F. Masud, M.D.

UPDATES ON CRITICAL CARE MANAGEMENT OF CARDIOVASCULAR PATIENTS

Faisal Masud, M.D.; Asma Zainab, M.D.; Iqbal Ratnani, M.D.; Christiane Perme, PT; Daynene Vykoukal, Ph.D.

Methodist DeBakey Heart & Vascular Center, The Methodist Hospital, Houston, Texas

Abstract

Cardiology and cardiovascular surgery patients have historically been one of the sickest populations that physicians encounter. With the inherent compromise of the cardiac and/or respiratory system and the added complexity of a major surgical procedure, this patient group requires a demanding level of care. As innovations in the treatment of cardiac patients have prolonged life, we have encountered patients who require redo-redo-redo procedures. There has been a tremendous increase in the use of a wide variety of mechanical assist devices, transplantation procedures, robotic surgery, and hybrid approaches in which cardiac surgeons and cardiologists work in the same room on the same patient.

Against this background, there have been quite a few changes taking place in the field of critical care. This report discusses the transformations being made in blood pressure management, blood product transfusion, prevention of healthcare-associated infections, physical therapy in cardiothoracic intensive care units (ICUs), ventilatory management, and the role of intensivists in cardiothoracic ICUs.

Blood Pressure Management

Hypertension (HTN) is a very common comorbidity in patients presenting for cardiovascular surgery. It is estimated that approximately 73 million Americans have chronic HTN, and 65% of them may have uncontrolled HTN.[1] In fact, studies have shown that up to 30–50% of patients undergoing routine cardiac surgery have perioperative HTN.[2] Acute HTN in these patients has both a direct and indirect impact on outcomes, ranging from an increased risk for surgical bleeding to myocardial ischemia, stroke, neurocognitive dysfunction, platelet activation, and an inflammatory response leading to compromised microvascular beds.[3-7] It is therefore no wonder that a survey of physicians who care for cardiac surgery patients indicated that more than 80% of patients required acute HTN treatment even though some of them did not have a history of HTN.[8] There are multiple points during the preoperative, intraoperative, and postoperative phases of treatment where there is an inherent risk of acute HTN, HTN urgency, and even HTN emergency — for example, preoperative anxiety and insertion of lines, induction of anesthesia, sternotomy, cross clamping of the aorta, transfer to the ICU, immediately before, during and after extubation, and in instances of inadequate sedation, pain management, or medication. Another area of investigation in acute blood pressure (BP) management is the effect of perioperative pulse pressure (PP) and its impact on coronary artery bypass graft (CABG) survival, particularly since increasing perioperative PP is being linked to poor long-term survival after CABG surgery.[9]

Management and prevention of acute HTN episodes is vital to quality care. The first step is to anticipate and proactively treat predictable episodes of HTN, e.g., during aortic cross clamping or extubation. Prior to starting any intravenous medication to control BP, pain, anxiety, and sedation have to be addressed and appropriately treated. Acute antihypertensive therapy has two objectives, namely, the rapid onset of medication for a short duration and with minimal side effects, and the initiation of therapy to wean the patient off of intravenous (IV) antihypertensive medication, especially when they are in the ICU.

With these objectives in mind, some of the commonly used IV medications in our arsenal are nitroglycerin (GTN), Sodium Nitroprusside (SNP), esmolol, nicardipine and clevidipine. Fenoldopam, hydralazine, and labetalol are not commonly used due to their profiles and side effects. SNP and GTN are commonly used IV antihypertensive agents; however, being nonselective vasodilators, they cause arterial and venous dilation, thereby potentially decreasing venous return[10, 11] and cardiac output and increasing the need for fluid resuscitation. The added issues of tolerance with GTN and SNP, cyanide toxicity, and rebound hypertension from SNP open the door for better agents to be used.[11, 12]

Esmolol is an ultra-short-acting, cardioselective, β-adrenergic blocking agent that has been extensively used in cardiac surgical patients.[13] The rapid on-and-off mechanism of action makes it a good agent for use in acute HTN scenarios. It mainly affects the myocardium without decreasing high systemic vascular resistance (SVR),[10, 11] although this somewhat limits its use as a solo agent in reducing acute HTN. Nicardipine (second generation) and clevidipine (third generation, ultra-short-acting) are dihydropyridine-derivative calcium channel blockers with high vascular selectivity, making them act as arterial vasodilators.[10, 14] Their selective effect on decreasing SVR without affecting venous filling and/or cardiac output makes them good agents for managing acute HTN in cardiac surgical patients. Both of these agents should be used with caution in patients with heart failure, as there can be potential for exacerbation of this condition.

