ATS Core Curriculum 2016: Part II. Adult Critical Care Medicine

Series Editor: Carey C. Thomson

Part II Editors: Jakob I. McSparron and Andrew M. Luks

Jakob I. McSparron¹, Margaret M. Hayes¹, Jason T. Poston², Carey C. Thomson³, Henry E. Fessler⁴, Renee D. Stapleton⁵, W. Graham Carlos⁶, Laura Hinkle⁶, Kathleen Liu^{7,8}, Stephanie Shieh⁹, Alyan Ali¹⁰, Angela Rogers¹⁰, Nirav G. Shah¹¹, Donald Slack¹¹, Bhakti Patel¹², Krysta Wolfe², William D. Schweickert¹², Rita N. Bakhru¹³, Stephanie Shin¹⁴, Rebecca E. Sell¹⁴, and Andrew M. Luks¹⁵

¹Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; ²Section of Pulmonary and Critical Care Medicine, Department of Medicine, University of Chicago, Chicago, Illinois; ³Division of Pulmonary and Critical Care, Mount Auburn Hospital, Harvard Medical School, Boston, Massachusetts; ⁴Division of Pulmonary and Critical Care Medicine, Johns Hopkins Hospital, Baltimore, Maryland; ⁵Division of Pulmonary Disease and Critical Care Medicine, University of Vermont College of Medicine, Burlington, Vermont; ⁶Division of Pulmonary, Critical Care, Sleep, and Occupational Medicine, Indiana University School of Medicine, Indianapolis, Indiana; ⁷Division of Nephrology, Department of Medicine, and ⁸Division of Critical Care Medicine, Department of Anesthesia, University of California San Francisco, San Francisco, California; ⁹Division of Nephrology, Department of Medicine, Saint Louis University, Saint Louis, Missouri; ¹⁰Division of Pulmonary and Critical Care Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, California; ¹¹Division of Pulmonary and Critical Care Medicine, University of Maryland Medical Center, Baltimore, Maryland; ¹²Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; ¹³Section of Pulmonary, Critical Care, Allergy, and Immunologic Diseases, Department of Internal Medicine, Wake Forest University School of Medicine, Winston Salem, North Carolina; ¹⁴Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of California San Diego, San Diego, California; and ¹⁵Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, Washington

Keywords: airway management; renal replacement therapy; hypoxemic respiratory failure; obstructive lung disease; noninvasive ventilation

The American Thoracic Society (ATS) Core Curriculum updates clinicians annually in adult and pediatric pulmonary disease, medical critical care, and sleep medicine, in a 3-year recurring cycle of topics. The 2016 course was presented in May during the annual International Conference. The four parts of the course are published in consecutive issues of *AnnalsATS*. Part II covers topics in adult critical care medicine. An American Board of Internal Medicine Maintenance of Certification module and a Continuing Medical Education exercise covering the contents of the CORE Curriculum can be accessed online at www.thoracic.org until July 2019.

Airway Emergencies

W. Graham Carlos and Laura Hinkle

Difficulty providing facemask ventilation or performing tracheal intubation constitute airway emergencies. A recently published

management algorithm from 2013 provides evidenced-based recommendations (1). Table 1 summarizes management strategies for several life-threatening airway emergencies discussed below, namely complications of tracheostomies, postextubation stridor (PES), and angioedema.

Complications of Tracheostomy

Bleeding from a tracheostomy may occur due to trauma, tissue erosion at the stoma, tracheoinnominate fistula, or more distal primary pulmonary processes. For proximal etiologies, hemostasis may be achieved by overinflating the tracheostomy cuff and compressing externally. The stoma should be carefully inspected to identify a bleeding source. Should this fail, a cuffed oral tracheal tube must be inserted to protect the patient from asphyxiation. If a tracheoinnominate fistula is suspected, the clinician should compress the innominate artery against the posterior surface of the manubrium with a finger inserted through the stoma (2). Ongoing bleeding may

(Received in original form January 18, 2016; accepted in final form February 16, 2016)

Author Contributions: J.I.M., M.M.H., J.T.P., C.C.T., H.E.F., R.D.S., and A.M.L. contributed to the conception/design of this work, revised the work, and provided final approval of the version submitted. W.G.C., L.H., K.L., S. Shieh, A.A., A.R., N.G.S., D.S., B.P., K.W., W.D.S., R.N.B., S. Shin, and R.E.S. contributed the initial draft, revisions, and final version of this manuscript for individual sections as indicated in the body of the manuscript.

Correspondence and requests for reprints should be addressed to Jakob I. McSparron, M.D., Beth Israel Deaconess Medical Center, 330 Brookline Avenue, KSB 23, Boston, MA 02215. E-mail: jmcsparr@bidmc.harvard.edu

CME will be available for this article at www.atsjournals.org

A Maintenance of Certification exercise linked to this summary is available at http://www.atsjournals.org/page/ats_core_curriculum

Ann Am Thorac Soc Vol 13, No 5, pp 731–740, May 2016

Copyright © 2016 by the American Thoracic Society

DOI: 10.1513/AnnalsATS.201601-050CME

Internet address: www.atsjournals.org

Table 1. Management of airway emergencies

Clinical Diagnosis	Management
Bleeding associated with tracheostomy	
Proximal	Overinflate tracheostomy cuff and apply external compression Insert oral tracheal tube and inflate cuff distal to bleeding site to protect airways if necessary
Tracheoinnominate fistula	Insert finger in stoma and compress against manubrium Slowly withdraw tracheal tube until cuff tamponades bleed Urgent otolaryngology consultation Ultimately requires surgical repair
Postextubation stridor	Nebulized epinephrine Corticosteroids Inhaled mixture of helium and oxygen for patients not <i>in extremis</i> and without significant hypoxemia
Angioedema	Careful attention to airway management
Anaphylaxis	Immediate administration of intramuscular epinephrine
Bradykinin induced	Consider bradykinin receptor antagonist (icatibant)

respond to slow withdrawal of the tracheal tube until the cuff tamponades the bleeding site. Definitive management requires surgery.

