Management of Acute Respiratory Failure

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Reviewed:	14 APR 2014	Approved:	16 APR 2014	
Supersedes:	**This is a new CPG and must be reviewed in its entirety.**			
☐ Minor Changes (***or)***		☐ Changes are substantial and require a thorough reading of this CPG (or)		
☐ Significant Changes				

1. **Goal**. Describe the risk factors, diagnosis and management of acute respiratory distress syndrome (ARDS) in the deployed environment and the resources available for safe aeromedical transport of these patients.

2. **Background**.

   a. Patients with multiple injuries are known to develop lung injury resulting in abnormal gas exchange which can result in long-term disability or even death.[1] The purpose of this guideline is to review the diagnostic criteria for ARDS, to describe the frequency of this problem in combat casualties, and to recommend a series of management strategies to permit safe aeromedical evacuation of these patients.

   b. Respiratory failure has been observed in combat casualties for over a century. In a recent review of the DoD Trauma Registry (DoDTR), 152 patients with ARDS were identified over a seven-year period.[2] Over a six-month rotation, Role III facilities managed between one and 34 of these patients depending on the operational tempo. These patients were more often female and presented in shock. Patients with ARDS had a significantly increased risk of death as compared to intubated controls (12.8% vs. 5.9%). Further analysis of this population identified that increased crystalloid and FFP infusion independently predicted ARDS.[3]

3. **Definitions**.

   a. ARDS develops as a result of both direct and indirect injury to the lungs. Common causes of ARDS following a direct injury include pneumonia or gastric aspiration. In combat casualties, direct insults resulting in ARDS also include pulmonary contusion, inhalation injury, and fat emboli. ARDS from indirect lung injury can occur in patients with polytrauma requiring multiple transfusions, septic shock, or severe acute pancreatitis. Several disease processes can mimic ARDS. These must be differentiated to ensure appropriate treatment include acute eosinophilic pneumonia (AEP), acute interstitial pneumonia (AIP), bronchiolitis obliterans organizing pneumonia (BOOP), and diffuse alveolar hemorrhage (DAH).[4]

   b. The definition of ARDS was updated in 2012. The new Berlin Definition of ARDS reflects a range of severity from mild to moderate to severe, specifically defines "acute onset" as within 1 week, and specifies the need for PEEP$\geq$5 cmH_20.[5] The terminology of Acute Lung Injury (ALI) and the original American-European Consensus Conference (AECC) definition of ARDS[6] are less practical; so this CPG will refer to the new Berlin Definition.

c. Timing of ARDS must occur within 1 week of a known clinical insult described in 3.a. above or must be in the context of new or worsening respiratory symptoms.

d. On chest imaging (CXR or CT scan), bilateral opacities must be present which are not fully explained by effusions, collapse, or pulmonary nodules.

e. Respiratory failure should not be due to cardiac failure or fluid overload.

f. If the above criteria are met, the degree of hypoxemia with a PEEP of at least 5 cm H_2O determines the severity of ARDS.

1) Mild ARDS = PaO_2 to FiO_2 ratio (P:F) of > 200 and ≤ 300.

2) Moderate ARDS = P:F of >100 and ≤ 200.

3) Severe ARDS = P:F of ≤ 100.

4) At significant elevations (>1000 m), these ranges decrease by a correction factor relative to the barometric pressure [P:F * (barometric Pressure/760)]. At Bagram Airfield (1,492 m), the barometric pressure is approximately 641 mmHg; so the adjustment factor is 0.84 for each of the above ranges. For example, severe ARDS at BAF would be defined as a P:F of ≤ 84.

g. The diagnosis of ARDS is typically made in patients who have respiratory insufficiency that requires intubation and mechanical ventilation.

4. Diagnosis.

a. Patients suspected of having ARDS on the basis of CXR findings and ventilator settings should have their diagnosis confirmed in the following way.

1) Verify that the patient is likely to have respiratory failure from either a direct or indirect pulmonary injury and the need for mechanical ventilation support.

2) Consider diagnoses which can mimic ARDS as described above.

3) Obtain a good quality AP upright CXR and look for diffuse infiltrates. Consider a Chest CT if this imaging modality is available.

