CHEST

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

Inspiratory Pressure Augmentation During Spontaneous Breathing Trials, Protocols Minimizing Sedation, and Noninvasive Ventilation Immediately After Extubation

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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 liberation from the ventilator.

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 multidisciplinary committee of experts in mechanical ventilation.

RESULTS: Recommendations for three population, intervention, comparator, outcome (PICO) questions concerning ventilator liberation are presented in this document. The guideline panel considered the balance of desirable (benefits) and undesirable (burdens, adverse effects, costs) consequences, 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 h. A strong recommendation was made to use preventive noninvasive ventilation (NIV) for high-risk patients ventilated for more than 24 h immediately after extubation to improve selected outcomes. The recommendations were limited by the quality of the available evidence.

CONCLUSIONS: The guideline panel provided recommendations for inspiratory pressure augmentation during an initial SBT, protocols minimizing sedation, and preventative NIV, in relation to ventilator liberation. CHEST 2017; 151(1):166-180

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

Summary of Recommendations

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.

2. For acutely hospitalized patients ventilated for more than 24 h, 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 h, 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, congestive heart failure (CHF), 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.

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 three 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 h, 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 h, do protocols attempting to minimize sedation compared with approaches that do not attempt to minimize sedation impact duration of ventilation,

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ABBREVIATIONS: ATS = American Thoracic Society; CHEST = American College of Chest Physicians; CHF = congestive heart failure; COI = conflict of interest; EtD = Evidence to Decision; GOC = Guidelines Oversight Committee; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; NIV = noninvasive ventilation; PICO = population, intervention, comparator, outcome; RR = relative risk; SBT = spontaneous breathing trial

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

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?

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 the 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 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, Guidelines Oversight Committee (GOC), and the ATS's Document Development and Implementation Committee selected and approved the cochairs of the panel. Prospective panelists were selected by the cochairs based on their expertise relative to the proposed guideline questions. The panelists were reviewed by representatives from both the ATS 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 cochairs and 14 panelists, who were then divided among six 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, whereas nominees with potential intellectual and financial COIs 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 COI. We created a grid associating panelists' COI with relevant population, intervention, comparator, outcome (PICO) questions for use during voting. The COI grid can be found in e-Table 1.

The final panel consisted of the six cochairs (T. D. G., J. P. K., P. E. M., D. R. O., G. A. S., and J. D. T.), seven pulmonary/critical care physicians, four critical care physicians, one critical care nurse, one physical therapist, and one critical care pharmacist. The panel worked with two methodologists (W. A. and S. P.), one of whom is also a critical care physician.

Formulation of Key Questions and Outcome Prioritization

The six cochairs drafted a total of six key clinical questions in a PICO format (Table 1). The cochairs were asked to rate the outcomes to be used for all six questions numerically on a scale of 1 to 9, according to the GRADE Working Group's three categories of outcomes for decision-making (1-3 = not important; 4-6 = important; 7-9 = critical). We used the cochairs' average score for each outcome to determine the outcome category, and we assessed only 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 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 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 e-Figures 1-3.

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 using a third reviewer was in place but never invoked.

Risk of Bias Assessment

The methodologist assessed the risk of bias in all included studies. We used the Cochrane Risk of Bias tool to assess risk of bias for randomized controlled trials.[2] We used the Documentation and Appraisal Review Tool 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 for continuous outcomes with accompanying 95% CIs. Statistical heterogeneity of the pooled results was assessed using the Higgins' I^2 test and the χ^2 test. A Higgins' I^2 value of $\geq$ 50% or a χ^2 $P < .05$ was considered to represent significant heterogeneity.