Obstruction of the tracheostomy tube is another common complication. An obstructed tracheostomy tube should first be addressed by removal and inspection of the inner cannula and attempted passage of a suction catheter. If resistance is encountered, deflate the cuff to allow airflow around the tube. Do not attempt to pass rigid objects through the tube to unblock it. If deflating the cuff does not improve ventilation, the tube should be removed while supplying oxygen to the face and stoma. In the case of a mature stoma, the tracheostomy tube should be replaced, taking care to avoid creating a false tract. If the tracheostomy tube cannot be easily reinserted, orotracheal intubation should be performed to secure the airway. This is the preferred approach for recently placed tracheostomy tubes (within 1 wk), as the stoma may not be mature, and the airway may be lost with attempts to replace the tracheostomy tube (3).

Postextubation Stridor

PES is a clinical marker of laryngeal edema. The cuff-leak test is a preextubation screen for PES, with a good negative predictive value. Although a cuff leak of less than 110 ml increases the risk for development of PES and need for reintubation, the positive predictive value of this finding is low (4). If there is high clinical suspicion of postextubation laryngeal edema, use of an exchange catheter to guide reintubation may be considered (1, 4).

Although nebulized racemic epinephrine, corticosteroids, and heliox are often used for treatment of PES, systematic evidence of benefit is lacking. Noninvasive positive pressure ventilation is not recommended, whereas reintubation should be pursued for patients in extremis or who worsen despite treatment (4). Prophylactic corticosteroids given for 24 to 48 hours before extubation may be effective in patients at risk for PES (5, 6).

Angioedema

Angioedema is classified as either mast cell mediated or bradykinin induced. Mast cell-mediated angioedema involves allergic reactions to foods or insect stings and may present with hypotension. Bradykinin-induced angioedema (such as angiotensin-converting enzyme inhibitor induced) is usually not associated with allergic symptoms and does not respond to epinephrine. In addition, this form of angioedema may be treated with drugs that act on the bradykinin pathway, such as the bradykinin receptor antagonist icatibant, found to be effective in a recent trial (7). When the diagnosis is suspected based on compatible history and physical findings, the highest priority is maintaining a patent airway.

Anaphylaxis can occur with angioedema and should be suspected when one of the following is present (8):

1. Sudden illness with skin or mucosal involvement and either respiratory symptoms or hypotension.
2. Two or more of the following occurring abruptly after exposure to a likely allergen: sudden illness with skin or mucosal involvement, respiratory symptoms, hypotension, or gastrointestinal symptoms.
3. Hypotension after exposure to a known allergen for the patient.

When suspected, anaphylaxis requires prompt treatment with intramuscular or intravenous epinephrine. Although antihistamines and β -agonists may be given as adjunctive treatments, these medications do not treat hypotension or upper airway edema (8).

References

- 1 Apfelbaum JL, Hagberg CA, Caplan RA, Blitt CD, Connis RT, Nickinovich DG, Hagberg CA, Caplan RA, Benumof JL, Berry FA, *et al.*; American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology* 2013;118:251–270.
- 2 Komatsu T, Sowa T, Fujinaga T, Handa N, Watanabe H. Tracheo-innominate artery fistula: two case reports and a clinical review. *Ann Thorac Cardiovasc Surg* 2013;19:60–62.
- 3 White AC, Kher S, O'Connor HH. When to change a tracheostomy tube. *Respir Care* 2010;55:1069–1075.
- 4 Wittekamp BHJ, van Mook WNKA, Tjan DHT, Zwaveling JH, Bergmans DCJJ. Clinical review: post-extubation laryngeal edema and extubation failure in critically ill adult patients. *Crit Care* 2009;13:233.
- 5 Jaber S, Jung B, Chanques G, Bonnet F, Marret E. Effects of steroids on reintubation and post-extubation stridor in adults: meta-analysis of randomised controlled trials. *Crit Care* 2009;13:R49.
- 6 François B, Bellissant E, Gissot V, Desachy A, Normand S, Boulain T, Brenet O, Preux PM, Vignon P; Association des Réanimateurs du Centre-Ouest (ARCO). 12-h pretreatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: a randomised double-blind trial. *Lancet* 2007;369:1083–1089.
- 7 Baş M, Greve J, Stelter K, Havel M, Strassen U, Rotter N, Veit J, Schossow B, Hapfelmeier A, Kehl V, *et al.* A randomized trial of icatibant in ACE-inhibitor-induced angioedema. *N Engl J Med* 2015;372:418–425.
- 8 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SGA, Camargo CA Jr, Cydulka R, Galli SJ, *et al.* Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–397.

Renal Replacement Therapy

Kathleen Liu and Stephanie Shieh

Renal Replacement in Critically Ill Patients

It was recently reported that approximately 6% of patients require some form of renal replacement therapy during their intensive care unit (ICU) stay (1). The scope of renal replacement therapy has grown over time to include intermittent as well as continuous therapies, whose use varies depending on clinical circumstances (Table 2).

The major indications for all forms of renal replacement therapy in the acute setting include correction of acid–base abnormalities, electrolyte management, fluid balance, and removal of toxins. Continuous renal replacement therapy (CRRT) is often preferred in the ICU because the slower rates of fluid removal and solute clearance are better tolerated by hemodynamically unstable patients. However, clinical trials have not demonstrated a mortality benefit (2). It is also the modality of choice in patients with neurologic injury when there is concern for elevated intracranial pressure (3, 4). Although fluid removal and solute clearance are slower per unit time in CRRT, there is greater ultrafiltration and clearance capacity over a 24-hour period compared with intermittent hemodialysis due to the continuous duration of therapy.

Toxic Ingestion

When renal replacement therapy is used for management of toxic ingestion, however, intermittent hemodialysis is preferred due to the faster rate of clearance. Low-molecular-weight substances (<500 Da) that are water soluble, such as lithium, are more dialyzable than

larger, protein- or lipid-bound molecules, such as digoxin. Because lipid-soluble molecules often have a large volume of distribution than water-soluble molecules, a rebound phenomenon may occur when dialysis is stopped. Patient characteristics including obesity, extracellular fluid status, renal function, and cardiac function also influence the volume of distribution and the utility of dialysis in toxic ingestions. Given the variety of issues that affect dialysis in these cases, a poison control center should always be consulted to determine if dialysis is indicated for toxin clearance.