4) If cardiogenic pulmonary edema and/or fluid overload cannot be fully excluded as the cause of respiratory failure, consider placing a central venous pressure catheter and obtain a trans-thoracic echocardiogram if possible.[7,8]

5) Place the patient on volume or pressure control ventilation [tidal volume (V_T) approximately 4-8 mL/kg using predicted body weight (see ARDSNet Card in Appendix B) and targeting a peak inspiratory pressure (PIP) ≤ 30 cm H_2O *OR* set the PIP to 30-35 cmH_2O and then decrease it gradually to achieve a V_T of 6 mL/kg). Set the respiratory rate between 6 and 35 and adjust to achieve a pH≥7.3. Set PEEP (minimum 5 cmH_2O) and FiO_2 according to the ARDSNet table to achieve a SaO_2 of up to 95%. Allow the patient's gas exchange to equilibrate for 30 minutes and then draw an ABG to calculate the patient's P:F ratio.

b. If ARDS is confirmed, document the grade (mild, moderate, severe) in the patient's record with the diagnostic criteria used.

5. Management.

a. The management of patients with ARDS should safely support gas exchange without further injuring the patient's lungs. In fact, using a lung protective ventilator strategy in all intubated patients appears to improve clinical outcomes.[9,10] Providers must also recognize that there are also some limitations imposed by the transport ventilators and that the patient's PaO_2 will always decrease during aeromedical transport.[11,12]

b. In patients with ARDS, the goal is to limit barotrauma (PIP≤30-35 cmH_2O) and volutrauma (V_T≤6 mL/kg predicted body weight) with a SaO_2≥88-90% and a pH≥7.3 (except in TBI where the target should be ≥7.35).

c. Role III patient management (Appendix A)

1) Ventilator management. Once ARDS has been diagnosed, the patient should be placed on lung protective ventilation (LPV) settings according to the ARDSNet ventilator management card (Appendix B). The patient's Predicted Body Weight (PBW) is determined by measuring their height and then using the appropriate gender-based calculation. During the initial management, a tidal volume (V_T) of 8 mL/kg may be used, but this should be decreased to 6 mL/kg within 2 hours. Other modes of ventilation besides volume assist control can be used, but this should be at the discretion of an intensivist experienced in the management of ARDS.

2) Neuromuscular blockade. If the patient has severe ARDS or rapidly worsening ARDS, a short course (48 hours) of neuromuscular blockade may facilitate the continued use of LPV while eliminating such problems as ventilator dyssynchrony.[13] This strategy also carries a mortality benefit in patients with confirmed ARDS. Cisatricurium (Nimbex) minimizes the risk of ICU-related neuropathy or myelopathy which is an important consideration in the ARDS population.[14,15]

3) Fluid management. Patients with ARDS in the setting of a positive fluid balance have an increased mortality.[16] Thus, early and aggressive limitation of unnecessary volume infusions is encouraged. Typically, this is done by eliminating any "maintenance IV fluid," maximally concentrating any necessary drips, and converting IV medications to enteral. If the patient's hemodynamics can tolerate diuresis, this should be pushed aggressively; if the patient's hemodynamics are marginal and there is any degree of volume overload, consider starting a furosemide (Lasix) or bumetanide (Bumex) drip. Some Role III facilities are also equipped with CVVH/D which can also be used to eliminate excess intravascular volume in the setting of poor renal function. If the patient is hypoproteinemic (i.e., total protein < 6 g/dL), consider administering Albumin 25 g q8h (100 mL 25% Albumin) for 3-5 days which has been demonstrated to improve oxygenation and diuresis in 2 prospective, randomized studies.[17,18] The goals of therapy include a CVP < 4 mmHg with evidence of effective circulation by exam (warm, no mottling and capillary refill < 2 s) and adequate urine output (≥ 0.5 mL/kg/hr).[19]

4) Blood product transfusions. Blood products carry a risk of initiating or exacerbating respiratory failure.[3,20–22] In a recent study of the DoDTR, moderate numbers of RBC transfusions (2-14) increased the risk of ARDS. Furthermore, each unit of additional

plasma transfused increased the risk of ARDS in intubated combat casualties by 7%.[3] Thus, it is imperative to balance the benefits of DCR against the risk of ARDS. If the patient is bleeding and needs blood volume replaced, blood products should not be withheld. On the other hand, a patient who is no longer bleeding who has asymptomatic anemia or a mildly elevated INR with a normal thromboelastogram (TEG) likely does not need additional blood products.

