Appendix 3

Detailed Risk of Bias Assessment

To generate randomization sequences, trials reported use of computer generated random tables at each centre (1), a computer generated randomization table using variable blocks of four (2), computer generated randomization (3), Kendall and Babington tables (4), a table of random numbers held by an investigator not involved with study enrolment (5) and a digital table (6). The remaining trials (7-15) did not provide specific information regarding sequence generation.

One study used a computer-generated randomization list held by investigators not involved in clinical decisions (1). To conceal allocation, trials reported using sealed envelopes (14), opaque envelopes (8), sealed, opaque envelopes (2,9) or sealed, opaque, sequentially numbered envelopes (5,7,15). The method of allocation concealment was not specified in five trials (4,6,11-13) and confirmed to be concealed through correspondence with one author of two trials (3,10). Due to the nature of the interventions, blinding of caregivers and patients was not possible; however, one trial (9) blinded individuals participating in data collection and analysis.

Methods

Initial management

Initial pre-randomization ventilation strategies integrated predominantly volume-cycled ventilation strategies (1,2,4,6-8,10-12,16) with or without concurrent or subsequent pressure support (PS). In four trials, screening for weaning eligibility occurred daily (1,3,9,10) and another two trials screened daily after 48 hours of invasive ventilation (5,8). Weaning candidates were identified after at least 24 hours (4), at 36 to 48 hours, including 6 to 8 hours of paralysis (7), after at least 48 hours (2,5,8,15), 48 to 60 hours (16), 72 hours, including 6 to 8 hours of paralysis, (3,10), or 3 days (1) of invasive ventilation. In four trials (6,11-13), evaluating COPD patients with pulmonary infection, patients were enrolled upon

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achieving 'pulmonary infection control' (PIC) window criteria (6,12,13) or after infection control was achieved (11).

Eligibility for study inclusion and randomization was based upon patients meeting predefined permissive weaning criteria (1-8,10-16) and failure of either a single 30 minute (9,14), one hour (7) or two hour (2-4,8,10,15) spontaneous breathing trial (SBT), or failure of a two hour T-piece trial on three consecutive days (1).

Invasive weaning

Patients in the control group were weaned using PS (1-5,7-10,13,16), assist control (AC) (1) or synchronized intermittent mandatory ventilation (SIMV) with PS (6,11,12), or SIMV alone (15). The level of PS was gradually reduced in three trials (1,2,7). Studies titrated PS by 2 cm H_2O every 4 hours to clinical tolerance, saturations and respiratory rate (4) or by 2 to 4 cm H_2O per day (3,10). Another trial decreased PS and PEEP by 2 cm H_2O every 2 hours until a minimum of 8 and 10 cm H_2O, respectively, were attained and titrated support to PaO_2/FiO_2, $PaCO_2$ and pH (5).

Trials of spontaneous breathing, using T-piece or continuous positive airway pressure (CPAP) < 5 cm H_2O or PS, were performed twice daily (7), daily (1,14,15) or at least once daily (2). One study included at least two observation periods per day during PS weaning with optional SBTs (8). To discontinue invasive ventilation, patients successfully completed a 30-minute (5), two hour (1,9), three hour (7,11,16) SBT, or two periods of observation with optional SBTs (8). Three trials did not specify SBT duration (2,14,15). Patients were considered weaned when they (i) remained stable for at least 4 hours on an SIMV rate of 5 breaths/minute with PS of 5 to 7 cm H_2O (12), (ii) blood gases were normalized and patients could breath spontaneously for more than 3 hours with low oxygen requirements ($FiO_2 \leq 0.40$), acceptable oxygen saturation ($SpO_2 \geq 90\%$) and a normal ($pH \geq 7.35$) (11), or (iii) when PS was titrated to $\leq$ 7cm H_2O (2), $\leq$ 8 cm H_2O (13), or $\leq$ 10 cm H_2O (4,6) with PEEP of 5 cm H_2O and satisfactory blood gases (4,5), saturations (6,13), respiratory rate (4-6,13), a tidal volume of

approximately 8 mL/kg (6,13) and arterial partial pressure of carbon dioxide ($PaCO_2$) between 45 and 60 mm Hg, or at baseline on low FiO_2 (4,6,13) for more than 4 hours (6,13). Two trials considered patients to be weaned from invasive PS with arterial saturations ≥ 90% on FiO_2 ≤ 40% with pH ≥ 7.35, RR < 35 breaths/min, hemodynamic stability, and the absence of severe dyspnea or depressed neurologic status (3, 10).

