Evidence-based Strategies for Weaning Patients with COVID-19 from Mechanical Ventilation

Endotracheal tube removal ("ventilator weaning") is a critical recovery milestone in intensive care unit (ICU) patients supported by mechanical ventilation because prolonged or repeated intubation and ventilation often results in serious complications and injuries. The need for effective weaning as quickly as possible is even more critical because of ventilator shortages during large-scale outbreaks of viral respiratory diseases, such as COVID-19. This report focuses on interventions to supplement standard weaning practices to reduce ventilator time and avoid repeat intubation in patients with COVID-19.

Evidence from randomized controlled trials (RCTs) synthesized in meta-analyses shows that adaptive ventilation software solutions (i.e., "automated weaning"), such as SmartCare® and corticosteroid prophylactic regimens, are safe and effective to reduce ventilator weaning times and prevent reintubation in critically ill patients. Nevertheless, clinical studies are needed to extend these conclusions to patients with COVID-19 and acute respiratory failure. Evidence on other pharmacotherapies (e.g., theophylline, donepezil) and interventions, such as inspiratory muscle training and temporary diaphragmatic pacing (e.g., TransAeris® and LungPacer™ systems), are inconclusive because evidence is at high risk of bias, mixed, or not available. A 2016 clinical guideline by the American Thoracic Society and American College of Chest Physicians recommends inspiratory training and corticosteroid prophylaxis in addition to standard ventilator weaning practices, such as use of spontaneous breathing tests (SBTs), before ventilator weaning.

**Evidence limitations:** Although meta-analysis of independent RCTs, including sham- and placebo-controlled studies, provide adequate evidence to support use of adaptive ventilation modes and corticosteroid prophylaxis to reduce the risks of ventilator weaning failure in critically ill patients at risk of ventilator-induced diaphragmatic dysfunction, additional studies would be useful to validate these interventions in patients with specific etiologies and risk factors. The evidence on other interventions is too limited to support conclusions. Studies of muscle training reported mixed findings. Studies of theophylline and donepezil pharmacotherapy are at high risk of bias from lack of randomization, retrospective design, or small sample size; and the single donepezil and diaphragm pacing studies require independent validation. Additional studies that address these limitations and evidence gap are needed to define optimal strategies to support patients undergoing weaning from ventilation in critical care settings.
Executive Summary

Findings
We assessed 3 systematic reviews (SRs) and 7 clinical studies that reported on ventilator weaning in critically ill patients.

- **Adaptive ventilation**: A meta-analysis of 21 RCTs (Rose et al. 2014) found that automated weaning reduced reintubation compared with manual SBTs (relative risk [RR]: 0.42, 95% confidence interval [CI]: 0.25 to 0.71). A meta-analysis of 10 RCTs (Burns et al. 2014) found that the SmartCare® software reduced weaning time by a mean 2.7 days (95% CI: 4.0 to 1.4). One RCT (Botha et al. 2018) reported shorter weaning time (84 versus 136 hours) and lower mortality (4% versus 5%) with the Puritan-Bennett proportional assist ventilation (PAV+) automated mode than with manual SBTs.

- **Temporary diaphragmatic pacing**: A sham-controlled pilot RCT (n = 20) reported no differences in ICU length of stay with intermittent pacing (30 minutes, twice a day) using the VentFree™ abdominal phrenic stimulation system. No studies were available on the TransAeris system.

- **Respiratory muscle training**: A sham-controlled RCT (Martin et al. 2011) reported higher weaning success rates in ICU patients who received training (71% [95% CI: 55% to 84%] versus 47% [95% CI: 31% to 63%], but CIs were wide. A blinded RCT (Sandoval Moreno et al. 2019) reported that adding respiratory exercise to physical chest therapy did not improve weaning time or success.

- **Pharmacotherapy**: A meta-analysis of 11 RCTs (Kuriyama et al. 2017) reported that corticosteroid prophylaxis reduced reintubation in ICU patients (RR: 0.42, 95% CI: 0.25 to 0.70). Two retrospective studies (Yu et al. 2019, Kim et al. 2016) reported no statistically significant risk reduction with theophylline. One prospective case series reported that 12/16 patients with >3 unsuccessful SBTs could be weaned after a donepezil course.