TABLE 1] PICO Questions

Study Characteristic	Inclusion Criteria	Exclusion Criteria
KQ 1: Spontaneous breathing trial		
Populations	Acutely hospitalized patients ventilated for > 24 h	Patients who did not pass first SBT
Interventions	SBT conducted with inspiratory pressure augmentation (ie, pressure support ventilation, automatic tube compensation)	None
Comparators	SBT conducted without inspiratory pressure augmentation	None
Outcomes	Duration of ventilation Ventilator-free d Extubation success Successful SBT Duration of ICU stay Short-term mortality (< 60 d) Long-term mortality	None
Study design	Systematic reviews, RCT, observational	None
KQ 2: Sedation protocols		
Populations	Acutely hospitalized patients ventilated for > 24 h	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 d Extubation success Duration of ICU stay Short-term mortality (< 60 d) Long-term mortality	None
Study design	Systematic reviews, RCT	None
KQ 3: Extubation to NIV		
Populations	Patients ventilated for > 24 h who have passed an SBT but are at high risk for extubation failure	None
Interventions	Extubation to preventive NIV	None
Comparators	Extubation without preventive NIV	None
Outcomes	Duration of ventilation Ventilator-free d Extubation success Duration of ICU stay Short-term mortality (< 60 d) Long-term mortality	None
Study design	Systematic reviews, RCT, observational	None

KQ = key question; NIV = noninvasive ventilation; PICO = population, intervention, comparator, outcome; RCT = randomized controlled trial; SBT = spontaneous breathing trial.

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

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, 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 (e-Tables 3-5). 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 use the wording "we suggest." The implications of the strength of recommendations 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 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 five-point Likert scale derived from the GRADE grid.[8,9] Panelists were also invited to provide feedback on each recommendation with suggestions for rewording. Panelists with COIs (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, 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.

TABLE 3] Implications of Strong and Weak (Conditional) Recommendations for Different Users of Guidelines

Guideline User	Strong Recommendation	Weak (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 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.	Clinicians must recognize that different choices will be appropriate for different patients and that one must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful in helping individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
Policy makers	The recommendation can be adapted as policy in most situations, including 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.

Results

Question 1: In acutely hospitalized patients ventilated more than 24 h, should the 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 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 toward 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). On the one hand, it could be argued that the patient demonstrating an ability to breathe while receiving no inspiratory pressure augmentation has convincingly shown weaning readiness (ie, 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 patients may be safely extubated (ie, this result may be more sensitive but less specific). There is no consensus about 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 patients 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 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 min to 2 h. The amount of pressure support provided was 5, 7, or 8 cm H_2O or through automatic tube compensation (which provides inspiratory pressure support to overcome 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 period and provided supplemental oxygen. "Extubation success" was defined as not requiring reintubation or NIV in the following 48 h.

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 through 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 toward lower ICU mortality (8.6% vs 11.6%; RR, 0.74; 95% CI, 0.45-1.24) (Table 4; e-Table 2).

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 (eg, 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 a 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 patients 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.

TABLE 4] Evidence Profile for Conducting the Spontaneous Breathing Trial With or Without Inspiratory Pressure Augmentation[12-15]

Quality Assessment							No. of Patients		Effect			
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	SBT Conducted With Pressure Augmentation	SBT Conducted Without Pressure Augmentation	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Extubation success												
4	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	312 of 423 (73.8%)	303 of 452 (67.0%)	RR, 1.09 (1.02-1.18)	60 more per 1,000 (from 13 more to 121 more)	Moderate[a]	Critical
Successful SBT												
3	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	388 of 488 (79.5%)	331 of 452 (73.2%)	RR, 1.11 (1.0-1.18)	81 more per 1,000 (from 22 more to 132 more)	Moderate[a]	Important
Short-term mortality (assessed with ICU mortality)												
2	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	26 of 300 (8.7%)	36 of 307 (11.7%)	RR, 0.74 (0.45-1.24)	30 less per 1,000 (from 28 more to 64 less)	Low[a,b]	Important

(Continued)

TABLE 4] *(Continued)*

Quality Assessment							No. of Patients		Effect			
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	SBT Conducted With Pressure Augmentation	SBT Conducted Without Pressure Augmentation	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
ICU LOS												
2	Randomized trials	Serious[c]	Not serious	Not serious	Not serious	None	Not pooled	Not pooled	ICU LOS was reported in 2 trials (Esteban et al[12] and Matić et al[14]) Estimated effects were reported as median values: 270 (235-290) and 331 (292-396) h 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 h and 240 h for SBT with pressure and t-tube		Moderate[c]	Important

LOS = length of stay; RR = relative risk.

[a]One study with unclear randomization methods, 1 study with unclear allocation concealment methods, and 2 studies with unclear reports on outcome assessment.

[b]Low number of events; 95% CI crosses line of no effect.