Tight BP control can offer some protection to these vulnerable patients, with newer pharmacological agents increasing the physician's options for treatment. The best result may be achieved by utilizing one or a combination of two agents as indicated.

Blood Product Transfusion

More than half a million U.S. adults undergo cardiac surgical procedures each year. About 15–20% of these patients consume 80% of the blood products used annually.[15] The annual transfusion costs of cardiac surgery are more than $500 million.[16]

Extensive transfusion of blood products has been associated with multiple adverse effects, which include transmission of viruses, infection, volume overload, and transfusion-related acute lung injury.[17] All of these complications lead to an increase in mortality. Blood conservation interventions are helpful. In one study, a 5-year mortality rate of 15% was calculated in transfused patients compared to only 5% in nontransfused patients.[18] Protocols to identify high-risk patients undergoing cardiovascular surgery should be established and implemented. Risk factors include advanced age, preoperative anemia, urgent surgery, antiplatelet therapy, clotting abnormalities, multiple comorbidities, and procedure-related variables like prolonged cardiopulmonary bypass time, reoperation, etc.[16]

These rules are based on guidelines from the American Society of Anesthesiologists (ASA), listed in Table 1.[19]

- Accept a hemoglobin level of up to 7 g/dL in hemodynamically stable patients who are not bleeding. Transfusion can be life-saving in patients who have a hemoglobin less than 6 g/dL.[15]
- A hemoglobin level of 7 g/dL or lower justifies transfusion in patients with chronic cardiovascular or respiratory disease.
- Transfusion is recommended in patients who are actively bleeding without immediate control.

Other ASA practice recommendations for limiting blood transfusion include reinfusion of shed mediastinal blood using the cell saver technique, and pharmacologic agents such as 1) lysine analogues, e.g., epsilon-aminocaproic acid and tranexamic acid, to reduce total blood loss after cardiac surgery (class Ia recommendation); 2) desmopressin acetate (DDAVP) to reduce excessive bleeding in patients with chronic renal failure, cardiopulmonary bypass-induced platelet dysfunction, or thrombocytopenia (class IIb), although routine prophylactic use of DDAVP is not recommended; and 3) factor VIIa concentrate for intractable nonsurgical bleeding that is unresponsive to other therapies (class IIb).[15]

Prevention of Healthcare-Associated Infections

Infections after cardiovascular surgery increase morbidity, mortality, and economic burden.[20] These infections can be classified as surgical site infections (SSI) or nosocomial (hospital-acquired) infections that occur remote from the surgical site. In 1999, The National Healthcare Safety Network (formerly known as the National Nosocomial Infection Surveillance System) reported an SSI rate of 2.6%.[20] One study utilizing the Society of Thoracic Surgeons (STS) National Cardiac Database reported an incidence of major infection in 3.51% of patients who underwent CABG procedures in a period from early 2002 to late 2003.[21] These infections are further divided into mediastinitis (25.1%), saphenous vein harvest site infection (32.6%), septicemia (35%), multiple site infections (6.8%), and thoracotomy infections (0.5%). These patients had a higher mortality rate (17.3%) and an average postoperative length of stay greater than 14 days.[21]

Prophylactic intravenous antibiotics should be routinely administered to cardiovascular surgical patients.[22] According to STS practice guidelines, antimicrobial prophylaxis of 48 hours duration is effective. There is no evidence that administration of antibiotics for more than 48 hours is more effective. Other measures to prevent SSI include appropriate antibiotic choice, maintaining glucose control, and hand hygiene.[23] Use of mupirocin nasal ointment in patients with positive nasal swabs for methicillin-resistant staphylococcus aureus has not been shown to reduce the rate of SSI.[24]

Hospital-acquired infection surveillance, prevention, and control is achieved through instituting proper guidelines.[23] Bloodstream infections related to central lines are prevented during placement