Evidence
Search dates: January 1, 2010, through April 20, 2020. We reviewed full text of 3 SRs and 8 studies not in the SRs (5 RCTs, 2 nonrandomized controlled studies, 1 case series) reporting on 5,197 patients.

- We included studies on all critically ill patients because we identified no studies of COVID-19. We assessed supplemental interventions to prevent reintubation and excluded standard practices, such as SBTs, airway clearance, and noninvasive ventilation.

- 2 SRs (Rose et al. 2014, n = 1,676; Burns et al. 2014, n = 654) compared conventional and automated ventilator weaning and reported on weaning success and duration and adverse events (AEs).

- 1 SR (Kuriyama et al. 2017, n = 2,742) reported on reintubation and AEs with corticosteroid prophylaxis.

- 2 RCTs compared respiratory muscle training with sham (Martin et al. 2011, n = 69) or no exercise (Sandoval Moreno et al. 2019, n = 126) and reported on ventilation time and weaning success.

- 1 RCT (Botha et al. 2018, n = 50) compared conventional weaning with PAV+ in patients and reported on weaning time and success, hospitalization length, and AEs.

- 1 RCT (McCaughey et al. 2019, n = 20) compared ICU stay lengths with diaphragm pacing or sham stimulation.

- 1 RCT (Cheng et al. 2011, n = 71) compared weaning success with prophylactic prednisolone or placebo.

- 2 nonrandomized studies (Yu et al. 2019, n = 160; Kim et al. 2016, n = 40) compared weaning time and success and AEs with and without theophylline prophylaxis.

- 1 case series (Abbasi et al. 2015, n = 16) reported on weaning in high-risk patients treated with donepezil.

Evidence limitations: Meta-analysis of RCTs provides conclusive data on adaptive ventilation and corticosteroid prophylaxis. However, studies to validate conclusions in patients with COVID-19 are needed. Studies of respiratory muscle training reported mixed findings; studies of theophylline and donepezil are at high risk of bias from lack of randomization or controls. A study of diaphragm pacing is at risk of bias from small size.

Guidelines, Position and Consensus Statements
Searched PubMed, EMBASE, and ECRI Guidelines Trust® (EGT) for relevant documents published January 1, 2015, through April 17, 2020. We identified 2 guidelines supported by SRs.


- American Thoracic Society and American College of Chest Physicians, 2016: recommends SBTs and physical rehabilitation before weaning and prophylactic corticosteroids in patients at high risk of reintubation.
Table of Contents

Background ........................................................................................................................................ 1
Guidelines, Position and Consensus Statements .................................................................................... 2
Clinical Literature ................................................................................................................................ 3
Selected Resources and Reference ....................................................................................................... 9
Policy Statement ................................................................................................................................... 13

Tables

Table 1. Systematic Review ................................................................................................................. 5
Table 2. Clinical Trials ......................................................................................................................... 6
Background

Mechanical Ventilation Termination in Critical Care

Mechanical ventilation uses life-support devices (i.e., ventilators) to insufflate the lungs of critically ill patients who cannot breathe on their own or who require assistance to breathe adequately. Circumstances that require mechanical ventilation include severe respiratory illness, trauma, congenital defects, or the effects of drugs (e.g., anesthetics). Mechanical ventilation may be delivered noninvasively with a breathing mask or helmet, but patients whose airways cannot be protected (e.g., sedated, comatose, with bulbar paralysis) require endotracheal intubation. Clinicians may also choose early intubation for practical reasons (e.g., when patients are expected to worsen or are infected with an airborne pathogen). (For additional information, see the Medscape article Mechanical Ventilation.)

Extubation—often referred to as “ventilator weaning,” even though continued noninvasive ventilation is common—is an important recovery milestone in critically ill patients because prolonged intubation and reintubation (i.e. “weaning failure”) are independent predictors of higher mortality and morbidity, according to Kulkarni and Agarwal. Despite being a lifesaving technique, mechanical ventilation carries a significant risk of complications and sequelae, including:

- **Airway infection and inflammation.** The endotracheal tube constitutes a potential entryway for pathogens, and its presence may cause airway inflammation and increased airway secretion. Inflammation impairs small airway recruitment and secretion clearance, creating conditions that favor opportunistic airway pathogens.

