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SPECIAL FEATURE

ECMO as a Rescue Strategy for Severe ARDS and Beyond

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Dr. Guttendorf reports no financial relationships relevant to this field of study.

Acute respiratory distress syndrome (ARDS) is a severe form of respiratory failure in a heterogeneous population of patients associated with acute onset of bilateral pulmonary infiltrates and severe hypoxemia not associated with cardiac failure. ARDS continues to be common in ICU patients and carries a high associated mortality. In the era of lung-protective ventilation strategies for ARDS, mortality has declined, but remains high. In a recent systematic review, the in-hospital mortality rate for ARDS since 2010 was 45%.[1] The ALIEN study, a one-year prospective evaluation of the incidence and mortality associated with ARDS in ICUs in Spain, reported hospital mortality of 47.8%.[2]

Extracorporeal membrane oxygenation (ECMO) has been used as a rescue therapy for patients with severe ARDS who fail to respond to traditional low tidal volume lung protective ventilation with optimal positive end-expiratory pressure (PEEP) interventions and other strategies, including prone positioning, high frequency oscillatory ventilation, neuromuscular blockade, and inhaled nitric oxide or epoprostenol.

The first use of ECMO for adult respiratory failure was reported in 1972 in a trauma patient with shock lung who was supported with venoarterial ECMO for 75 hours and survived.[3] Following that, there were several efforts to conduct randomized, controlled trials to study the use of ECMO for respiratory support in adults; but overall, those studies reported unfavorable results, and most centers abandoned efforts.[4-6] Then, with improvements in technology, primarily in pumps and oxygenators, and continued success in neonates and children, efforts resurfaced to apply the technology to adults. Between 1997 and 2009, a number of single-center and registry reports demonstrated improvement in survival of ECMO for respiratory failure to about 50%, which, at the time, was an improvement over the expected survival for a patient with ARDS treated with conventional therapies.[7-11] The CESAR trial, conducted in 2009, was a randomized, controlled trial of referral for ECMO therapy vs. conventional support in adults with severe ARDS. The trial reported increased survival without

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disability at six months with survival in the referral for ECMO group at 63%, compared with those not referred at 47% (relative risk [RR], 0.69; 95% confidence interval [CI], 0.05-0.97; $P = 0.03$).[12] Although the trial was criticized for the lack of standardized therapy in the control arm, the overall results were very favorable for the use of ECMO for severe ARDS with improvement in survival. This prompted more widespread use of this technology in adults. Likewise, the successful treatment of increased numbers of patients with influenza-associated ARDS during the H1N1 influenza pandemic of 2009 led to an increase in the number of centers performing ECMO in adults and a sharp rise in the number of adult patients treated with ECMO.

Tsai et al reported a single-center, retrospective, case-controlled study matching ARDS patients over a six-year period by age and APACHE II scores in both ECMO and non-ECMO treatment groups and demonstrated improved hospital survival and lower six-month mortality ($P < 0.001$) in patients presenting with ARDS treated with ECMO compared to those not treated with ECMO, suggesting that ECMO may be beneficial over standard medical therapy for ARDS.[13] The Extracorporeal Life Support Organization (ELSO) maintains a registry of ECMO or extracorporeal life support (ECLS) cases by voluntary reporting from centers worldwide. As of January 2017, cumulative adult respiratory ECLS cases numbered 12,346, with 57% of patients surviving to hospital discharge.[14]

INDICATIONS

The primary indication for ECMO in adults is hypoxic respiratory failure with a potentially reversible cause that is refractory to conventional and rescue treatments with optimal care for six hours or more. ECMO is indicated when the PaO_2/FiO_2 ratio is < 100-150 on fraction of inspired oxygen (FiO_2) of 90% or greater and Murray lung injury score of 3-4. Other indications for respiratory support include hypercarbic respiratory failure with pH ≤ 7.20, severe air leak syndromes (such as bronchopleural fistula), patients awaiting lung transplant, and patients experiencing sudden cardiac or respiratory collapse.[15]

There are few absolute contraindications to ECMO support, but the reversible nature of the primary disorder should be considered carefully. Relative contraindications include duration of mechanical ventilation at high settings for longer than seven days, major pharmacologic immunosuppression, recent or expanding central nervous system hemorrhage, and increased age, as multiple studies have shown increasing age as a predictor of poorer outcome.