ASA Guidelines on Intraoperative and Postoperative Management of Blood Loss and Transfusions
I. Recommendations for red blood cell transfusion
a. Monitor the amount of blood loss
b. Monitor hemoglobin or hematocrit
c. Monitor for the presence of inadequate perfusion and oxygenation of vital organs (e.g., blood pressure, heart rate, temperature, blood oxygen saturation)
d. Transfusion of allogeneic red blood cells or autologous blood (i.e., normovolemic hemodilution and intraoperative red blood cell recovery)
II. Recommendations for management of coagulopathy
a. Visual assessment of the surgical field and laboratory monitoring for coagulopathy
b. Transfusion of platelets
c. Transfusion of fresh frozen plasma
d. Transfusion of cryoprecipitate
e. Administration of drugs to treat excessive bleeding (e.g., desmopressin, topical hemostatics)
f. Recombinant activated factor VII
III. Monitoring and treatment of adverse effects of transfusions
a. Bacterial contamination
b. Transfusion-related acute lung injury
c. Transmission of infectious diseases
d. Transfusion reaction

Table 1. American Society of Anesthesiologists (ASA) guidelines on intraoperative and postoperative management of blood loss and transfusions.[19]

by using full barrier precautions, hand hygiene, and chlorhexidine skin antisepsis. Daily review of line necessity and removal of unnecessary lines is useful.

Ventilator-associated pneumonia and other related respiratory illnesses are prevented with head elevation to greater than 30 degrees unless contraindicated, sedation interruption to evaluate for extubation, and gastrointestinal/deep vein thrombosis prophylaxis. Hand hygiene and barrier techniques for Clostridium difficile diarrhea and other drug-resistant organisms are also routinely used in the ICU to limit the spread of infection.

Physical Therapy: Early Mobility and Walking Program for Patients in Cardiothoracic ICU

Critical illness is associated with a wide range of serious impairments that interfere with optimal functional outcome. They include long-term physical impairments with loss of independence and reduced quality of life. It is imperative that physicians, nurses, and physical therapists identify patients in the ICU who are at high risk of developing physical and nonphysical limitations. Some examples are patients with advanced age, comorbidities, and high severity of illness. After discharge from the ICU, these patients will face extended periods of rehabilitation and significant morbidity.

Several publications have noted the benefits of early mobility and walking in the ICU. They include minimizing the complications of bed rest, promoting weaning from the ventilator as the patient's overall strength and endurance improve, maximizing independent function, and decreasing the length of the ICU and hospital stay.[25, 26] Schweickert et al. used a strategy for rehabilitation in the earliest days of critical illness that included interruption of sedation and physical and occupational therapy (PT, OT). The interventions were safe and well tolerated, and they resulted in better functional outcomes at hospital discharge, a shorter duration of delirium, and more ventilator-free days compared with standard care.[27]

Early mobility and walking interventions in the cardiothoracic ICU should be provided by nurses and physical therapists. The nursing mobility program in The Methodist Hospital's cardiothoracic ICU includes routinely assisting patients with sitting on the side of the bed, standing at the bedside, and sitting in a regular chair or stretcher chair for variable lengths of time. Whenever possible, nurses should assist patients with walking as long as they only require minimal physical assistance.

Physical therapists are an integral member of the interdisciplinary team caring for a patient in the ICU and are uniquely qualified to design and implement treatment plans that help improve function.[28] Patients should be referred to PT if they are unable to stand at the bedside with nursing assistance or if any neuromuscular, orthopedic, or cardiopulmonary dysfunction that impairs functional mobility is present prior to admission or after the surgical procedure. Physical therapists working in the cardiothoracic ICU should perform a comprehensive clinical assessment to identify current functional limitations as well as the rehabilitation goals and plan of care. A PT program should include individualized therapeutic interventions to improve functional mobility.

An early mobility and walking program for patients in the ICU has been described by Perme and Chandrashekar, and it provides a practical approach with specific guidelines to assist clinicians in managing these patients, especially when they require mechanical ventilation.[25] The program is divided into 4 phases and includes the types of patients suitable for each phase. It also includes guidelines for bed mobility, transfers, gait, therapeutic exercises, positioning, education, and duration and frequency of mobility sessions. The general criteria for progression of therapeutic interventions are also offered.[25]

Patients with an endotracheal tube or tracheostomy should be encouraged to walk with a portable ventilator whenever appropriate and with all safety measures in place. A strong collaborative multidisciplinary approach among physicians, nurses, physical therapists, and respiratory therapists must be used in the care of these patients.

An early mobility and walking program in the cardiothoracic ICU is an approach that can potentially help patients regain their physical and psychological function and ultimately maximize functional independence.