5) Corticosteroid administration. Intravenous steroids have generally shown no benefit in the initial treatment of ARDS, and have been associated with potential adverse effects and complications. Recognized complications of this approach include superinfections, a blunted febrile response, increased GI bleeding, hyperglycemia, and muscle weakness especially when combined with neuromuscular blockade. However, initiation of moderate-dose corticosteroids in highly-select patients can improve pulmonary mechanics and reduce ventilator and ICU days.[23] This highly-select population is primarily those with "late-phase" or "prolonged" ARDS, defined as duration of >/= 7 days. The ARDSnet LASRS Trial demonstrated a potential benefit of steroids in the subgroup of patients with ARDS duration between 7-13 days, but potential harm of steroids when administered to patients who were at >/=14 days of duration. In patients without contraindications, the recommended regimen is methylprednisolone 2 mg/kg IV x1 followed by an infusion of 2 mg/kg/day (can be divided to q6 hour doses) x14 days (or for the duration of intubation—whichever is shorter). The infusion can then be tapered over 7-21 days based on clinical judgment. If steroids have not been initiated within 2 weeks of an ARDS diagnosis, they should be avoided due to an increased mortality with delayed therapy.[24]

6) Nutrition and prophylaxis. Patients with ARDS should be on nutritional support. Enteral feeds are preferred if the GI system is functional. Consideration should be given to positioning a naso-jejunal feeding tube for this purpose. GI stress ulcer prophylaxis is typically used in critically ill patients with ARDS, and all patients with ARDS should be considered for chemical DVT prophylaxis.

7) Sedation management and physical therapy. The major morbidity of ARDS in the long term is neurologic and/or musculoskeletal disability related to prolonged inactivity.[14,15] Consequently, at the earliest and safest time, patients should undergo a daily awakening trial ("sedation vacation")[25] and should be started on an aggressive program of early mobilization. This consists of a staged approach even while still intubated beginning with passive range of motion (performed daily by providers, nurses, therapists, co-workers, and family), sitting up at the side of the bed, moving from bed to chair, and ambulating with assistance.[26,27]

8) Rescue oxygenation therapies. To limit the volutrauma and barotrauma of mechanical ventilation in these patients and to permit better venous return to the right heart, the initial maneuver for patients with moderate to severe ARDS is to decrease the ventilator tidal volumes to 4 mL/kg (or to lower the PIP delivered if using pressure control ventilation) targeting a PIP of $\leq$ 35 cm H_2O (and preferably $\leq$ 30 cm H_2O) and tolerating a saturation of 90%[28] so long as there is evidence for adequate oxygen delivery to peripheral tissues (no rising lactate or worsening base deficit).

Advanced therapies for ARDS patients are limited in an austere environment. If the patient's disease is primarily in the lower lobes (based on CXR or CT findings), a trial of prone positioning twice daily for 2–6 hours per session should be performed.[29] A recent study of patients with moderate to severe ARDS (P:F <150) demonstrated a mortality benefit to proning for 16 hours/day.[30] This is best done by an experienced team able to avoid tube/line dislodgment during the proning maneuver. The EKG electrodes are placed on the patient's back and the eyes are taped shut. This approach is best implemented in the setting of a proning protocol (Appendix C) which includes indications/contraindications, a pre-proning checklist, and a description of nursing care of the proned patient. Low-level recruitment maneuvers performed by holding 40 cm H_2O pressure for 40 seconds can be performed by the patient's provider, but the team should be prepared to manage unstable hemodynamics due to decreased venous return. Other measures such as inhaled Nitric Oxide (iNO) or inhaled prostacyclin (Flolan) are not typically available in Role III facilities. Advanced rescue ventilator modes such as inverse ratio ventilation/APRV should be utilized under the supervision of an experienced intensivist.

d. CCATT capabilities

1) Intubated patients are transported out of theater by CCATT.[31,32] From October 2001 to May 2006, this consisted of 1,265 of 1,995 total CCATT patients (63%).[33] The decision to transport a patient with ARDS should be made jointly with the Theater CCATT Director and the validating flight surgeon, the on-site CCATT physician, and the Role III Trauma Czar and/or ICU Medical Director taking into consideration the severity of the patient's respiratory failure, the trajectory of that respiratory failure (improving or worsening), and the experience of the team.[12]

2) CCATT has both the Impact 731 ventilator and the LTV 1000 ventilator for use in transport.[34] The Impact 731 operates in Volume Control, Pressure Control, SIMV, and CPAP with and without Pressure Support. Up to 100% O_2 can be applied as can PEEP of up to 25 cm H_2O. Flow rates range from 0 to 100 L/min @ 40 cm$H_2$0. Peak inspiratory pressures range from 10 to 80 cmH20. Inverse ratio ventilation is not possible.

