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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

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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?

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 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 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

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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).

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.

Bibliography: 1) Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, Hermans G, Decramer M, Gosselink R. Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med 2009; 37:2499-505. 2) Chang MY, Chang LY, Huang YC, Lin KM, Cheng CH. Chair-sitting exercise intervention does not improve respiratory muscle function in mechanically ventilated intensive care unit patients. Respir Care 2011; 56:1533-8. 3) Denehy L, Skinner EH, Edbrooke L, Haines K, Warrillow S, Hawthorne G, Gough K, Hoorn SV, Morris ME, Berney S. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. Crit Care 2013; 17:R156. 4) Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009; 373:1874-82.

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.

Bibliography: 1) Strickland JH, Jr., Hasson JH. A computer-controlled ventilator weaning system. A clinical trial. Chest 1993; 103: 1220-1226. 2) Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, Johnson MM, Browder RW, Bowton DL, Haponik EF. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 1996; 335: 1864-1869. 3) Kollef MH, Shapiro SD, Silver P, St John RE, Prentice D, Sauer S, Ahrens TS, Shannon W, Baker-Clinkscale D. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. Crit Care Med 1997; 25: 567-574. 4) Marelich GP, Murin S, Battistella F, Inciardi J, Vierra T, Roby M. Protocol weaning of mechanical ventilation in medical and surgical patients by respiratory care practitioners and nurses: effect on weaning time and incidence of ventilator-associated pneumonia. Chest 2000; 118: 459-467. 5) Namen AM, Ely EW, Tatter SB, Case LD, Lucia MA, Smith A, Landry S, Wilson JA, Glazier SS, Branch CL, Kelly DL, Bowton DL, Haponik EF. Predictors of successful extubation in neurosurgical patients. Am J Respir Crit Care Med 2001; 163: 658-664. 6) de Carvalho Oliveira LR, Jose A, Dias EC, dos Santos VLA, Chiavone PA. Weaning protocol for mechanical ventilation: Effects of its use in an intensive care unit. A controlled, prospective and randomized trial. Revista Brasileira Terapia Intensiva 2002; 14: 22-32. 7) Simeone F, Biagioli B, Scolletta S, Marullo AC, Marchet- Ti L, Caciorgna M, Giomarelli P. Optimization of mechanical ventilation support following cardiac surgery. J Cardiovasc Surg 2002; 43: 633-641. 8) Ogica A, Droc G, Tomescu D, Popescu H, Tulbure D. Weaning from mechanical ventilation: Protocol vs. physician decision. Eur J Anaesthesiol 2007; 24: 147-148. 9) Navalesi P, Frigerio P, Moretti MP, Sommariva M, Vesconi S, Baiardi P, Levati A. Rate of reintubation in mechanically ventilated neurosurgical and neurologic patients: evaluation of a systematic approach to weaning and extubation. Crit Care Med 2008; 36: 2986-2992. 10) Rose L, Presneill JJ, Johnston L, Cade JF. A randomised, controlled trial of conventional versus automated weaning from mechanical ventilation using SmartCare/PS. Intensive Care Med 2008; 34: 1788-1795. 11) Stahl C, Dahmen G, Ziegler A, Muhl E. Comparison of automated protocol-based versus non-protocol-based physician-directed weaning from mechanical ventilation. Intensivmedizin und Notfallmedizin 2009; 46: 441-446. 12) Chaiwat O, Sarima N, Niyompanitpattana K, Komoltri C, Udomphorn Y, Kongsayreepong S. Protocol-directed vs. physician-directed weaning from ventilator in intra-abdominal surgical patients. J Med Assoc Thai 2010; 93: 930-936. 13) Reardon CC, Walkey AJ. Clinical trial of a computer-driven weaning system for patients requiring mechanical ventilation. 2011 Jan 16. Available from: https://clinicaltrials.gov/ct2/show/NCT00606554. 14) Roh JH, Synn A, Lim CM, Suh HJ, Hong SB, Huh JW, Koh Y. A weaning protocol administered by critical care nurses for the weaning of patients from mechanical ventilation. J Crit Care 2012; 27: 549-555. 15) Fan LL, Su YY, Zhang Y, Zhang YZ, Gao DQ, Ye H, Zhao JW, Chen WB. A randomized controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation in neuro-critical patients. Chinese J Neurol 2013; 46: 320-323. 16) Krishnan JA, Moore D, Robeson C, Rand CS, Fessler HE. A prospective, controlled trial of a protocol-based strategy to discontinue mechanical ventilation. Am J Respir Crit Care Med 2004; 169: 673-678. 17) Piotto RF, Maia LN, Machado MN, Orrico SP. Effects of the use of mechanical ventilation weaning protocol in the Coronary Care Unit: randomized study. Rev Bras Cir Cardiovasc 2011; 26: 213-221.