Ventilatory Strategies in ICU

One of the major challenges in ICUs is managing hypoxemia or respiratory insufficiency in patients. Mechanical ventilation is the most common invasive treatment modality for acute respiratory failure, while noninvasive positive pressure ventilation (NIPPV) modes like continuous positive airway pressure or pressure support ventilation are considered the gold standard for treating chronic obstructive pulmonary disease exacerbations. NIPPV can also be used to manage mild to moderate respiratory insufficiencies.

Conventional modes of ventilation based on volume or pressure control are usually sufficient in most cases of respiratory failure. Bi-level ventilation can be used in patients who are difficult to oxygenate due to failed lungs. Other modalities that can be used in severe hypoxemia include initiation of nitric oxide[29] and high frequency oscillatory ventilation.[30] The updated studies in pulmonary management (e.g., the FACTT trial)[31-33] and the physiological bases on which patients with acute respiratory distress syndrome are treated (e.g., use of low tidal volumes[34] and optimum use of positive end-expiratory pressure[35]) are important intensive care milestones.

Pulmonary hypertension management with Flolan® (Epoprostenol sodium), Tracleer® (bosentan), Revatio® (sildenafil) and others is another evolving area.[36] In cases of extreme hypoxemia in which mechanical ventilation alone is not helpful, support with extracorporeal membrane oxygenator (ECMO) is applied.[37] ECMO and extracorporeal life support have been indicated as treatment for acute respiratory and cardiac failure.

Role of Intensivist in Cardiothoracic ICU

Since the inception of the first organized ICU in 1953,[38] the practice of intensive care medicine has come a long way. The intensivist's role in critical care is firmly established. The Leapfrog Group for patient safety recommends the presence of intensivists in the ICU as a standard practice.[39] The presence of an intensivist is not only crucial for delivery of medical care in a timely fashion, but it also leads to improvement in overall care through decreased length of stay, shorter ventilator times, decreased rate of infections, avoidance of unnecessary transfusions, proper utilization of medications and antibiotics, avoidance of errors, direction of multidisciplinary rounds, coordination of care among different subspecialties, and implementation of various bundles. Intensivists are also trained to perform life-saving procedures.

By being abreast of the latest guidelines and emerging new literature, intensivists can provide state-of-the-art care. Procedures such as therapeutic hypothermia after cardiac arrest,[40] proper ventilation in acute respiratory distress syndrome,[34] early goal-directed therapy in sepsis,[41] and other measures have clearly demonstrated improved outcomes in this vulnerable population, with a 30% reduction in hospital mortality and a 40% reduction in ICU mortality.[42]

Traditionally, cardiothoracic surgical ICUs have been managed directly by surgeons during postoperative care. A landmark paper

	SICU	CICU	P Value	Odds Ratio (95% CI)
ICU outcomes				
Mechanical ventilation on admission, n	620 (66.5%)	408 (43.7%)	<0.001	0.39 (0.33, 0.47)
Median ICU LOS, days (IQR)	0.96 (0.82, 1.83)	0.98 (0.85, 1.93)	0.02	—
ICU recidivism, n	38 (4.07%)	29 (3.11%)	0.26	0.76 (0.46, 1.24)
ICU mortality, n	14 (1.50%)	12 (1.29%)	0.69	0.86 (0.39, 1.86)
Postoperative outcome				
Reoperation for bleeding, n	61 (6.54%)	65 (6.97%)	0.71	1.07 (0.75, 1.54)
Perioperative myocardial infarction, n	6 (0.64%)	8 (0.86%)	0.59	1.34 (0.46, 3.87)
Postoperative atrial fibrillation, n	250 (26.8%)	243 (26.1%)	0.71	0.96 (0.78, 1.18)
Postoperative renal dysfunction, n	70 (7.50%)	78 (8.36%)	0.49	1.12 (0.80, 1.57)
Postoperative cerebrovascular event, n	16 (1.71%)	18 (1.93%)	0.73	1.13 (0.57, 2.25)
Postoperative infections (all), n	63 (6.75%)	58 (6.22%)	0.64	0.92 (0.63, 1.32)
Median hospital LOS, days (IQR)	7.0 (5.0, 9.0)	6.0 (5.0, 8.0)	<0.001	—
Thirty-day mortality, n	20 (2.14%)	16 (1.71%)	0.50	0.80 (0.41, 1.55)

Table 2. Postoperative outcomes related to full-time intensivist care in cardiothoracic surgical ICUs. Reprinted from Kumar et al. with permission from Elsevier.[43] Copyright © 2009. CI: confidence interval; CICU: cardiac surgery intensive care unit; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; SICU: traditional mixed surgical intensive care unit

published in 2009 showed that a full-time intensivist program in cardiothoracic surgical ICUs is associated with "reduced transfusion of blood components, decreased requirement for mechanical ventilation, and shorter hospital length of stay" (Table 2).[43] At the Methodist DeBakey Heart & Vascular Center, 24-hour intensivist service has been in place for the last 10 years and has shown similar results, with many lives saved.