CIRCUIT AND CANNULATION

Large cannulas are placed in the patient's blood vessels to continuously route blood out of the body (extracorporeal) through a circuit that includes, at a minimum a pump, an oxygenator, and a heat exchanger. Additional circuit configurations are possible and can include access ports for drawing samples and administering medications, a reservoir for fluid administration, and in-line point-of-care blood sampling.

Blood is drawn from the patient via a venous drainage cannula aided by a centrifugal pump, routed through a membrane oxygenator where oxygen and carbon dioxide are exchanged, then returned to the patient via either a venous return cannula or an arterial return cannula. An integral heat exchanger is a mandatory circuit component to prevent excessive heat loss as the blood transits extracorporeally. Other extracorporeal circuits can be integrated easily into the ECMO circuit as needed for continuous renal replacement therapy or plasmapheresis.

The type of support (respiratory or cardiac) depends on the placement of the cannulas. Venovenous cannulation provides respiratory support, whereas venoarterial cannulation provides either cardiac support or respiratory support. Common venovenous cannulation techniques include femoral vein to femoral vein, femoral vein to internal jugular (IJ) vein, or a double lumen IJ vein cannula. Common venoarterial cannulation techniques in adults include femoral vein to femoral artery performed percutaneously or via cutdown. With this peripheral cannulation technique, blood is returned via the femoral artery and supplies the aorta and upper extremity vessels in a retrograde fashion. To prevent distal limb ischemia with peripheral venoarterial cannulation, frequently a smaller bore cannula is placed from the arterial return cannula to provide directed antegrade (femoral artery or superficial femoral artery) or retrograde (posterior tibial artery) perfusion to the distal extremity. An alternative to peripheral venoarterial cannu-

lation is placement of cannulas centrally via sternotomy, from right atrium to aorta. Central cannulation provides antegrade return via the ascending aorta, and often can permit larger cannula size.

MOBILITY AND AMBULATION

The bicaval double lumen venous cannula placed via the IJ vein contains two inlets, one in the superior vena cava and one in the inferior vena cava, and a single return port that directs flow into the right atrium and across the tricuspid valve. This cannula is placed under either fluoroscopic or echocardiographic guidance to assure correct positioning. For adults, 27 or 31 French cannula size can facilitate blood flows of 5 to 6 liters per minute. One primary advantage of using the single bicaval dual lumen catheter is patient mobility. Patients can be mobilized easily to sit out of bed in the chair and to exercise and ambulate. This has revolutionized ECMO care, in particular for patients cannulated as a bridge to lung transplant. Patients who tolerate it can be managed with little to no sedation, participate in aggressive physical conditioning programs, and even improve their functional status while awaiting transplant. The bicaval IJ cannula also facilitates prone positioning while on ECMO in patients who require additional recruitment techniques. Whenever possible, patients with ARDS should be cannulated in a venovenous configuration, as outcomes are better than those patients requiring venoarterial cannulation for respiratory support. From the January 2016 ELSO registry data, patients with respiratory failure with venovenous cannulations experienced slightly improved survival (59-65%) over those patients requiring venoarterial cannulation for a respiratory indication who had survival rates of 43-46%.[16]

ANTICOAGULATION

Anticoagulation is required to prevent thrombosis in the circuit and in venoarterial cannulation ECMO to prevent cardiac thrombus formation since most blood flow is deflected away from the non-beating heart (or one generating minimal pulsatility). Generally, either heparin infusion or a direct thrombin inhibitor (such as bivalirudin) is used. Activated clotting time, partial thromboplastin time, or anti-Xa levels can be used to monitor anticoagulation. Protamine infusion should be avoided due to clotting risk, as most cannula and tubing are heparin-bonded. Similarly, fresh frozen plasma, platelets, and cryoprecipitate may increase risk of clotting in the system (oxygenator, pump, or cannula).