- **Ventilator induced injury.** Mechanical ventilation places significant stress on lung tissues and may cause life-threatening injuries if airflow parameters are not properly set or if the patient’s condition evolves rapidly or unpredictably. Experts also argue that even without critical injury, the resulting mechanical stress may result in lung inflammation and scarring.

- **Neuromuscular deficits.** Neurogenic weakness affecting the diaphragm and chest wall muscles develops in up to 75% of patients receiving mechanical ventilation. The etiology of ventilator-induced diaphragmatic dysfunction is not fully understood, but experts have proposed multiple contributing factors, including neuromuscular pathway inactivity, infection and immune responses, and medications (e.g., corticosteroids, sedatives).

These complications may be compounded by underlying etiologies and prevent patients from breathing adequately on their own, resulting in ventilation weaning delay or failure (i.e., reintubation). Despite advances in ventilator technology and clinical practices, reintubation rates reported in critical care settings range between 10% and 20% of patients. Thus, improving outcomes of ventilator weaning in critically ill patients remains an unmet clinical need. (For additional information, see the Clinical Review: The ABC of Weaning Failure - A Structured Approach and the review Ventilator-Induced Diaphragm Dysfunction: Translational Mechanisms Lead to Therapeutical Alternatives in the Critically Ill.)

Reintubation Prevention Strategies

Minimizing reintubation risk is a major intervention goal in critical care, and contemporary ventilator weaning practices reflect this goal. The decision to extubate follows a comprehensive evaluation of the patient’s respiratory function, general physiologic condition, and underlying etiology evolution and prognosis. If a patient is not already breathing independently, clinicians conduct an SBT. Several SBT protocols are available, with pressure-supported ventilation as the preferred spontaneous ventilation testing mode. After a successful SBT, patients may be temporarily reconnected to the ventilator so they rest before actual extubation. Typically, patients receive continued respiratory support with noninvasive positive pressure airway ventilation, high-flow oxygen therapy, or low-pressure oxygen supplementation depending on their condition. (For additional information, see the UpToDate article Extubation Management in the Intensive Care Unit and Ventilator Weaning and Spontaneous Breathing Trials; an Educational Review.)

In addition, several supplemental interventions have been proposed to specifically reduce reintubation’s risk, including:

- **Adaptive ventilation:** also referred to as “automated weaning,” this intervention uses computer software to continuously monitor and adjust the ventilator settings to progressively reduce respiratory support as the patient’s own breathing recovers. Automated weaning modes are intended to minimize weaning time and

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reintubation risks when used instead of conventional SBTs. (For additional information, see Automated versus Non-Automated Weaning for Reducing the Duration of Mechanical Ventilation for Critically Ill Adults and Children: A Cochrane Systematic Review and Meta-Analysis.)

- **Inspiratory muscle training.** Daily exercise regimens with respiratory training devices (e.g., spirometers) to strengthen respiratory muscles. Inspiratory training is intended to prevent ventilator-induced diaphragmatic dysfunction in patients with prolonged mechanical ventilation and who are conscious with minimal or no sedation. (For additional information, see the review Inspiratory Muscle Training for Intensive Care Patients: A Multidisciplinary Practical Guide for Clinicians.)

- **Temporary diaphragmatic pacing:** This technique uses diaphragmatic muscle neurostimulation with surgically implanted electrodes to reproduce breathing motion. Diaphragmatic pacing has a long research history for treating patients with chronic respiratory muscle weakness (e.g., spinal cord injury), but experts have yet to agree on its optimal use. It is an emerging technique for supporting ventilator weaning in critical care. (For more information, see Ventilator-Induced Diaphragm Dysfunction: Translational Mechanisms Lead to Therapeutical Alternatives in the Critically Ill.)

- **Prophylactic pharmacotherapy:** Corticosteroids are powerful anti-inflammatory agents used to treat acute respiratory distress syndrome, and some experts propose that corticosteroid properties may also reduce reintubation risks in other patients. However, others argue that corticosteroids may contribute to respiratory muscle weakness onset. Theophylline, a bronchodilator, has also been explored to support ventilator weaning. (For more information, see Ventilator-Induced Diaphragm Dysfunction: Translational Mechanisms Lead to Therapeutical Alternatives in the Critically Ill and the review Weaning From Mechanical Ventilation.)