Novel Modalities

More recently, a number of hybrid modalities (collectively called prolonged intermittent renal replacement therapy, or PIRRT) have been developed. Many of these modalities use conventional intermittent dialysis machines that are customized to tolerate lower blood flow and dialysate rates to allow for more gentle fluid removal over a 6- to 12-hour period of time. PIRRT is a potentially cost-effective alternative to CRRT, although there is a paucity of data and use is limited to experienced centers (5).

Medication Dosing

Renal replacement therapy can affect the dosing of medications, particularly antibiotics. Factors that may impact clearance include changes in renal function, the renal replacement therapy modality, and fluctuating body mass and fluid status, which may change the volume of distribution of the antibiotic (6). Because clearance is continuous with CRRT, higher dosing is generally required than with intermittent hemodialysis. Small studies have shown that there is a tendency toward underdosing with antibiotics in the setting of

Table 2. Modalities of renal replacement therapy

Modality	Description	Indications
Intermittent hemodialysis	An acute or chronic therapy where blood runs countercurrent to a dialysate through a filter allowing for diffusive clearance and fluid removal through a conventional hemodialysis machine	The modality of choice in clinical scenarios in which rapid clearance is desired (e.g., ingestions). Maintenance therapy in outpatients
Ultrafiltration	Therapy using a conventional hemodialysis machine for fluid removal only (no clearance)	Volume removal with hemodynamic stability
Prolonged intermittent renal replacement therapy (PIRRT) Slow low-efficiency dialysis (SLED)	Therapy that uses a conventional intermittent hemodialysis machine with lower blood flow and dialysate flow rates over longer periods of time for hemodynamic stability	Typically used in patients with hemodynamic instability and other clinical scenarios in which large fluid shifts are not desired; alternative to CRRT
Continuous renal replacement therapy (CRRT) Continuous venovenous hemofiltration (CVVH)	Continuous convective clearance with pre- or postfilter replacement fluid and fluid removal using specialized dialysis machines	Typically used in patients with hemodynamic instability and other clinical scenarios in which large fluid shifts are not desired. Studies have not shown any advantage between CVVH, CVVHD, and CVVHDF
Continuous venovenous hemodialysis (CVVHD)	Continuous diffusive clearance and fluid removal	Same scenarios as CVVH
Continuous venovenous hemodiafiltration (CVVHDF)	Continuous convective and diffusive clearance and fluid removal	Same scenarios as CVVH
Slow continuous ultrafiltration (SCUF)	Continuous fluid removal without clearance	Volume removal in patients with borderline hemodynamics

CRRT (7, 8). Consultation with an ICU pharmacist is recommended, and whenever possible dosing should be based on drug levels. The data to guide medication dosing for PIRRT are limited, which represents a disadvantage of this modality at present.

References

- 1 Thongprayoon C, Cheungpasitporn W, Ahmed AH. Trends in the use of renal replacement therapy modality in intensive care unit: a 7 year study. *Ren Fail* 2015;37:1444–1447.
- 2 Palevsky PM. Renal replacement therapy in acute kidney injury. *Adv Chronic Kidney Dis* 2013;20:76–84.
- 3 Ronco C, Bellomo R, Brendolan A, Pinna V, La Greca G. Brain density changes during renal replacement in critically ill patients with acute renal failure: continuous hemofiltration versus intermittent hemodialysis. *J Nephrol* 1999;12:173–178.
- 4 Davenport A. Renal replacement therapy in the patient with acute brain injury. *Am J Kidney Dis* 2001;37:457–466.
- 5 Berbece AN, Richardson RMA. Sustained low-efficiency dialysis in the ICU: cost, anticoagulation, and solute removal. *Kidney Int* 2006;70:963–968.
- 6 Bayliss G. Dialysis in the poisoned patient. *Hemodial Int* 2010;14:158–167.
- 7 Lewis SJ, Mueller BA. Antibiotic dosing in patients with acute kidney injury: “enough but not too much”. *J Intensive Care Med* 2016;31:164–176.
- 8 Lewis SJ, Mueller BA. Antibiotic dosing in critically ill patients receiving CRRT: underdosing is overprevalent. *Semin Dial* 2014;27:441–445.

Severe Hypoxemic Respiratory Failure

Alyan Ali and Angela Rogers

Severe hypoxemic respiratory failure is characterized by impairment in gas exchange due to ventilation–perfusion mismatch and shunt. There is no widely accepted definition for this entity or means of grading severity and prognosis across all potential causes of the entity. The Berlin definition categorizes the severity of hypoxemia in acute respiratory distress syndrome (ARDS) as mild ($200 < \text{PaO}_2/\text{FiO}_2 \leq 300$), moderate ($100 < \text{PaO}_2/\text{FiO}_2 \leq 200$), or severe ($\text{PaO}_2/\text{FiO}_2 \leq 100$). Although these

categories provide important information about disease severity, depending on their age and comorbidities, individual patients will have varied tolerances of various degrees of hypoxemia. Management approaches for severe hypoxemic respiratory failure are largely based on randomized controlled trials in ARDS (Table 3), but several of the strategies discussed below may have utility in non-ARDS hypoxemic respiratory failure.

Hypoxemic Respiratory Failure without Immediate Need for Intubation

Select patients with hypoxemic respiratory failure can be managed without invasive mechanical ventilation. A 2015 trial randomized patients with hypoxemic respiratory failure to receive high-flow oxygen, standard oxygen therapy, or noninvasive ventilation. Although intubation rates did not differ between groups, the hazard ratio for death by 90 days was lowest in those randomized to high-flow oxygen (1). Importantly, this trial excluded patients with hypercarbic respiratory failure and does not inform practice for hypoxemic patients with concurrent ventilatory failure.