3) The LTV 1000 provides similar features to the Impact 731. Additionally, it provides inverse ratios of up to 4:1, and flow rates from 100 L/min (in volume control modes) to 160 L/min (in pressure control modes).

e. Indications for calling the ALRT lung team from Landstuhl Regional Medical Center (LRMC)

1) In 2005, a specialized Acute Lung Rescue Team (ALRT) was formed out of the staff in the LRMC ICU.[35] This team consists of a medical/pulmonary critical care physician, a surgical intensivist, an ICU nurse, and a respiratory therapist, all experienced in advanced ventilator management.

2) In addition to the Impact 731 and LTV 1000 ventilators offered by CCATT, this team also brings a high frequency percussive ventilator (Percussionaire VDR-4), inhaled prostacyclin (Flolan), and extracorporeal life support (ECLS) for the management of

patients with moderate to severe ARDS who cannot otherwise be safely transported.[36–38]

3) This team can be contacted by calling the LRMC ICU at DSN 314-486-7141

4) In addition the San Antonio Military Medical Center (SAMMC) ECMO Transport Team can be contacted at DSN 312-429-BURN (2876).

5) Indications for calling LRMC ALRT (this should be done by the Trauma Czar or ICU Medical Director in association with the Theater CCATT Director) for transport of a US or coalition soldier or civilian include the following:

- PaO_2: FiO_2 < 100 (after correction for elevation).
- PaO_2: FiO_2 < 200 + Inhalation injury (after correction for elevation).
- FiO_2 > 0.7 or pH < 7.25 while on lung protective strategy.
- PEEP > 15 cmH_20 w/ Pplat > 30 cmH_20.
- Severe brain injury w/ PCO_2 > 35-40 mmHg on a transport ventilator.
- Cardiogenic shock refractory to maximal medical therapy.
- Anatomic derangement (e.g., bronchopleural fistula, pneumonectomy).
- Use of advanced ventilator modes such as APRV.
- Acute PE with right heart strain or hypoxemia.
- Multi-system organ failure (e.g., ARDS + Renal Failure).

6) Patients with these indications may require advanced support modalities for safe long-range transport. The LRMC ALRT is specifically trained in the indications for and the use of these modalities which have all been appropriately vetted in the combat casualty care and transport communities.

a) High frequency percussive ventilation can be helpful in cases of purulent pneumonia or inhalation injury by mobilizing secretions while affording safe gas exchange.[39]

b) PECLA requires arterial cannulation and adequate patient blood pressure but can quickly normalize $PaCO_2$ in patients with a head injury and respiratory failure.[40]

c) ECLS is used for adult respiratory failure with good outcomes as demonstrated in recent series using modern equipment.[41, 42] Most adult ECLS is venovenous which can be performed through either single site internal jugular (IJ) vein cannulation or combined IJ/femoral vein (FV) or dual-FV cannulation. Systemic heparin should be administered once surgical bleeding has been controlled. This approach has been done safely in trauma patients both in the US and in Germany including patients with TBI.[43–45]

6. Outcomes. ARDS is an independent risk factor for death in combat casualties. To mitigate this risk, early LPV should be implemented along with minimizing unnecessary IV infusions, eliminating unnecessary blood product transfusions, and implementation of an aggressive

physical therapy regimen. From Nov 2005 – Mar 2007, 524 intubated patients were transported via CCATT. Of these, 5 were moved by the ALRT which had been called on a total of 11 patients. Of the 5 ALRT patients requiring advanced support modes, 4 survived to hospital discharge.[35] In a separate study previously mentioned, of 152 patients with ARDS in the DoDTR, 133 survived to discharge with 19 deaths.[2] Finally, of 10 US combat casualties transported on either PECLA or ECMO, 9 survived to hospital discharge.[36] These data underscore the importance of utilizing available resources for transporting these tenuous patients to definitive care.

7. Performance Improvement (PI) Monitoring.

a. Intent (Expected Outcomes).