### Ventilation and Reintubation during the COVID-19 Outbreak

Most patients with COVID-19 experience only mild symptoms, but some develop acute respiratory failure with features similar to acute respiratory distress syndrome. Among patients with a COVID-19 diagnosis in China through March 2020, 3.2% required mechanical ventilation, 39% to 72% died, and median hospitalization length was 10 to 14 days. Rapid disease spread and long ventilator dependence resulted in worldwide ventilator shortages, putting additional pressure on ICU teams to reduce weaning times and reintubation risks. Nevertheless, guidance on specific interventions to achieve these goals is lacking. (For more information, see the UpToDate article Coronavirus Disease 2019 (COVID-19): Critical Care Issues and Centers for Disease Control and Prevention Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease [COVID-19].)

On March 24, 2020, FDA began issuing Emergency Use Authorization (EUA) for ventilators and other medical devices to address ventilator shortages during the COVID-19 outbreak. On April 13 and 14, FDA issued EUAs for the Lungpacer Diaphragm Pacing Therapy System (Lungpacer Medical Inc., Exton, PA, USA) and the TransAeris Diaphragmatic Pacing Therapy System (Synapse Biomedical, Inc., Oberlin, OH, USA).

### Guidelines, Position and Consensus Statements

We searched PubMed, EMBASE, EGT, and other web-based resources for relevant guidelines and documents published between January 1, 2015, and April 17, 2020. We sought guidelines that are clearly supported by published SRs or included in EGT. EGT is a publicly available online repository of guidelines supported by systematic reviews and developed by nationally and internationally recognized medical organizations and specialty societies. These guidelines must meet certain U.S. National Academy of Medicine criteria.

We identified two relevant guidelines supported by SRs. Both guidelines provide practice recommendations for mechanical ventilation weaning in critically ill patients, and one discusses supplemental interventions, as follows:


  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 H2O) 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.


1. For acutely hospitalized adults who have been mechanically ventilated for more than 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 more than 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 postextubation 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).

Clinical Literature

We searched PubMed, EMBASE, the Cochrane Library, and selected web-based resources for documents relevant to this topic and published between January 1, 2010, and April 20, 2020. Our search strategies included the following keywords: diaphragm pacing, mechanical ventilation, ventilator-induced diaphragm dysfunction, weaning failure. Please see the Selected Resources and References section for detailed search strategies.

We included SRs and clinical studies of any design that were not included in those SRs that reported on supplemental interventions intended to prevent failure of mechanical ventilation weaning in critically ill patients and reporting on patient-centered clinical outcomes, including ventilator and hospitalization time, weaning success, and AEs.

We did not assess interventions that are part of usual critical patient care or that are not specifically intended for reintubation prevention, such as airway secretion clearance therapies, noninvasive ventilation following extubation, and conventional (i.e., manual) SBT devices or protocols. We did not review respiratory or hemodynamic parameters that reflect respiratory function but may not accurately predict reintubation in all patients.

We identified but excluded two studies that reported on patients recovering from nonemergency surgery(1,2) and four studies that reported on multicomponent interventions but included no appropriate control groups allowing outcome attribution to any particular intervention.(3-6) We also excluded conference abstracts.
We identified and reviewed full text of three SRs and eight clinical studies and abstracts of one clinical study described below. Table 1 summarizes the SR findings. Table 2 summarizes the clinical study findings. We reviewed full text of articles available through open access or our library subscriptions.

**Systematic Reviews**

- 2 overlapping SRs compared conventional and automated ventilator weaning (i.e., adaptive ventilation) and reported on reintubation, ventilation duration, hospitalization length, and AEs. (7,8)
  - 1 SR (Rose et al. 2014, 21 RCTs, n = 1,676) included all automated systems.
  - 1 SR (Burns et al. 2014, 10 RCTs, n = 654) focused on SmartCare automated weaning software (Dragerwerk AG, Lubeck, Germany).

