubation												
11	other design [1]	serious [2]	not serious [3]	serious [4]	serious [5]	none	44/1807 (2.4%)	76/1807 (4.2%)	**RR 0.58** (0.40 to 0.83)	**18 fewer per 1,000** (from 7 fewer to 25 fewer) [6]	⊕◯◯◯ VERY LOW	CRITICAL
Post Extubation Stridor												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CLT	No CLT	Relative (95% CI)	Absolute (95% CI)		
13	other design [1]	serious [2]	not serious	serious [4]	not serious	none	95/2347 (4.0%)	158/2347 (6.7%)	**RR 0.60** (0.47 to 0.77)	**27 fewer per 1,000** (from 15 fewer to 36 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Delayed Extubation												
13	other design	serious [1]	not serious	serious [4]	not serious	none	217/2347 (9.2%)	0/2347 (0.0%)	not estimable	**92 fewer per 1,000** (from 80 fewer to 100 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. The data for this outcome is derived from 11 cohort studies that examined the accuracy of cuff leak test in predicting failed extubation, we used the pooled observational data to simulate a randomized trial comparing doing CLT versus not, we assumed that all patients in the control arm were extubated, and that all patients with no leak detected in the intervention arm were not extubated.
2. We downgraded for risk of bias by one level, most studies were at high risk of bias
3. We assessed inconsistency for the pooled result from observational studies, there was no inconsistency in the results, therefore, we did not downgrade for the simulated results
4. We downgraded for indirectness by one level, the design of the study is simulated based on the results of observational studies.
5. We downgraded by one level for imprecision, the number of events were small

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Table 6: Evidence profile for the comparison of systemic steroid therapy versus placebo in patients who failed a cuff leak test.

Bibliography: 1) Cheng KC, Chen CM, Tan CK, Chen HM, Lu CL, Zhang H. Methylprednisolone reduces the rates of postextubation stridor and reintubation associated with attenuated cytokine responses in critically ill patients. Minerva anestesiologica 2011; 77: 503-509. 2) Cheng KC, Hou CC, Huang HC, Lin SC, Zhang H. Intravenous injection of methylprednisolone reduces the incidence of postextubation stridor in intensive care unit patients. Crit Care Med 2006; 34: 1345-1350. 3) Lee CH, Peng MJ, Wu CL. Dexamethasone to prevent postextubation airway obstruction in adults: a prospective, randomized, double-blind, placebo-controlled study. Crit Care 2007; 11: R72.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroids	Placebo	Relative (95% CI)	Absolute (95% CI)		
Post Extubation Stridor												
3	randomized trials	not serious	not serious	not serious	serious [1]	none [2]	13/120 (10.8%)	30/94 (31.9%)	**RR 0.35** (0.20 to 0.63)	207 fewer events per 1000 (from 118 fewer to 255 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Re-intubation												
3	randomized trials	not serious	not serious	not serious	serious [3]	none [2]	7/120 (5.8%)	16/94 (17.0%)	**RR 0.32** (0.14 to 0.76)	116 fewer events per 1000 (from 41 fewer to 146 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

MD – mean difference, RR – relative risk, CI – confidence interval

1. We downgraded by one level for imprecision because the CI is wide (0.2 to 0.63) and the number of events is small (43 events)
2. We could not reliably assess for publication bias due to small number of studies
3. We downgraded by one level for imprecision, the CI is wide (0.14, 0.76) and the number of events is small (23 events).