Ventilator Strategies for Acute Respiratory Distress Syndrome

Lung-protective ventilation targeting a tidal volume of 6 ml/kg or less ideal body weight and a plateau pressure 30 cm H₂O or lower has been the standard of care for ARDS since the landmark ARMA trial, but whether the observed mortality benefit is due to lower tidal volumes *per se* or the lower pressure needed to achieve those volumes remains controversial (2). A recent meta-analysis suggested that lowering the driving pressure ($\Delta P = V_T/\text{compliance}$ of the respiratory system) is the critical factor in ventilating patients with ARDS; lower tidal volume and plateau pressures typically targeted by lung-protective ventilation were noted to be beneficial only when ΔP was limited (3). Limited data suggest initiating lung-protective ventilation at the time of intubation may lower the risk of ARDS, but large randomized trials of this approach are lacking (4).

Although several trials showed no benefit of a high positive end-expiratory pressure (PEEP) strategy relative to the standard PEEP used in the ARMA trial, more recent analyses suggest that

Table 3. Studies demonstrating mortality benefit in hypoxemic respiratory failure

Study	Target Patients	Intervention	Major Finding
Frat et al., 2015 (1)	Nonintubated patients with ARF	RCT of noninvasive ventilation, high-flow O ₂ , or standard O ₂	High-flow oxygen reduced rate of intubation, reduced ICU and 90-d mortality (secondary endpoints)
Amato et al., 2015 (3)	ARDS	Metaanalysis of 9 ARDS clinical trials, testing whether lung volumes or pressure matter	The traditional lung-protective ventilation strategies of increasing PEEP and limiting V _T were beneficial if they resulted in a lower ΔP
Briel et al., 2010 (6)	ARDS	Meta-analysis of 3 RCTs of high and low PEEP	Patients with moderate to severe ARDS (P:F < 200) have improved mortality with high PEEP strategies
Guérin et al., 2013 (9)	Moderate to severe ARDS (P:F < 150)	RCT of prone positioning 16 h vs. standard care ARDSNet	28- and 90-d improvement in mortality in prone group
Papazian et al., 2010 (10)	Moderate to severe ARDS (P:F < 150)	RCT of 48 h cisatracurium vs. placebo	Improved 90-d mortality

Definition of abbreviations: ARDS = acute respiratory distress syndrome; ARF = acute respiratory failure; ICU = intensive care unit; PEEP = positive end-expiratory pressure; P:F = $\text{PaO}_2/\text{FiO}_2$; RCT = randomized controlled clinical trial.

higher PEEP may benefit subsets of patients with ARDS (5). One metaanalysis showed that high PEEP benefits patients with moderate to severe ARDS but is harmful in those with less severe disease (6). An individualized PEEP strategy based on esophageal manometry may improve oxygenation, but this has not been shown to improve mortality (7). A novel strategy of classifying patients into inflammatory and noninflammatory subtypes demonstrated that higher PEEP is beneficial only in the inflammatory subtype (8).

Nonventilator Strategies for Severe Hypoxemic Respiratory Failure

After earlier trials that failed to show a mortality benefit, both prone positioning and neuromuscular blockade have been shown to improve mortality in separate randomized controlled trials that included a more narrow group of patients with moderate to severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$) (9, 10). Inhaled nitric oxide causes transient improvement in oxygenation but does not improve mortality and may be associated with acute kidney injury (11). Extracorporeal membrane oxygenation is increasingly used for management of severe hypoxemic respiratory failure, although explicit criteria for initiating this therapy are lacking, and a clear mortality benefit has not been established.

References

1. Frat J-P, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottreau A, et al.; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372:2185–2196.
2. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.
3. Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747–755.
4. Fuller BM, Mohr NM, Drewry AM, Carpenter CR. Lower tidal volume at initiation of mechanical ventilation may reduce progression to acute respiratory distress syndrome: a systematic review. *Crit Care* 2013;17:R11.
5. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327–336.
6. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010;303:865–873.
7. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008;359:2095–2104.
8. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA; NHLBI ARDS Network. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014;2:611–620.
9. Guérin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, et al.; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159–2168.
10. Papazian L, Forel J-M, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal J-M, Perez D, Seghboyan J-M, et al.; ACURASYS

- Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;363:1107–1116.
11. Griffiths MJ, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med* 2005;353:2683–2695.

Management of Acute Exacerbations of Obstructive Lung Disease

Nirav G. Shah and Donald Slack

Acute exacerbations of asthma and chronic obstructive pulmonary disease (COPD) often require intensive care unit-level care for monitoring and mechanical ventilation.

Asthma

Life-threatening asthma is characterized by an inability to speak due to severe dyspnea, a reduced peak expiratory flow rate of less than 25% of their personal best, and a failed response to frequent bronchodilators and systemic steroids (1). A PaO_2 less than 60 mm Hg, a normal or increased PaCO_2 , and signs of respiratory fatigue, including altered mental status and shallow respirations, indicate the need for mechanical ventilation. Although evidence surrounding the use of noninvasive ventilation for asthma exacerbation is limited, and its use has been deemed “controversial” by a recent Cochrane Review (2), time-limited trials are still widely used in clinical practice. Heliox, a lower-density gas that decreases turbulent flow and airway resistance, and ketamine, a potent bronchodilator, may provide therapeutic benefit in some patients, but neither has been demonstrated to improve outcomes (3).

Chronic Obstructive Pulmonary Disease

Acute exacerbation of COPD, a clinical diagnosis characterized by changes in dyspnea, cough, and/or sputum production in a patient with COPD, is associated with significantly worse outcomes, with 3-month mortality as high as 5 to 7% (4, 5). Advanced age, respiratory failure, need for mechanical ventilation, and multiple comorbidities are associated with an increase in both in-hospital and postdischarge mortality (6).