- 1 SR (Kuriyama et al. 2017, 11 RCTs, n = 2,742) reported on reintubation and AEs in ICU patients who received corticosteroid prophylaxis before ventilator weaning. (9)

**Clinical Studies**

- 2 RCTs compared respiratory muscle training with sham (Martin et al. 2011, n = 69) or no exercises (Sandoval Moreno et al. 2019, n = 126) in ICU patients and reported on ventilation time and weaning success. (10,11)

- 1 RCT (Botha et al. 2018, n = 50) compared conventional SBTs in pressure-supported ventilation mode with the PAV+ automated weaning mode for Puritan Bennett ventilator (Medtronic plc., Dublin, Ireland) in ICU patients and reported on weaning time and success, hospitalization length, and AES. (12)

- 1 RCT (Cheng et al. 2011, n = 71) compared a single 40 mg prednisolone dose with placebo in ICU patients at high risk of ventilator weaning failure and reported on weaning success. (13)

- 1 RCT (McCaughey et al. 2019, n = 20) compared abdominal functional stimulation (a form of diaphragm pacing) with sham stimulation in critically ill patients and reported on ICU length of stay. (14) Pacing involved the VentFree™ muscle stimulator (Liberate Medical LLC., Louisville, KY, USA).

- 2 retrospective studies (Yu et al. 2019, n = 160; Kim et al. 2016, n = 40) compared ICU patients treated with and without theophylline (200 mg to 400 mg/day) during ventilation and reported on weaning time and success and AEs. (15)

- 1 prospective case series (Abbasi et al. 2015, n = 16) reported on ventilator weaning success in ICU patients with >3 unsuccessful weaning attempts who were then treated with donepezil (10 mg/day) for 2 to 4 weeks. (16)

**Evidence limitations.** Although meta-analysis of independent RCTs, including sham- and placebo-controlled studies, provide adequate evidence to support the use of adaptive ventilation modes and corticosteroid prophylaxis to reduce the risks of ventilator weaning failure in critically ill patients at risk of ventilator-induced diaphragmatic dysfunction, additional studies would be useful to validate these interventions in patients with specific etiologies and risk factors. The evidence on other interventions is too limited to support conclusions. Studies of muscle training reported mixed findings. Studies of theophylline and donepezil pharmacotherapy are at high risk of bias from lack of randomization, retrospective design, or small sample size; and the single donepezil and diaphragm pacing studies require independent validation. Additional studies that address these limitations and evidence gap are needed to define optimal strategies to support patients undergoing weaning from ventilation in critical care settings.
Table 1. Systematic Reviews

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Purpose</th>
<th>Searches and Inclusion Criteria</th>
<th>Findings Reported By Authors</th>
<th>Authors’ Conclusions</th>
</tr>
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<tbody>
<tr>
<td>Kuriyama et al. 2017(9) Reviewed full text</td>
<td>“We updated a systematic review to identify which patients would benefit from prophylactic corticosteroid administration before elective extubation.”</td>
<td>Searched PubMed, EMBASE, Wanfang, China Academic Journal Network Publishing Database, and Cochrane CENTRAL in February 2016 for relevant randomized controlled trials (RCTs). Included 11 studies (n = 2,742).</td>
<td>“Use of prophylactic corticosteroids was associated with a reduced incidence of postextubation airway events (risk ratio [RR], 0.43; 95% CI, 0.29-0.66) and reintubation (RR, 0.42; 95% CI, 0.25-0.71) compared with placebo or no treatment… Adverse events were rare.”</td>
<td>“Administration of prophylactic corticosteroids before elective extubation was associated with significant reductions in the incidence of postextubation airway events and reintubation, with few adverse events.”</td>
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<tr>
<td>Rose et al. 2014(7) Reviewed full text</td>
<td>“To compare mechanical ventilator weaning duration for critically ill adults and children when managed with automated systems versus non-automated strategies.”</td>
<td>Searched MEDLINE, EMBASE, Cochrane CENTRAL, CINAHL, LILACS, Web of Science, DARE, and the HTA Database in September 2013 for relevant RCTs. Included 21 studies (n = 1,676).</td>
<td>“Automated systems reduced the geometric mean weaning duration by 30% (95% confidence interval (CI) 13% to 45%), with substantial heterogeneity (I² = 87%, P &lt;0.00001).… Automated systems reduced ventilation duration with no heterogeneity (10%, 95% CI 3% to 16%) and ICU LOS (8%, 95% CI 0% to 15%)… Automated systems reduced prolonged mechanical ventilation and tracheostomy. Overall quality of evidence was high.”</td>
<td>“Automated systems may reduce weaning and ventilation duration and ICU stay. Due to substantial trial heterogeneity an adequately powered, high quality, multi-centre [RCT] is needed.”</td>
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## Clinical Evidence Assessment