Noninvasive weaning

Similar to invasive weaning, trials utilized different noninvasive weaning procedures and protocols. Initial support was delivered continuously in seven studies (1,4,5,7,9,15,16) and, continuously initially and subsequently intermittently in one study (2). Alternatively, NIV was delivered intermittently in one study (8) or for at least 2 (6) or 6 (2) hours during the initial application and in one study until tolerated for 20 to 22 hours per day, spaced by periods of spontaneous ventilation with oxygen for meals and expectoration (3,10).

Following extubation, NIV was administered in pressure mode in 13 trials (1,2,4-9,11-14,16) of which six trials specified use of a spontaneous timed mode (1,3,4,6,8,9) or a flow mode (8). Two trials used Proportional Assist Ventilation (10,15) and two trials (2,5) did not specify the mode. NIV was preferentially delivered by face mask (1-4,6-10,12-15) or nasal mask (1,3,6,8-10,13). One trial (5) used a helmet, but also permitted use of full-face and oronasal mask to improve tolerance. Some trials permitted fixed or gradually increasing periods of spontaneous breathing (1,3,7-10), with at least three trials (3,7,10) specifying two periods of spontaneous breathing per day. Other trials enabled spontaneous breathing when selected criteria were met (5) or intermittently between NIV periods (2). Criteria for discontinuing noninvasive support included successful completion of a three (7,16), two (9) hour or 30 (5) minute period of spontaneous breathing, a period of observation of undetermined duration (2), or at least two periods of spontaneous breathing observed by an attending physician (8). One trial (15) did not conduct post-randomization periods of spontaneous breathing.

The level of support was gradually decreased (6,13,15) and noninvasive ventilation time gradually reduced (6,13). In some trials clinicians titrated PS by 2 cm H_2O every 2 (5) or 4 (4) hours until PS and PEEP targets were achieved (5) or by 2 to 4 cm H_2O each day (3,10) according to patient tolerance. In one trial (5), the goal of the weaning protocol was specified to maintain a $PaO_2/FiO_2 \geq 225$, $PaCO_2 \leq 50$ mm Hg, and pH $\geq$ 7.35. Whereas in some trials, clinicians decreased the level of inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) to 8 and 4 cm H_2O, respectively (4), in other trials, IPAP was reduced to < 10 cm H_2O (with NIV applied for less than 2 hours per day) (6,13) or until the difference between IPAP and EPAP was $\leq$ 5 cm H_2O (12). Other trials considered patients to be weaned from noninvasive support when arterial saturation was $\geq$ 90% on $FiO_2 \leq$ 40% with pH $\geq$ 7.35, RR < 35 breaths/min, hemodynamic stability, and absence of severe dyspnea or depressed neurologic status (3,10) or according to blood gases, clinical status or mechanical ventilation parameters (2,5,11). One trial (2) specified the need for daily NIV for less than 6 hours or respiratory stability with standard oxygen therapy for at least 12 hours with ABGs: $PaO_2 \geq 64$ mm Hg with pH $\geq$ 7.35 and $PaCO_2 \leq 60$ mm Hg.

Effects of Interventions (selected outcomes)

Mortality

Sixteen trials involving 994 patients provided mortality data. Mortality was reported at 30 days (4,15), 60 days (7), 90 days (1,8), at ICU (2,5) and hospital discharge (3,5,6,8,10,12-14) and at an undefined time point (9,11,16).

Proportion of Weaning Failures

Eight trials, involving 605 patients, reported the proportion of patients successfully weaned (2,3,5,7-9, 10,15). Successful weaning was not defined in two studies (2,10) and defined in two studies as either: not

requiring initiation of NPPV or reintubation within 72 hours (7,15), or not requiring reintubation within 48 hours (9). For one trial (2), we considered reintubation or death within 7 days to represent a weaning failure. Another trial (8) defined weaning failure as the need for reintubation by day five following extubation or, when extubation was not possible, within 5 days of initiation of weaning efforts in the IPPV group. In this trial (8), all patients with weaning failure were reintubated within 5 days. In another trial, successful weaning was defined as the absence of reintubation within 3 days after extubation (15) or if reintubation or noninvasive ventilation was not required within 72 hours of suspension of ventilation (3). Similarly, Vaschetto et al (5) defined extubation failure as the inability to sustain spontaneous unassisted breathing for 48 consecutive hours, without developing respiratory failure requiring ventilatory support (either invasive or noninvasive).

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