Severe exacerbations warrant antibiotic therapy for 5 to 10 days (5), although there is no evidence to guide the choice of agent for this purpose. A recent retrospective study found that 7% of patients had documented *Pseudomonas aeruginosa*, yet adherence to health care-associated pneumonia treatment recommendations did not result in improved outcomes (7). Adherence to standard therapies, including short acting β_2 -agonists, systemic corticosteroids, and short-acting antimuscarinics, reduces the risk of treatment failure and hospital length of stay. A 5-day course of 40 mg of prednisone daily is noninferior to a 14-day course with respect to recurrent exacerbation rates within 6 months of discharge (8).

Mechanical Ventilation in Obstructive Lung Diseases

Noninvasive ventilation has been clearly demonstrated to improve mortality in acute exacerbations of COPD compared with invasive mechanical ventilation (9). A recent multicenter, retrospective study evaluated the comparative effectiveness of noninvasive versus invasive mechanical ventilation in acute exacerbations of COPD and demonstrated that patients who initially received noninvasive ventilation had a 41% lower risk of death than those initially treated with invasive ventilation (11). When patients

require invasive mechanical ventilation, care should be taken to ensure adequate time for exhalation, as failure to do so can lead to dynamic hyperinflation and its associated adverse hemodynamic consequences (10). Limited evidence suggests extracorporeal carbon dioxide removal may be effective at preventing intubation for select patients with severe COPD exacerbations, although experience with this emerging strategy is limited (11).

References

- 1 National Heart, Lung, and Blood Institute. Expert Panel Report 3: guidelines for the diagnosis and management of asthma. 2007 [accessed 2016 Feb 5]. Available from: <http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines>
- 2 Lim WJ, Mohammed Akram R, Carson KV, Mysore S, Labiszewski NA, Wedzicha JA, Rowe BH, Smith BJ. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev* 2012;12: CD004360.
- 3 Rodrigo GJ, Castro-Rodriguez JA. Heliox-driven β_2 -agonists nebulization for children and adults with acute asthma: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2014;112: 29–34.
- 4 Almagro P, Soriano JB, Cabrera FJ, Boixeda R, Alonso-Ortiz MB, Barreiro B, Diez-Manglano J, Murio C, Heredia JL; Working Group on COPD, Spanish Society of Internal Medicine. Short- and medium-term prognosis in patients hospitalized for COPD exacerbation: the CODEX index. *Chest* 2014;145:972–980.
- 5 Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2016 [accessed 2016 Feb 5]. Available from: <http://www.goldcopd.org/>
- 6 Hartl S, Lopez-Campos JL, Pozo-Rodriguez F, Castro-Acosta A, Studnicka M, Kaiser B, Roberts CM. Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. *Eur Respir J* 2016;47:113–121.
- 7 Planquette B, Péron J, Dubuisson E, Roujansky A, Laurent V, Le Monnier A, Legriel S, Ferre A, Bruneel F, Chiles PG, et al. Antibiotics against *Pseudomonas aeruginosa* for COPD exacerbation in ICU: a 10-year retrospective study. *Int J Chron Obstruct Pulmon Dis* 2015; 10:379–388.
- 8 Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, Duerring U, Henzen C, Leibbrandt Y, Maier S, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA* 2013;309:2223–2231.
- 9 Stefan MS, Nathanson BH, Higgins TL, Steingrub JS, Lagu T, Rothberg MB, Lindenauer PK. Comparative effectiveness of noninvasive and invasive ventilation in critically ill patients with acute exacerbation of chronic obstructive pulmonary disease. *Crit Care Med* 2015;43:1386–1394.
- 10 Parrilla FJ, Morán I, Roche-Campo F, Mancebo J. Ventilatory strategies in obstructive lung disease. *Semin Respir Crit Care Med* 2014;35:431–440.
- 11 Bonin F, Sommerwerck U, Lund LW, Teschler H. Avoidance of intubation during acute exacerbation of chronic obstructive pulmonary disease for a lung transplant candidate using extracorporeal carbon dioxide removal with the Hemolung. *J Thorac Cardiovasc Surg* 2013;145:e43–e44.

Noninvasive Ventilation

Bhakti Patel and Krysta Wolfe

Noninvasive ventilation has been shown to be beneficial in acute exacerbations of chronic obstructive pulmonary disease (COPD),

acute cardiogenic pulmonary edema, and selected instances of acute hypoxemic respiratory failure (1, 2). Provided that patients do not have any obvious contraindications, such as cardiac or respiratory arrest, inability to clear secretions, nonrespiratory organ failure, facial surgery/trauma/deformity, or recent esophageal anastomosis (3), most practitioners trial noninvasive ventilation in these cases.

Chronic Obstructive Pulmonary Disease Exacerbations

The use of noninvasive ventilation decreases the need for intubation and mortality in acute exacerbation of COPD (4). A Cochrane Review of 14 randomized controlled trials showed that noninvasive ventilation plus usual care reduced mortality in COPD exacerbations (relative risk [RR], 0.52; 95% confidence interval [CI], 0.35–0.76). Noninvasive ventilation also decreased the need for intubation, the rate of treatment failure, and hospital length of stay (4). Another use of noninvasive ventilation in the COPD population is in the postextubation setting. Patients with COPD, especially those with elevated PaCO_2 levels during spontaneous breathing trials, are less likely to develop postextubation respiratory failure when extubated to noninvasive ventilation (5). However, this intervention has not been shown to improve mortality or reintubation rates.

Prevention of Postextubation Respiratory Failure in Cases Other than Chronic Obstructive Pulmonary Disease

Application of noninvasive ventilation immediately after extubation has been shown to prevent postextubation respiratory failure in patients with congestive heart failure, ineffective cough, more than one comorbid condition, age older than 65 years, and Acute Physiology and Chronic Health Evaluation II score greater than 12 on the day of extubation (6, 7). Initiation of noninvasive ventilation after the development of postextubation respiratory failure, however, has not been shown to reduce reintubation rates and may lead to increased mortality (7, 8).