1) Presence of triggers for ALRT consultation.

2) Use of prone positioning in a Role II or III facility.

3) Use of ECMO in a Role II, III, or IV facility.

b. Performance/Adherence Measures.

1) ALRT team consulted appropriately.

2) Prone position utilized appropriately at Role II or III facilities.

c. Data Source.

1) Patient Record.

2) Department of Defense Trauma Registry (DoDTR).

d. System Reporting & Frequency.

The above constitutes the minimum criteria for PI monitoring of this CPG. System reporting will be performed annually; additional PI monitoring and system reporting may be performed as needed.

The system review and data analysis will be performed by the Joint Theater Trauma System (JTTS) Director, JTTS Program Manager, and the Joint Trauma System (JTS) Performance Improvement Branch.

8. Responsibilities. It is the trauma team leader's responsibility to ensure familiarity, appropriate compliance and PI monitoring at the local level with this CPG.

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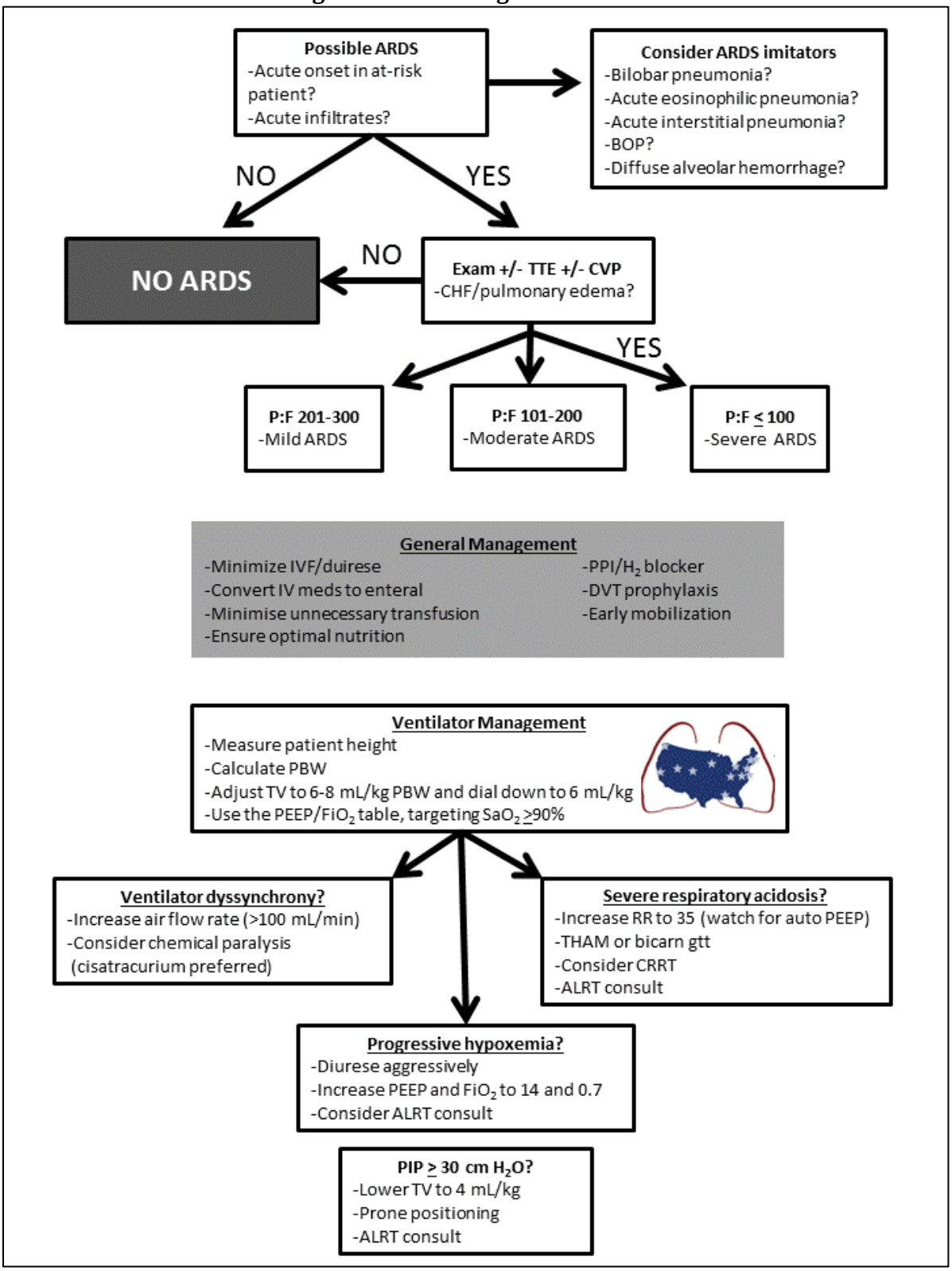
Approved by CENTCOM JTTS Director, JTS Director and CENTCOM SG