Conclusion

Critical care medicine is a rapidly changing field with new areas of development, research, and clinical information. Several underlying themes are critical to the care of patients in the cardiothoracic ICU. Implementation of screening and treatment guidelines facilitates delivery of consistent, quality care that is based in current clinical information. Up-to-date knowledge of the available medications, techniques, and equipment is crucial. Prevention of avoidable problems through an anticipatory approach to patient care, such as recognition of events that may trigger an episode of acute hypertension, or the use of antimicrobial prophylaxis to prevent SSIs, can go a long way towards improving patient outcomes. Familiarity with the latest evidence-based thinking on critical care issues, such as the role of transfusion management and the importance of early implementation of physical therapy among ICU patients, is also important. Intensivists with clinical knowledge and training serve not only to implement these advances in critical care but also to educate members of the ICU team about providing the best possible care to this vulnerable patient population.

References

1. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008 Jan 29;117(4):e25-146. Epub 2007 Dec 17.
2. Cheung AT. Exploring an optimum intra/postoperative management strategy for acute hypertension in the cardiac surgery patient. J Card Surg. 2006 Mar-Apr;21 Suppl 1:S8-S14.
3. Aronson S, Boisvert D, Lapp W. Isolated systolic hypertension is associated with adverse outcomes from coronary artery bypass grafting surgery. Anesth Analg. 2002 May;94(5):1079-84.
4. Weitz HH. Perioperative cardiac complications. Med Clin North Am. 2001 Sep;85(5):1151-69.
5. Kobzar G, Mardla V, Rätsep I, Samel N. Platelet activity before and after coronary artery bypass grafting. Platelets. 2006 Aug;17(5):289-91.
6. Weiss SJ, Longnecker DE. Perioperative hypertension: an overview. Coron Artery Dis. 1993 May;4(5):401-6.
7. Estafanous FG, Tarazi RC. Systemic arterial hypertension associated with cardiac surgery. Am J Cardiol. 1980 Oct;46(4):685-94.
8. Vuylsteke A, Feneck RO, Jolin-Mellgård A, Latimer RD, Levy JH, Lynch C 3rd, et al. Perioperative blood pressure control: a prospective survey of patient management in cardiac surgery. J Cardiothorac Vasc Anesth. 2000 Jun;14(3):269-73.
9. Nikolov NM, Fontes ML, White WD, Aronson S, Bar-Yosef S, Gaca JG, et al. Pulse pressure and long-term survival after coronary artery bypass graft surgery. Anesth Analg. 2010 Feb 1;110(2):335-40. Epub 2009 Dec 8.
10. Levy JH. The ideal agent for perioperative hypertension and potential cytoprotective effects. Acta Anaesthesiol Scand Suppl. 1993;99:20-5.
11. Nordlander M, Pfaffendorf M, van Wezel HB. Calcium antagonists for perioperative blood pressure control. Sem Cardiothorac Vasc Anesth.1998;2(3):231-42.
12. Gray RJ. Postcardiac surgical hypertension. J Cardiothorac Anesth.1988 Oct;2(5):678-82.
13. van Zwieten PA, van Wezel HB. Antihypertensive drug treatment in the perioperative period. J Cardiothorac Vasc Anesth.1993 Apr;7(2):213-26.

14. Bailey JM, Lu W, Levy JH, Ramsay JG, Shore-Lesserson L, Prielipp RC, et al. Clevidipine in adult cardiac surgical patients: a dose-finding study. Anesthesiology. 2002 May;96(5):1086-94.

15. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA 2nd, Haan CK, Royston BD, et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. Ann Thorac Surg. 2007 May;83(5 Suppl):S27-86.

16. Steiner ME, Despotis GJ. Transfusion algorithms and how they apply to blood conservation: the high-risk cardiac surgical patient. Hematol Oncol Clin North Am. 2007 Feb;21(1):177-84.

17. Shander A. Emerging risks and outcomes of blood transfusion in surgery. Semin Hematol. 2004 Jan;41(1 Suppl 1):117-24.

18. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ. Effect of blood transfusion on long-term survival after cardiac operation. Ann Thorac Surg. 2002 Oct;74(4):1180-6.

19. American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology. 2006 Jul;105(1):198-208.

20. Fry DE. A systems approach to the prevention of surgical infections. Surg Clin North Am. 2009 Apr;89(2):521-37.

21. Fowler VG Jr, O'Brien SM, Muhlbaier LH, Corey GR, Ferguson TB, Peterson ED. Clinical predictors of major infections after cardiac surgery. Circulation. 2005 Aug 30;112(9 Suppl):I358-65.

22. Edwards FH, Engelman RM, Houck P, Shahian DM, Bridges CR; Society of Thoracic Surgeons. The Society of Thoracic Surgeons Practice Guideline Series: Antibiotic Prophylaxis in Cardiac Surgery, Part I: Duration. Ann Thorac Surg. 2006 Jan;81(1):397-404.

23. Yokoe DS, Classen D. Improving patient safety through infection control: a new healthcare imperative. Infect Control Hosp Epidemiol. 2008 Oct;29 Suppl 1:S3-11.

24. Perl TM, Cullen JJ, Wenzel RP, Zimmerman MB, Pfaller MA, Sheppard D, et al. Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. N Engl J Med. 2002 Jun 13;346(24):1871-7.

25. Perme C, Chandrashekar R. Early mobility and walking program for patients in intensive care units: creating a standard of care. Am J Crit Care. 2009 May;18(3):212-21. Epub 2009 Feb 20.

26. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med. 2008 Aug;36(8):2238-43.

27. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009 May 30;373(9678):1874-82. Epub 2009 May 14.

28. Perme C, Chandrashekar R. Managing the patient on mechanical ventilation in ICU: early mobility and walking program. Acute Care Perspectives. 2008;17(1):10-5.

29. Rossaint R, Falke KJ, López F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med. 1993 Feb 11;328(6):399-405.

30. Galvin I, Krishnamoorthy R, Saad RS. Management of advanced ARDS complicated by bilateral pneumothoraces with high-frequency oscillatory ventilation in an adult. Br J Anaesth. 2004 Sep;93(3):454-6. Epub 2004 Jun 11.

31. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wheeler AP, Bernard GR, Thompson BT, Schoenfeld D, Wiedemann HP, deBoisblanc B, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med. 2006 May 25;354(21):2213-24. Epub 2006 May 21.

32. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006 Jun 15;354(24):2564-75. Epub 2006 May 21.

33. Rivers EP. Fluid-management strategies in acute lung injury—liberal, conservative, or both? N Engl J Med. 2006 Jun 15;354(24):2598-600. Epub 2006 May 21.

34. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000 May 4;342(18):1301-8.

35. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004 Jul 22;351(4):327-36.

36. Humbert M, McLaughlin VV. The 4th World Symposium on Pulmonary Hypertension. Introduction. J Am Coll Cardiol. 2009 Jun 30;54(1 Suppl):S1-2.

37. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009 Oct 17;374(9698):1351-63. Epub 2009 Sep 15.

38. Berthelsen PG, Cronqvist M. The first intensive care unit in the world: Copenhagen 1953. Acta Anaesthesiol Scand. 2003 Nov;47(10):1190-5.

39. The Leapfrog Group for Patient Safety [Internet]. Washington, DC: The Leapfrog Group c/o Academy Health; c2001-2011. Fact Sheet: ICU Physician Staffing; 2011 Apr 1 [cited 2011 Aug 29]. Available from: http://www.leapfroggroup.org/media/file/Leapfrog-ICU_Physician_Staffing_Fact_Sheet.pdf.

40. Nadkarni VM, Nolan JP, Billi JE, Bossaert L, Böttiger BW, Chamberlain D, et al. International Collaboration in Resuscitation Science. 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Circulation. 2010;122(16 Suppl 2):SR76-82.

41. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001 Nov 8;345(19):1368-77.

42. Pronovost P, Thompson DA, Holzmueller CG, Dorman T, Morlock LL. Impact of the Leapfrog Group's intensive care unit physician staffing standard. J Crit Care. 2007 Jun;22(2):89-96. Epub 2007 Feb 2.

43. Kumar K, Zarychanski R, Bell DD, Manji R, Zivot J, Menkis AH, et al. Impact of 24-hour in-house intensivists on a dedicated cardiac surgery intensive care unit. Ann Thorac Surg. 2009 Oct;88(4):1153-61.