### Evidence-based Strategies for Weaning Patients with COVID-19 from Mechanical Ventilation

<table>
<thead>
<tr>
<th>Author/Year</th>
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<td>Burns et al. 2014(8)</td>
<td>“To compare weaning time (time from randomization to extubation as defined by study authors) between invasively ventilated critically ill adults weaned by automated weaning and SBT [spontaneous breathing test] systems versus non-automated weaning strategies.”</td>
<td>Searched MEDLINE, EMBASE, CI NAHL, Cochrane CENTRAL, Evidence-Based Medicine Reviews, and HEalthSTAR in May 2013 for RCTs of mechanical ventilation with the SmartCare automated weaning system. Included 10 studies (n = 654).</td>
<td>“Compared with non-automated strategies, SmartCare™ decreased weaning time (mean difference (MD) -2.68 days, 95% confidence interval (CI) -3.99 to -1.37; P value &lt; 0.0001, seven trials, 495 participants, moderate-quality evidence), time to successful extubation (MD -0.99 days, 95% CI -1.89 to -0.09; P value 0.03, seven trials, 516 participants, low-quality evidence), length of ICU stay (MD -5.70 days, 95% CI -10.54 to -0.85; P value 0.02, six trials, 499 participants, moderate-quality evidence) and proportions of participants receiving ventilation for longer than seven days and 21 days.”</td>
<td>“Compared with non-automated weaning strategies, weaning with SmartCare™ significantly decreased weaning time, time to successful extubation, ICU stay and proportions of patients receiving ventilation for longer than seven days and 21 days.”</td>
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### Table 2. Clinical Trials