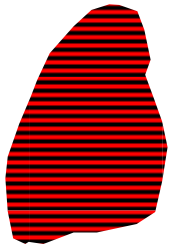
APPENDIX A

Diagnosis and Management of ARDS



APPENDIX B

ARDSNet Ventilator Management Protocol for Patients with ARDS[46] *(page 1 of 2)*



INCLUSION CRITERIA: Acute onset of

1. $PaO_2/FiO_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

PART I: VENTILATOR SETUP AND ADJUSTMENT

1. Calculate predicted body weight (PBW)
   Males = 50 + 2.3 [height (inches) - 60]
   Females = 45.5 + 2.3 [height (inches) -60]
2. Select any ventilator mode
3. Set ventilator settings to achieve initial V_T = 8 ml/kg PBW
4. Reduce V_T by 1 ml/kg at intervals $\leq$ 2 hours until V_T = 6ml/kg PBW.
5. Set initial rate to approximate baseline minute ventilation (not > 35 bpm).
6. Adjust V_T and RR to achieve pH and plateau pressure goals below.

ay increase V_T in 1ml/kg increments to 7 or 8 ml/kg if Pplat remains $\leq$ 30 cm H_2O.

ARDSNet Ventilator Management Protocol for Patients with ARDS[46] *(page 2 of 2)*

pH GOAL: 7.30-7.45
Acidosis Management: (pH < 7.30)
If pH 7.15-7.30: Increase RR until pH > 7.30 or $PaCO_2$ < 25 (Maximum set RR = 35).
.
If pH < 7.15: Increase RR to 35.
If pH remains < 7.15, V_T may be increased in 1 ml/kg steps until pH > 7.15 (Pplat target of 30 may be exceeded).
May give $NaHCO_3$
Alkalosis Management: (pH > 7.45) Decrease vent rate if possible.

I: E RATIO GOAL: Recommend that duration of inspiration be ≤ duration of expiration.

PART II: WEANING

A. Conduct a SPONTANEOUS BREATHING TRIAL daily when:

1. $FiO_2 \leq 0.40$ and PEEP ≤ 8 OR $FiO_2 \leq 0.50$ and PEEP ≤ 5.
2. PEEP and FiO_2 ≤ values of previous day.
3. Patient has acceptable spontaneous breathing efforts. (May decrease vent rate by 50% for 5 minutes to detect effort.)
4. Systolic BP ≥ 90 mmHg without vasopressor support.
5. No neuromuscular blocking agents or blockade.

B. SPONTANEOUS BREATHING TRIAL (SBT):
If all above criteria are met and subject has been in the study for at least 12 hours, initiate a trial of UP TO 120 minutes of spontaneous breathing with FiO2 ≤ 0.5 and PEEP ≤ 5:

1. Place on T-piece, trach collar, or CPAP ≤ 5 cm H_2O with PS ≤ 5
2. Assess for tolerance as below for up to two hours.
   a. $SpO_2 \geq 90$: and/or $PaO_2 \geq 60$ mmHg
   b. Spontaneous $V_T \geq 4$ ml/kg PBW
   c. RR ≤ 35/min
   d. pH ≥ 7.3
   e. No respiratory distress (distress= 2 or more)
      - HR > 120% of baseline
      - Marked accessory muscle use
      - Abdominal paradox
      - Diaphoresis
      - Marked dyspnea
3. If tolerated for at least 30 minutes, consider extubation.
4. If not tolerated resume pre-weaning settings.