Cardiogenic Pulmonary Edema

Continuous positive airway pressure (CPAP) is beneficial in patients with acute cardiogenic pulmonary edema because it not only changes transmural pressure across the alveolar wall, promoting alveolar recruitment, but also decreases both preload and afterload. Noninvasive ventilation and CPAP in this population have been shown to decrease heart rate and improve hypercapnia and dyspnea (9). A Cochrane Review of 32 trials involving the use of CPAP and noninvasive ventilation in cardiogenic pulmonary edema found that this intervention significantly reduced hospital mortality (RR, 0.66; 95% CI, 0.48–0.89) and rate of endotracheal intubation (RR, 0.52; 95% CI, 0.36–0.75) in this population (10). A caveat to this metaanalysis is that data were pooled from multiple small studies, and thus some experts believe larger studies are needed to confirm the mortality benefit.

Acute Hypoxemic Respiratory Failure

The role of noninvasive support for other causes of acute hypoxemic respiratory failure is not as well established. Although immunocompromised patients have previously been shown to benefit from noninvasive ventilation in acute respiratory failure, a more recent trial found no difference in 28-day mortality when compared with oxygen therapy alone (11, 12). Lung recruitment

with expiratory pressure is limited by difficulties achieving adequate facemask seal, resulting in decreased efficacy in acute hypoxemic respiratory failure. High-flow nasal cannula has also recently been shown to be as effective as noninvasive ventilation in patients with isolated hypoxemic respiratory failure, which may lead to a shift toward use of this mode of support rather than noninvasive ventilation in non-hypercarbic patients who do not require intubation (13). Given the lack of strong evidence supporting its use in acute hypoxemic respiratory failure, patients started on noninvasive ventilation for this purpose require frequent reassessment of their response to that intervention.

References

- 1 Hess DR. Noninvasive ventilation for acute respiratory failure. *Respir Care* 2013;58:950–972.
- 2 Barreiro TJ, Gemmel DJ. Noninvasive ventilation. *Crit Care Clin* 2007; 23:201–222, ix. (ix.).
- 3 Organized jointly by the American Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, and the Société de Réanimation de Langue Française, and approved by ATS Board of Directors, December 2000. International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute Respiratory failure. *Am J Respir Crit Care Med* 2001;163:283–291.
- 4 Ram FSF, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2004;3:CD004104.
- 5 Girault C, Bubenheim M, Abroug F, Diehl JL, Elatrous S, Beuret P, Richecoeur J, L'Her E, Hilbert G, Capellier G, et al.; VENISE Trial Group. Noninvasive ventilation and weaning in patients with chronic hypercapnic respiratory failure: a randomized multicenter trial. *Am J Respir Crit Care Med* 2011;184:672–679.
- 6 Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. *Am J Respir Crit Care Med* 2006;173: 164–170.
- 7 Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apezteguia C, González M, Epstein SK, Hill NS, Nava S, Soares M-A, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med* 2004;350:2452–2460.
- 8 Keenan SP, Powers C, McCormack DG, Block G. Noninvasive positive-pressure ventilation for postextubation respiratory distress: a randomized controlled trial. *JAMA* 2002;287:3238–3244.
- 9 Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J; 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med* 2008;359:142–151.
- 10 Vital FMR, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *Cochrane Database Syst Rev* 2013;5:CD005351.
- 11 Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, Reiffers J, Cardinaud JP. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 2001;344:481–487.
- 12 Lemiale V, Mokart D, Resche-Rigon M, Pène F, Mayaux J, Faucher E, Nyunga M, Girault C, Perez P, Guittion C, et al.; Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH). Effect of noninvasive ventilation vs oxygen therapy on mortality among immunocompromised patients with acute respiratory failure: a randomized clinical trial. *JAMA* 2015;314:1711–1719.
- 13 Frat J-P, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottereau A, et al.; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372: 2185–2196.

Sedation, Delirium, and Early Mobilization

William D. Schweickert and Rita Bakhrui

Patient Assessment

Endotracheal tubes and delirium create a communication barrier that makes patient assessment difficult. Assessment tools for pain, agitation, and delirium in this setting have been validated for accuracy and reproducibility. These assessments guide drug selection and administration to foster wakefulness and physical activity.

Assessment for pain is a priority for distressed patients. A numerical rating scale is the standard; however, noncommunicative patients can be reliably assessed through observations of facial expressions, body movements, muscle tension, and ventilator tolerance. These tools correlate with the presence of pain and scores improve with analgesia (1). Opioid administration is the standard treatment.

Sedation and agitation scores can be used to assess severity and guide sedative administration. Although tolerance of mechanical ventilation is a domain common to both pain and agitation scales, pain should be addressed first. A single-center trial of “no sedation,” including attentive opioid prescribing, occasional neuroleptics and one-to-one observation, showed reduced duration of mechanical ventilation when compared with opioids and routine propofol administration (2). The trial was conducted at an institution with extensive prior experience with this approach, raising questions about the wider applicability of the results. Isolated ventilator asynchrony, particularly breath stacking during low tidal volume ventilation, is more effectively managed with ventilator manipulation versus sedation administration alone (3).

Daily sedation score targets can be met through sedation protocols, which have been shown to reduce mortality, hospital length of stay, and tracheostomy rates compared with usual care (4). Deep sedation, even limited to the first 48 hours of critical illness, has been associated with delayed extubation and increased mortality (4). Practicing daily interruption of continuous sedative infusions avoids deep sedation, and past trials yielded shorter durations of mechanical ventilation. However, a recent multicenter randomized trial demonstrated no additional benefit to superimposing daily sedation interruption on a targeted sedation protocol (5). Among the usual sedative options, analyses demonstrate inferior outcomes with benzodiazepines compared with propofol or dexmedetomidine (6).