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<tr>
<th>Author/Year</th>
<th>Study Type and Patients</th>
<th>Intervention</th>
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<th>Authors’ Conclusions</th>
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<tr>
<td>McCaughey et al. 2019(14)</td>
<td>Double-blind, single-center study of 20 patients receiving mechanical ventilation in an intensive care unit (ICU)</td>
<td>Abdominal functional stimulation (FES, n = 10) or sham stimulation n = 10) (2 x 30 min/day) with surface electrodes using the VentFree VF03-K synchronizer</td>
<td>“While this pilot study is not adequately powered to make an accurate statistical conclusion… ICU length of stay (p = 0.011) and ventilation duration (p = 0.039) appeared to be shorter in the intervention compared to the control group.”</td>
<td>“While abdominal FES did not lead to differences in abdominal muscle or diaphragm thickness, it may be an effective method to reduce ventilation duration and ICU length of stay in this patient group.”</td>
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<tr>
<td>Sandoval Moreno et al. 2019(10)</td>
<td>Double-blind, single-center study of 126 ICU patients receiving mechanical ventilation</td>
<td>Daily physical therapy with or without respiratory muscle training until weaning</td>
<td>“There were no statistically significant differences in the median weaning time of the MV between the groups or in the probability of extubation between groups (HR: 0.82; 95%CI: 0.55–1.20; p=0.29).”</td>
<td>“Respiratory muscle training did not demonstrate efficacy in the reduction of the weaning period of mechanical ventilation nor in the increase of respiratory muscle strength in the study population.”</td>
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<td>Botha et al. 2018(12)</td>
<td>Open-label, single-center study of 50 ICU patients receiving mechanical ventilation</td>
<td>Pressure supported ventilation (PSV, n = 25) or proportional assist ventilation with load adjustable gain factors (PAV+, n = 25)</td>
<td>“There was no significant difference between the PAV+ and PSV groups in time to successful weaning (84.3 v 135.9 hours, respectively; P = 0.536). Four patients randomised to PAV+ were crossed over to PSV during weaning. There was no significant difference between groups for rescue ventilation, reintubation within 48 hours, tracheostomy, sedatives and analgesics prescribed, and ICU and hospital LOS [length of stay]. ICU mortality was higher in the PSV group (25% v 4 %; P = 0.002).”</td>
<td>“Both modes of ventilation were comparable in time to liberation from the ventilator.”</td>
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<td>Martin et al. 2011(11)</td>
<td>Single-blind, single-center study of 69 ICU patients who could not be weaned from ventilator at first attempt</td>
<td>Respiratory muscle training 5 days/week with a threshold inspiratory pressure device (n = 35) or a sham device (n = 34) for 1 month or until weaning</td>
<td>“There were no adverse events observed during IMST [inspiratory muscle strength training] or SHAM treatments. Twenty-five of 35 IMST subjects weaned (71%, 95% confidence interval (CI) = 55% to 84%), while 16 of 34 (47%, 95% CI = 31% to 63%) SHAM subjects weaned, P = .039. The number of patients needed to be treated for effect was 4 (95% CI = 2 to 80).”</td>
<td>“An IMST program can lead to increased MIP [maximal inspiratory pressure] and improved weaning outcome in FTW [failure to wean] patients compared to SHAM treatment.”</td>
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<td>Cheng et al. 2011(13)</td>
<td>Double-blind, single-center study of 71 ICU patients at high risk of extubation failure (cuff leak &gt;24%)</td>
<td>Methylprednisolone (40 mg, n = 38) or placebo (n = 33) as a single intravenous injection</td>
<td>“The incidences of PES [post-extubation stridor] (15.8% vs. 39.4%, P&lt;0.05) and reintubation rate (7.9% vs. 30.3%, P&lt;0.05) were lower in the treated group compared to the placebo group.”</td>
<td>“A single injection of methylprednisolone at the dose used 4 h prior to planned extubation effectively reduced the incidence of PES and the reintubation rate.”</td>
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<td>Yu et al. 2019(15)</td>
<td>Retrospective, single-center study of 160 ICU patients receiving mechanical ventilation</td>
<td>Aminophylline (87.5% anhydrous theophylline, 200 mg twice a day through a nasogastric tube, n = 84) or no additional pharmacotherapy (n = 76) until ventilator weaning</td>
<td>“No patient experienced any adverse effects of theophylline... The weaning success rate was higher in the theophylline group than in the non-theophylline group, but the difference was not statistically significant (78.6% vs 65.8%, P=.071). The mechanical ventilation time tended to be shorter in the theophylline group, but again, the difference was not statistically significant.”</td>
<td>“Theophylline might improve respiratory muscle strength in patients with prolonged mechanical ventilation and it needs further prospective studies to confirm.”</td>
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<td>Kim et al. 2016(17)</td>
<td>Retrospective, single-center study of 40 ICU patients with radiographic evidence of ventilator-induced diaphragmatic dysfunction (VIDD)</td>
<td>Theophylline (200 to 400 mg/day) during ventilation (minimum 72 hours, n = 21) or no additional treatment (n = 19)</td>
<td>“Both weaning time and total ventilation time tended to be shorter, but not statistically significant, in the theophylline group than in the nontheophylline group. Weaning success rates and ICU and in-hospital mortality rates tended to be favorable in the theophylline than in the nontheophylline group.” “Theophylline was well tolerated by study patients, with no significant adverse drug reactions as to mandate discontinuation.”</td>
<td>“Theophylline significantly improved diaphragmatic movements in patients with VIDD. Our results warrant a larger study to determine whether theophylline use has benefits during weaning from mechanical ventilation.”</td>
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Evidence-based Strategies for Weaning Patients with COVID-19 from Mechanical Ventilation

Case Series

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<thead>
<tr>
<th>Author/Year</th>
<th>Study Type and Patients</th>
<th>Intervention</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Abbasi et al. 2015(16)</td>
<td>Prospective, single-center study of 16 ICU patients who could not be extubated after 3 attempts</td>
<td>Donepezil (10 mg/day) for 2 to 4 weeks</td>
<td>“Twelve out of 16 studied patients experienced successful results to facilitate weaning with donepezil intervention. The mean duration of donepezil treatment until outcome measurement was 12 days. There were not any significant differences in [arterial blood gas] parameters among patients with successful and failed weaning trial on day of donepezil initiation.”</td>
<td>“Our results in the clinical setting suggest that, the use of donepezil can expedite weaning presumably by stimulation of respiratory center and obviate the need to re-intubation in cases of respiratory drive problem in difficult to wean patients.”</td>
</tr>
</tbody>
</table>

Selected Resources and Reference

Search Summaries

Our master’s-level medical librarians searched the following databases to identify the literature and related materials.