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.

Bibliography: 1) Darmon JY, Rauss A, Dreyfuss D, Bleichner G, Elkharrat D, Schlemmer B, Tenaillon A, Brun-Buisson C, Huet Y. Evaluation of risk factors for laryngeal edema after tracheal extubation in adults and its prevention by dexamethasone. A placebo-controlled, double-blind, multicenter study. Anesthesiology 1992; 77: 245-251; 2) Antonaglia V, Vergolini A, Pascotto S, Bonini P, Renco M, Peratoner A, Buscema G, De Simoni L. Cuff-leak test predicts the severity of postextubation acute laryngeal lesions: a preliminary study. Eur J Anaesthesiol 2010; 27: 534-541. 3) Chung YH, Chao TY, Chiu CT, Lin MC. The cuff-leak test is a simple tool to verify severe laryngeal edema in patients undergoing long-term mechanical ventilation. Crit Care Med 2006; 34: 409-414. 4) De Bast Y, De Backer D, Moraine JJ, Lemaire M, Vandenborght C, Vincent JL. The cuff leak test to predict failure of tracheal extubation for laryngeal edema. Intensive Care Med 2002; 28: 1267-1272. 5) Engoren M. Evaluation of the cuff-leak test in a cardiac surgery population. Chest 1999; 116: 1029-1031. 6) Erginel S, Ucgun I, Yildirim H, Metintas M, Parspour S. High body mass index and long duration of intubation increase post-extubation stridor in patients with mechanical ventilation. Tohoku J Exp Med 2005; 207: 125-132. 7) Fisher MM, Raper RF. The 'cuff-leak' test for extubation. Anaesthesia 1992; 47: 10-12. 8) Jaber S, Chanques G, Matecki S, Ramonatxo M, Vergne C, Souche B, Perrigault PF, Eledjam JJ. Post-extubation stridor in intensive care unit patients. Risk factors evaluation and importance of the cuff-leak test. Intensive care medicine 2003; 29: 69-74. 9) Kriner EJ, Shafazand S, Colice GL. The endotracheal tube cuff-leak test as a predictor for postextubation stridor. Respir Care 2005; 50: 1632-1638. 10) Miller RL, Cole RP. Association between reduced cuff leak volume and postextubation stridor. Chest 1996; 110: 1035-1040. 11) Sandhu RS, Pasquale MD, Miller K, Wasser TE. Measurement of endotracheal tube cuff leak to predict postextubation stridor and need for reintubation. J Am Coll Surg 2000; 190: 682-687. 12) Shin SH, Heath K, Reed S, Collins J, Weireter LJ, Britt LD. The cuff leak test is not predictive of successful extubation. Am Surg 2008; 74: 1182-1185. 13) Sukhupanyarak S. Risk factors evaluation and the cuff leak test as predictors for postextubation stridor. J Med Assoc Thai 2008; 91: 648-653. 14) Wang CL, Tsai YH, Huang CC, Wu YK, Ye MZ, Chou HM, Shu SC, Lin MC. The role of the cuff leak test in predicting the effects of corticosteroid treatment on postextubation stridor. Chang Gung Med J 2007; 30: 53-61.

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).