Delirium

Delirium—a syndrome defined by mental status changes, inattention, and either altered level of consciousness or disorganized thinking—is common, especially during mechanical ventilation. Observations link delirium duration with longer lengths of stay, higher cost of care, long-term cognitive dysfunction, and higher mortality (7, 8). Nonpharmacologic strategies to reduce delirium include sleep protocols controlling environmental stimuli, early physical activity during mechanical ventilation, and standardized reorientation of patients. Although commonly administered for agitated delirium, haloperidol did not reduce the incidence or duration of delirium in a recent

Table 4. Select recent sedation and delirium studies

Reference	Study Findings
Sedation	
Girard et al., 2008 (12)	RCT demonstrated combination of daily sedative interruption with sequential spontaneous breathing trial had more ventilator-free days, shorter length of stay, and decreased 1-yr mortality than titrated sedation with protocol spontaneous breathing trial alone.
Jakob et al., 2012 (13)	RCTs of dexmedetomidine compared with midazolam and propofol demonstrated noninferiority of dexmedetomidine in maintenance of light sedation.
Strøm et al., 2010 (2)	RCT of no sedation (morphine as needed) vs. propofol with daily interruption showed that no-sedation patients had more ventilator-free days and shorter lengths of stay.
Mehta et al., 2012 (5)	RCT comparing protocol-guided, targeted sedation with or without daily sedative interruption demonstrated no differences in time to successful extubation, lengths of stay, or rates of delirium.
Shehabi et al., 2013 (14)	Prospective cohort study of patients ventilated and sedated for >1 d showed that early deep sedation was independently associated with longer duration of mechanical ventilation and increased mortality.
Lonardo et al., 2014 (15)	Matched cohort study demonstrated that patients receiving propofol had reduced hospital mortality, duration of mechanical ventilation, and ICU length of stay than those receiving benzodiazepines.
Delirium	
Pandharipande et al., 2013 (7)	Prospective cohort study of patients with respiratory failure or shock demonstrated that delirium was highly prevalent and associated with poor global cognition and impairment in executive function.
Page et al., 2013 (9)	Placebo-controlled trial of mechanically ventilated patients demonstrated that patients receiving standing haloperidol had the same number of days alive without delirium or coma.
Kamdar et al., 2013 (16)	Quality improvement study demonstrated that multiple interventions to promote sleep (especially environmental control) were not associated with change in sleep quality or quantity but did reduce rates of delirium and coma.

Definition of abbreviation: ICU = intensive care unit; RCT = randomized controlled clinical trial.

randomized trial (9). Atypical antipsychotics need further trials to assess their efficacy. In mechanically ventilated patients requiring sedation, dexmedetomidine has been shown to reduce the duration of delirium compared with benzodiazepines (10).

Early mobilization, particularly in patients undergoing mechanical ventilation via an endotracheal tube, has been shown to be safe and feasible. Trials have demonstrated shorter ICU and hospital lengths of stay, reduced durations of ventilation and delirium, and improved physical outcomes (11). Additionally, small case series have demonstrated that perceived barriers to mobilization, such as femoral catheterization, continuous renal replacement therapy, obesity, and extracorporeal membrane oxygenation, may be safely overcome.

In current practice, methods to link assessment of pain, agitation and delirium, sedative minimization, ventilator weaning, and early exercise, such as bundle use, may be one of the most potent means to improve outcomes for the mechanically ventilated patient. Table 4 summarizes recent notable publications related to sedation and delirium in the ICU.

References

- Chanques G, Pohlman A, Kress JP, Molinari N, de Jong A, Jaber S, Hall JB. Psychometric comparison of three behavioural scales for the assessment of pain in critically ill patients unable to self-report. *Crit Care* 2014;18:R160.
- Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet* 2010;375:475–480.
- Chanques G, Kress JP, Pohlman A, Patel S, Poston J, Jaber S, Hall JB. Impact of ventilator adjustment and sedation-analgesia practices on severe asynchrony in patients ventilated in assist-control mode. *Crit Care Med* 2013;41:2177–2187.
- Minhas MA, Velasquez AG, Kaul A, Salinas PD, Celi LA. Effect of protocolized sedation on clinical outcomes in mechanically ventilated intensive care unit patients: a systematic review and meta-analysis of randomized controlled trials. *Mayo Clin Proc* 2015; 90:613–623.
- Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, Herridge M, Ferguson N, Devlin J, Tanios M, et al.; SLEAP Investigators; Canadian Critical Care Trials Group. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. *JAMA* 2012; 308:1985–1992.
- Fraser GL, Devlin JW, Worby CP, Alhazzani W, Barr J, Dasta JF, Kress JP, Davidson JE, Spencer FA. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2013;41:S30–S38.
- Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, et al.; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–1316.
- Pisani MA, Kong SYJ, Kasl SV, Murphy TE, Araujo KLB, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med* 2009;180: 1092–1097.
- Page VJ, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, Jackson J, Perkins GD, McAuley DF. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2013;1:515–523.
- Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, et al.; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009;301:489–499.
- Stiller K. Physiotherapy in intensive care: an updated systematic review. *Chest* 2013;144:825–847.

- 12 Girard TD, Kress JP, Fuchs BD, Thomason JWW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, *et al.* Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371:126–134.
- 13 Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J; Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* 2012;307:1151–1160.
- 14 Shehabi Y, Chan L, Kadiman S, Alias A, Ismail WN, Tan MATI, Khoo TM, Ali SB, Saman MA, Shaltut A, *et al.*; Sedation Practice in Intensive Care Evaluation (SPICE) Study Group investigators. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. *Intensive Care Med* 2013;39:910–918.
- 15 Lonardo NW, Mone MC, Nirula R, Kimball EJ, Ludwig K, Zhou X, Sauer BC, Nechodom K, Teng C, Barton RG. Propofol is associated with favorable outcomes compared with benzodiazepines in ventilated intensive care unit patients. *Am J Respir Crit Care Med* 2014;189:1383–1394.
- 16 Kamdar BB, King LM, Collop NA, Sakamuri S, Colantuoni E, Neufeld KJ, Bienvenu OJ, Rowden AM, Touradji P, Brower RG, *et al.* The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU. *Crit Care Med* 2013;41:800–809.