**ECRI Resources [searched January 1, 2015, through April 17, 2020]**

*Search Strategy:*

Diaphragm pacing, diaphragmatic pacing, mechanical ventilation, reintubation, ventilator, ventilator induced diaphragm dysfunction, weaning

Universal Medical Device Nomenclature System (UMDNS) Codes: Ventilators, Intensive Care [17-429], Ventilators, Intensive Care, Adult [18-792]

*Results:* We identified seven related reports and no records in the Healthcare Product Alerts database.

- Preparing for the Unexpected with Mechanical Ventilators. [PSO]. 2017 Nov.
- Healthcare Product Alerts database. [searched January 1, 2017, through April 23, 2020]. Note: we did not identify any alerts for lungpacer, smartcare, transaeris, or ventfree


*Search Strategy:*

- #1 "Respiration, Artificial"[Mesh] OR "Ventilators, Mechanical"[Mesh] OR "mechanical ventilation"
- #2 "Diaphragm Pacing" OR "diaphragmatic pacing"
- #3 #1 AND #2
CLINICAL EVIDENCE ASSESSMENT
Evidence-based Strategies for Weaning Patients with COVID-19 from Mechanical Ventilation

Results: We identified 68 records.


Search Strategy:

Results: We identified 5 records.


Search Strategy:

Results: We identified seven unique records.

Guidelines, Position, and Consensus Statements [searched January 1, 2015, through April 17, 2020]

Search Strategy:

Results: We identified two relevant documents.

Selected Standards and Guidelines


Search Strategy: diaphragm pacing, diaphragmatic pacing, mechanical ventilation, weaning

Results: We did not identify any National or Local Coverage Policies.

Selected Web Resources. [searched April 16, 2020].

Food and Drug Administration (FDA). [cited 2020 Apr 16].
- Emergency Use Authorizations. Ventilators and Other Medical Device EUAs. [cited 2020 Apr 16].

Manufacturers
- Liberate Medical, Inc. VentFree Respiratory Muscle Stimulator. [cited 2020 Apr 24].
- Lungpacer Medical, Inc. Lungpacer DPT System. [cited 2020 Apr 16].
- Synapse Biomedical, Inc. Synapse Biomedical, Inc. has received an Emergency Use Authorization for the emergency use of its TransAeris® DPS. [cited 2020 Apr 16].

Other Selected Web Resources
- UpToDate. [cited 2020 Apr 16]. Note: requires subscription to view documents.
  - Han M. Management and prognosis of patients requiring prolonged mechanical ventilation. [updated 2019 Jul 21].

References Reviewed (PubMed and EMBASE search dates were January 1, 2010, through April 20, 2020)
3. Davies, MG, Quinnell, TG, Oscroft, NS, Clutterbuck, SP, Shneerson, JM, and Smith, IE. Hospital outcomes and long-term survival after referral to a specialized weaning unit. Br J Anaesth. 2017;118(4):563-569. PubMed abstract | Full text


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Policy Statement

The information presented in this Clinical Evidence Assessment is highly perishable and reflects the state of the literature on this topic at the time at which searches were conducted and the Clinical Evidence Assessment was prepared. Clinical Evidence Assessments provide a guide to the published clinical literature and other information about a topic on which we received a client inquiry. The scope is customized to address the specific information needs of the requestor. The content reflects the information identified from searches of the available, published, peer-reviewed scientific literature, gray literature, and websites at the time the searches were conducted. Publications referenced in this Clinical Evidence Assessment are generally limited to the English language. Clinical Evidence Assessments are developed by a multidisciplinary staff of doctoral level research analysts, clinicians, and medical librarian information specialists. For quality assurance, all reports are subject to review within ECRI before publication. Neither ECRI nor its employees accept gifts, grants, or contributions from, or consult for medical device or pharmaceutical manufacturers. The Clinical Evidence Assessment may be based on review of abstracts of published articles as well as full text articles. Abstracts do not always accurately reflect the methods and findings of full-length articles and limit full interpretation of published data. This Clinical Evidence Assessment is not intended to provide specific guidance for the care of individual patients. ECRI implies no warranty and assumes no liability for the information contained in the Clinical Evidence Assessment.

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