[c]Unclear randomization methods and unclear if outcome assessors were blinded in Matić et al.[14]

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

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 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 pharmacologic effects may impede liberation from mechanical ventilation. Strategies to minimize the effects of these drugs (eg, 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 cohorts of patients managed with 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 through meta-analysis for the outcome of duration of mechanical ventilation (695 patients received protocolized sedation and 699 patients received no protocolized sedation [e-Table 2]). 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 (ie, wide CIs around the absolute effect). Accordingly, the evidence was noted to be of very low quality.

Six trials were pooled through meta-analysis for the outcome of ICU length of stay (695 patients received protocolized sedation and 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 through meta-analysis for the outcome of short-term mortality (203 of 695 cases of mortality had protocolized sedation and 217 of 699 cases of mortality had 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 day shorter; 95% CI, from 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% CI, –3.41 to –0.14). The summary of the pooled evidence showed no significant difference in short-term mortality in the

TABLE 5] Evidence Profile for Protocols Attempting to Minimize Sedation Compared With No Attempt to Minimize Sedation[17-22]

Quality Assessment							No. of Patients		Effect		Quality	Importance
No. 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 by d)												
6	Randomized trials	Serious[a]	Serious[b]	Not serious	Serious[c]	None	528	531	. . .	MD 1 d less (2.14 d less to 0.14 d more)	Very low	Important
ICU length of stay												
6	Randomized trials	Serious[a]	Serious[d]	Not serious	Serious[c]	None	695	699	. . .	MD 1.78 d less (3.41 d less to 0.14 d less)	Very low	Important
Short-term mortality												
6	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	203 of 695 (29.2%)	217 of 699 (31.0%)	RR, 0.93 (0.77-1.11)	22 d less per 1,000 (from 34 d more to 71 d less)	Moderate	Important

MD = mean difference. See Table 4 legend for expansion of other abbreviations.

[a]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.

[b]$I^2 = 62\%$.

[c]Fairly wide CIs around absolute effect.

[d]$I^2 = 71\%$.

protocolized sedation group (RR, 0.93; 95% CI, 0.77-1.11; $P = .42$).

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 with 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 et al[24] 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. Of the patients who were alive and receiving mechanical ventilation after 48 h, 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

2. For acutely hospitalized patients ventilated for more than 24 h, 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 h who have passed an SBT, does extubation to preventive 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?

Background: Patients intubated for acute respiratory failure are at increased risk for complications including infection and multisystem 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 stays when compared with patients extubated in a timely manner.[27] Conversely, studies have found that patients requiring reintubation (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 with respiratory failure due to acute exacerbations of COPD reduces the need for intubation, the frequency of complications, the hospital length of stay, and the mortality rate compared with 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 used 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]

Although 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 in patients following extubation. In one randomized trial in 221 patients who experienced respiratory failure a mean of 9 h after extubation, NIV was not effective in reducing the need for reintubation 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 SBT but subsequently experienced respiratory failure.[32] In contrast, other trials show that NIV applied immediately after extubation may reduce reintubation rates in critically ill patients, with meta-analyses of these studies indicating that duration of mechanical ventilation, 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 reintubation, ICU length of stay, and short- and long-term mortality.

Summary of the Evidence

Five randomized controlled trials met criteria for our assessment of the data. Nava et al[35] randomized 97 high-risk patients who were extubated following successful SBT to receive either NIV or standard care 1 h after extubation. High-risk patients were those who failed more than one SBT, had a $Paco_2 > 45$ mm Hg after extubation, more than one comorbid condition, a weak cough, or upper airway stridor that did not require immediate reintubation. The NIV group had a reduced need for reintubation (4 of 48 vs 12 of 49; $P = .027$) and a reduction in ICU mortality (3 of 48 vs 9 of 49; $P < .01$).

Ferrer et al[36] randomized 162 patients to NIV or standard care after extubation. Patients were selected following a successful SBT if they had risk factors for reintubation defined as age > 65 years, cardiac failure as a cause for respiratory failure, or an APACHE II score > 12 on the day of extubation. Patients receiving NIV had reduced reintubation rates (13 of 79 vs 27 of 83; $P = .029$) and ICU mortality (2 of 79 vs 12 of 83; $P = .015$) 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 postextubation (0 of 27 vs 4 of 22; $P = .035$). In follow-up, Ferrer et al[37] randomized 106 mechanically ventilated patients who had hypercapnia with a $Paco_2 > 45$ mm Hg during a successful SBT to postextubation NIV or conventional oxygen treatment. Respiratory failure defined by predetermined criteria was more frequent in the conventional oxygen group than in the NIV group (25 of 52 vs 8 of 54; $P < .0001$). Reintubation 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 experiencing respiratory failure. Mortality at 90 days, a secondary end point for this study, was lower in the patients receiving NIV than in the patients receiving conventional oxygen treatment (6 of 54 vs 16 of 52; $P = .0244$).