Definition of UNASSISTED BREATHING
(Different from the spontaneous breathing criteria as PS is not allowed)

1. Extubated with face mask, nasal prong oxygen, or room air, OR
2. T-tube breathing, OR
3. Tracheostomy mask breathing, OR
4. CPAP less than or equal to 5 cm H_20 **without pressure support or IMV assistance.**

Maintain pH > 7.35 in patients with traumatic brain injury (TBI)

APPENDIX C

Prone Positioning in Patients with ARDS.[30, 47]

Preparation:

1. Check for contraindications.
    a. Facial or pelvic fractures
    b. Anterior torso wounds or burns
    c. Spinal instability
    d. Increased ICP
2. Confirm ETT placement with recent CXR.
3. Ensure that ETT and all invasive lines/monitors (chest tubes, IVs, central lines) are secured.
4. Consider how patient's head, neck, shoulder girdle will be supported.
5. Stop tube feedings, evacuate stomach, cap/clamp feeding and gastric tubes.
6. Prepare airway suctioning equipment.
7. Prepare all IV tubing, catheters, etc., for prone connections.
    a. Assure sufficient tubing length
    b. Relocate drainage bags to opposite side of bed
    c. Move chest tube drains to between legs
    d. Reposition IV tubing to patient's head on opposite side of bed

Turning:

1. Place personnel on both sides and head of bed.
2. Increase FiO_2 to 1.0, and note TV, minute ventilation, peak/plateau pressures.
3. Place new draw sheet, put patient into lateral decubitus position.
4. Remove EKG leads and patches. Suction airway, oropharynx, nares as necessary.
5. Continue to proning, and reposition patient in center of bed.
6. Turn patient's face toward ventilator. Ensure airway is not kinked and has not migrated.
7. Support face/shoulders appropriately; ensure no contact of padding with eyes/orbits.
8. Position patient's arms for comfort. Avoid arm extension that might cause brachial plexopathy.
9. Auscultate chest for mainstem intubation; reassess TV and minute ventilation.
10. Reconnect and adjust all tubing, check functions.
11. Reattach ECG patches and leads to back.
12. Tilt patient in reverse Trendelenburg. Intermittent slight (20^0) lateral repositioning every 2 hours, if possible.
13. Document skin assessment on weight-bearing surfaces every shift.

APPENDIX D
ADDITIONAL INFORMATION REGARDING OFF-LABEL USES IN CPGs

1. **Purpose**. The purpose of this Appendix is to ensure an understanding of DoD policy and practice regarding inclusion in CPGs of "off-label" uses of U.S. Food and Drug Administration (FDA)–approved products. This applies to off-label uses with patients who are members of the armed forces.

2. **Background**. Unapproved (i.e., "off-label") uses of FDA-approved products are extremely common in American medicine and are usually not subject to any special regulations. However, under Federal law, in some circumstances, unapproved uses of approved drugs are subject to FDA regulations governing "investigational new drugs." These circumstances include such uses as part of a clinical trial, and in the military context, command required, unapproved uses. Some command requested unapproved uses may also be subject to special regulations.

3. **Additional Information Regarding Off-Label Uses in CPGs**. The inclusion in CPGs of off-label uses is not a clinical trial, nor is it a command request or requirement. Further, it does not imply that the Military Health System requires that use by DoD health care practitioners or that it considers this to be the "standard of care". Rather, the inclusion in CPGs of off-label uses is to inform the clinical judgment of the responsible health care practitioner by providing information regarding potential risks and benefits of treatment alternatives. The decision is for the clinical judgment of the responsible health care practitioner within the practitioner-patient relationship.

4. **Additional Procedures**.

   a. Balanced Discussion. Consistent with this purpose, CPG discussions of off-label uses specifically state that they are uses not approved by the FDA. Further, such discussions are balanced in the presentation of appropriate clinical study data, including any such data that suggest caution in the use of the product and specifically including any FDA-issued warnings.

   b. Quality Assurance Monitoring. With respect to such off-label uses, DoD procedure is to maintain a regular system of quality assurance monitoring of outcomes and known potential adverse events. For this reason, the importance of accurate clinical records is underscored.

   c. Information to Patients. Good clinical practice includes the provision of appropriate information to patients. Each CPG discussing an unusual off-label use will address the issue of information to patients. When practicable, consideration will be given to including in an appendix an appropriate information sheet for distribution to patients, whether before or after use of the product. Information to patients should address in plain language: a) that the use is not approved by the FDA; b) the reasons why a DoD health care practitioner would decide to use the product for this purpose; and c) the potential risks associated with such use.