Transfusion in the Intensive Care Unit

Stephanie Shin and Rebecca E. Sell

Transfusion Strategy in the Intensive Care Unit

Whereas older practice standards relied on liberal transfusion strategies based on theoretical and untested physiologic explanations, an ever-increasing body of evidence suggests that liberal transfusion strategies are associated with complications including infection, coagulopathy, acute respiratory distress syndrome, and death (1). Early adverse reactions include hemolysis, allergic reactions, transfusion-related acute lung injury, and transfusion-associated circulatory overload. Transfusion-related acute lung injury usually occurs within 6 hours of transfusion with the sudden development of noncardiogenic pulmonary edema, whereas transfusion-associated circulatory overload generally presents as cardiogenic pulmonary edema in patients at risk for volume overload and is managed supportively with diuretics. Both may require mechanical ventilation, although noninvasive positive pressure ventilation may be sufficient in select patients.

After the Transfusion Requirements in Critical Care Trial (TRICC) (2) demonstrated that a restrictive transfusion threshold (hemoglobin, 7 mg/dl) was noninferior to a liberal level (hemoglobin, 9 mg/dl) among a broad population of critically ill patients, a restrictive transfusion approach has been increasingly used in the intensive care unit (ICU).

More recent evidence has shown this approach to be of benefit in specific patient populations, including those with septic shock (3) and gastrointestinal hemorrhage after early endoscopy to treat the source of bleeding (4). The optimal strategy for patients with myocardial ischemia remains unclear, although limited evidence suggests that patients with acute coronary syndrome as well as

postoperative cardiothoracic surgery patients have worse outcomes with a restrictive strategy (5, 6).

Massive Transfusion

Massive red blood cell transfusion, defined as transfusion of more than 10 units of packed red blood cells (PRBC) in 24 hours, independently predisposes patients to coagulopathy and death. Damage-control resuscitation with early transfusion of matched products (PRBC, platelets, and plasma), prevention and early correction of coagulopathy, and minimizing chloride-rich fluids may mitigate complications, although the optimal ratio of product administration is unclear. In 2015, the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial found no significant difference in mortality for patients with severe traumatic injury randomized to resuscitation in a 1:1:1 (plasma:platelet: PRBC) ratio versus a 1:1:2 ratio (7). Of note, significantly more patients achieved hemostasis and fewer died from exsanguination within the first 24 hours in the 1:1:1 group.

Management of Patients on Therapeutic Anticoagulation

Patients who develop hemorrhage while receiving therapeutic anticoagulation require urgent reversal of their coagulopathy. This is complicated by the use of the new direct oral anticoagulants that inhibit the activity of thrombin or activated factor X (Table 5), many of which do not have specific antidotes. For patients on warfarin, fresh frozen plasma transfusions will rapidly reverse an elevated international normalized ratio, as opposed to vitamin K, which requires 18 to 24 hours to realize the full effect. Activated factor VII has a quicker onset than either plasma or vitamin K and is effective in reducing hematoma volume in intracranial hemorrhage, although there is an elevated risk of arterial

Table 5. Oral anticoagulants

Agent	Mechanism of Action	Antidote(s)
Warfarin generic (Coumadin)	Vitamin K antagonist	Vitamin K Fresh frozen plasma Prothrombin complex concentrates Activated factor VII Andexanet*
Rivaroxaban (Xarelto)	Direct factor Xa inhibitor	Fresh frozen plasma Prothrombin complex concentrates Activated factor VII Andexanet*
Apixaban (Eliquis)	Direct factor Xa inhibitor	Fresh frozen plasma Prothrombin complex concentrates Activated factor VII Andexanet*
Edoxaban (Savaysa)	Direct factor Xa inhibitor	Fresh frozen plasma Prothrombin complex concentrates Activated factor VII Andexanet*
Dabigatran etexilate (Pradaxa)	Direct thrombin inhibitor	Idaricizumab Fresh frozen plasma Activated factor VII Hemodialysis

*Not approved by the U.S. Food and Drug Administration at the time of this writing.

thrombosis in the elderly. Current formulations of prothrombin complex concentrates, which include proteins C and S, may have lower thrombotic risk profile and can be used to quickly reverse anticoagulation in patients on warfarin and the novel oral anticoagulants. Idarucizumab, an antibody fragment, completely and quickly reverses the anticoagulant effect of dabigatran and is now approved by the U.S. Food and Drug Administration for this purpose (8). Other agents are under development and may soon be available for the other novel non-vitamin K anticoagulants.

Special Populations

Management of profound anemia or active bleeding can be challenging for those who refuse blood product transfusions. Respecting the patient's right to refuse while optimizing their red blood cell production with intravenous iron and erythropoietin is recommended and, on the basis of published case series, may be associated with acceptable outcomes, even after cardiac surgery (9). Care should be taken to minimize routine laboratory testing and unnecessary phlebotomy in these patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

- 1 Ahmed AH, Litell JM, Malinchoc M, Kashyap R, Schiller HJ, Pannu SR, Singh B, Li G, Gajic O. The role of potentially preventable hospital exposures in the development of acute respiratory distress syndrome: a population-based study. *Crit Care Med* 2014;42:31–39.
- 2 Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;340:409–417.
- 3 Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, Johansson PI, Åneman A, Vang ML, Winding R, *et al.*; TRISS Trial Group; Scandinavian Critical Care Trials Group. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med* 2014;371:1381–1391.
- 4 Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, *et al.* Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013;368:11–21.
- 5 Carson JL, Brooks MM, Abbott JD, Chaitman B, Kelsey SF, Triulzi DJ, Srinivas V, Menegus MA, Marroquin OC, Rao SV, *et al.* Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. *Am Heart J* 2013;165:964–971.e1.
- 6 Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, Reeves BC; TITRe2 Investigators. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med* 2015;372:997–1008.
- 7 Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, del Junco DJ, Brasel KJ, Bulger EM, Calicut RA, *et al.*; PROPPR Study Group. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA* 2015;313:471–482.
- 8 Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kamphuisen PW, *et al.* Idarucizumab for dabigatran reversal. *N Engl J Med* 2015;373:511–520.
- 9 Vaislic CD, Dalibon N, Ponzio O, Ba M, Jugan E, Lagneau F, Abbas P, Olliver Y, Gaillard D, Baget F, *et al.* Outcomes in cardiac surgery in 500 consecutive Jehovah's Witness patients: 21 year experience. *J Cardiothorac Surg* 2012;7:95.