Khilnani et al[38] studied 40 patients with an acute exacerbation of COPD requiring mechanical ventilation. After passing a weaning assessment, patients were randomized to receive NIV immediately following extubation vs conventional therapy, with no significant difference found between groups regarding reintubation or ICU length of stay. Mohamed and Abdalla[39] examined outcomes in 120 patients randomized to NIV or an oxygen mask. They found that patients treated with NIV had reduced ICU mortality (6.6% vs 16.6%; $P < .035$) and reintubation rates (15% vs 25%; $P = .04$) when compared with control subjects.

In assessing the aggregate data, all five studies 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 length of stay: 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 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 comorbidities that included COPD, CHF, hypercapnia, older age, and a higher severity of illness. Patients < 65 years of age who pass their first SBT have a normal Pco_2, have no significant respiratory or cardiac comorbidities, and can protect their airway would be considered to be at low risk for reintubation in all the included studies.

Two studies suggest that a high-flow nasal cannula may improve patient outcomes after extubation in patients receiving mechanical ventilation. Maggiore et al[40] assigned 105 patients mechanically ventilated for more than 24 h to either a Venturi mask or nasal high-flow therapy after extubation. Patients receiving high-flow nasal therapy were less likely to be reintubated than were patients receiving treatment by Venturi mask (4% vs 21%; $P = .01$). Hernandez et al[41] treated 264 patients receiving mechanical ventilation at low risk for reintubation after extubation with a high-flow nasal cannula and compared this group with 263 patients receiving conventional oxygen therapy. Patients receiving high-flow nasal cannula treatment had less respiratory failure (22 of 264 vs 38 of 263; $P = .03$) and a lower rate of reintubation at 72 h (13 of 264 vs 32 of 263; $P = .004$).

TABLE 6] Evidence Profile for Extubation to Noninvasive Ventilation Compared With Extubation Without Noninvasive Ventilation[35-39]

Quality Assessment							No. of Patients		Effect			
No. 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)	Quality	Importance
Extubation success												
5	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	230 of 261 (88.1%)	204 of 264 (77.3%)	RR, 1.14 (1.05-1.23)	11 less per 100 (from 4 less to 18 less)	Moderate	Critical
ICU LOS												
4	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	241	244	. . .	MD 2.48 d less (4.03 d less to 0.93 d less)	Moderate	Important
Short-term mortality (ICU mortality)												
4	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	12 of 241 (5.0%)	35 of 244 (14.3%)	RR, 0.37 (0.19-0.70)	9 less per 100 (from 4 less to 12 less)	Low	Important
Long-term mortality (follow-up: 90 d)												
2	Randomized trials	Not serious	Serious[c]	Not serious	Serious[d]	None	24 of 133 (18.0%)	40 of 135 (29.6%)	RR, 0.58 (0.27-1.22)	12 less per 100 (from 7 more to 22 less)	Low	Important

See Table 4 legend for expansion of abbreviations.

[a]Unclear randomization methods and allocation concealment in studies. Many studies did not blind outcome assessors or research personnel.

[b]Low number of events.

[c]$I^2 = 57\%$.

[d]Low number of events/fairly wide 95% CI.

These studies became available after the literature search was conducted but may inform clinicians about postextubation strategies similar to preventive 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

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 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 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, 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 a 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 an SBT be extubated to preventive 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 use protocols to minimize sedation in patients ventilated for more than 24 h. 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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Additional information: The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Girard TD, Alhazzani W, Kress JP, et al. 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. *Am J Respir Crit Care Med*. 2017;195(1):120-133.
2. Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for systematic reviews of interventions, version 5.1.0 (updated March 2011), Chapter 8. The Cochrane Collaboration, 2011. Available at http://www.cochrane-handbook.org. 2011.
3. Diekember RL, Ireland BK, Merz LR. Development of the documentation and appraisal review tool for systematic reviews. *World J Metaanal*. 2015;3(3):142-150.
4. Review Manager (RevMan), version 5.2. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration; 2014.
5. Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions, version 5.1.0 (updated March 2011), chapter 9. The Cochrane Collaboration, 2011. Available at http://www.cochrane-handbook.org. 2011.
6. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406.
7. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol*. 2013;66(7):719-725.
8. Jaeschke R; The GRADE Working Group. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ*. 2008;337:327-330.

9. Lewis SZ, Diekemper R, Ornelas J, Casey KR. Methodologies for the development of CHEST guidelines and expert panel reports. *Chest*. 2014;146(1):182-192.
10. Brochard L, Rauss A, Benito S, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med*. 1994;150(4):896-903.
11. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med*. 1995;332(6):345-350.
12. Esteban A, Alia I, Gordo F, et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. *Am J Respir Crit Care Med*. 1997;156(2 Pt 1):459-465.
13. Haberthur C, Mols G, Elsasser S, Bingisser R, Stocker R, Guttmann J. Extubation after breathing trials with automatic tube compensation, T-tube, or pressure support ventilation. *Acta Anaesth Scand*. 2002;46(8):973-979.
14. Matić I, Majerić-Kogler V. Comparison of pressure support and T-tube weaning from mechanical ventilation: randomized prospective study. *Croat Med J*. 2004;45(2):162-166.
15. Zhang B, Qin YZ. Comparison of pressure support ventilation and T-piece in determining rapid shallow breathing index in spontaneous breathing trials. *Am J Med Sci*. 2014;348(4):300-305.
16. Ezingeard E, Diconne E, Guyomarc'h S, et al. Weaning from mechanical ventilation with pressure support in patients failing a T-tube trial of spontaneous breathing. *Intensive Care Med*. 2006;32(1):165-169.
17. Anifantaki S, Prinianakis G, Vitsaksaki E, et al. Daily interruption of sedative infusions in an adult medical-surgical intensive care unit: randomized controlled trial. *J Adv Nurs*. 2009;65(5):1054-1060.
18. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med*. 1999;27(12):2609-2615.
19. Bucknall TK, Manias E, Presneill JJ. A randomized trial of protocol-directed sedation management for mechanical ventilation in an Australian intensive care unit. *Crit Care Med*. 2008;36(5):1444-1450.
20. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-134.
21. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471-1477.
22. Mansouri P, Javadpour S, Zand F, et al. Implementation of a protocol for integrated management of pain, agitation, and delirium can improve clinical outcomes in the intensive care unit: a randomized clinical trial. *J Crit Care*. 2013;28(6):918-922.
23. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. *JAMA*. 2012;308(19):1985-1992.
24. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet*. 2010;375(9713):475-480.
25. Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA*. 2002;287(3):345-355.
26. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. *Crit Care Med*. 2005;33(6):1266-1271.
27. Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. *Am J Respir Crit Care Med*. 2000;161(5):1530-1536.
28. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest*. 1997;112(1):186-192.
29. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 1995;333(13):817-822.
30. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med*. 2008;359(2):142-151.
31. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med*. 2001;344(7):481-487.
32. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med*. 2004;350(24):2452-2460.
33. Burns KE, Adhikari NK, Keenan SP, Meade M. Use of non-invasive ventilation to wean critically ill adults off invasive ventilation: meta-analysis and systematic review. *BMJ*. 2009;338:b1574.
34. Burns KE, Adhikari NK, Meade MO. A meta-analysis of noninvasive weaning to facilitate liberation from mechanical ventilation. *Can J Anaesth*. 2006;53(3):305-315.
35. Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. *Crit Care Med*. 2005;33(11):2465-2470.
36. 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.
37. 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.
38. 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.
39. Mohamed KAE, Abdalla MH. Role of noninvasive ventilation in limiting reintubation after planned extubation. *Egypt J Chest Dis Tuberc*. 2013;62(4):669-674.
40. Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. *Am J Respir Crit Care Med*. 2014;190(3):282-288.
41. Hernandez G, Vaquero C, Gonzalez P, et al. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial. *JAMA*. 2016;315(13):1354-1361.