OUTCOMES AND SPECIAL POPULATIONS

Survival is in part related to diagnosis. Viral, bacterial, and aspiration pneumonia have reported survival between 61-66%, while ARDS, non-ARDS acute respira-

Table 1: ECMO for Influenza A (H1N1) Summary

Year	Author	N	Survival	Mortality	Design
2009	ANZ-ECMO[18]	68	71%		Observational; Australia, New Zealand; multicenter
2010	Chan[19]	7	86%		Observational; Hong Kong; multicenter
2010	Freed[20]	6	67%		6 ECMO of 168 H1N1 pts. Cohort; Canadian; multicenter
2010	Roch[21]	9	56%		9 ECMO of 18 H1N1 pts. France; single center. No change in survival ECMO or non-ECMO groups.
2010	Holzgraefe[22]	13	92% (3 months)		Observational; Karolinska Institutet (Sweden), ECMO Referral Center
2011	Noah[23]	150		24% ECMO 53% control	Cohort; matched pairs
2011	Patroniti[24]	60	68%		Prospective cohort; Italy; multicenter
2012	Takeda[25]	14	36%		Observational; Japan; multicenter
2012	Hou[26]	9	56%		Observational; Beijing, China; single center
2013	Pham[27]	123 ECMO 53 matched		50% ECMO 40% control	Cohort, propensity matched
2013	Weber-Carstens[28]	61		54% ECMO 38% overall	61 ECMO of 116 H1N1 pts. German; multicenter
2013	Zangrillo[29]	266		28%	Systematic review and meta-analysis. Eight studies (n = 266). Mortality ranged 8-65%. Pooled mortality, 28% (95% CI, 18-37%; I^2 = 64%)

tory failure, and trauma-associated ARDS survival have been reported to be around 54-56%.[16]

ECMO FOR INFLUENZA A (H1N1)

As mentioned, the H1N1 pandemic of 2009 prompted an increase in the use of ECMO. This experience is summarized in Table 1.[17-28] Of these studies, with the exception of the Japanese study (Takeda et al; survival of 36%), survival ranges from 67-86%. For those studies reporting mortality, only one demonstrated significantly lower mortality with ECMO (Noah 2011; ECMO vs. non-ECMO of 24% vs. 53%, respectively).[22] A systematic review and meta-analysis in 2013 evaluating the use of ECMO for H1N1 patients included eight studies consisting of 266 patients. Results included a wide-ranging mortality of between 8% and 65%. The pooled estimate of mortality overall was 28% (95% CI, 18-37%; I^2 = 64%).[28]

In addition to the more traditional indications for ECMO (e.g., ARDS, pneumonia, influenza, bridge to lung transplant), there has been growing support for the use of ECMO for a number of other categories of patients with increasing success, including pregnancy, trauma patients with acute lung injury and transfusion-related lung injury, sepsis and septic shock, post-lung transplant primary graft dysfunction, and acute pulmonary embolism.

ECMO IN TRAUMA

At least five studies have been about trauma patients receiving ECMO with good outcomes. In trauma, because of the risk of bleeding, some centers reported using pumpless systems and high flows to avoid anticoagulation. Of these studies, the overall survival ranged from 60-79%.[29-32] Guirand et al reported that adjusted survival was greater in the ECLS group (adjusted odds ratio, 0.193; 95% CI, 0.042-0.884; P = 0.034).[33]

ECMO FOR SEPTIC SHOCK

The experience with septic shock shows more varied results. Of four studies included, 106 patients were treated with ECMO, with survival ranging from 15-70%, with the larger studies of 52 and 32 patients reporting lower survival at 15% and 22%, respectively.[34-37] Although the numbers are not large and the populations are not homogeneous, it looks as though ECMO provides benefit in at least some of these patients with sepsis and septic shock. Careful patient selection will be important in determining which patients with sepsis will benefit from ECMO support.

ECMO IN PREGNANCY

A systematic review included 26 papers over 25 years looking at the use of ECMO in pregnancy. It yielded 45 patients with the primary indication H1N1 influenza.[38] Overall, maternal survival was 78%, and fetal survival was 65%. The majority of patients were treated with venovenous cannulation ECMO for respiratory failure.

ECMO FOR MASSIVE PULMONARY EMBOLISM

Another systematic review looking at the use of ECMO in massive pulmonary embolus patients included 19 studies over 20 years (78 patients).[39] Overall survival was 70%. Only three studies included ≥ 10 patients, so individual center experience was low. Overall, the duration of ECMO was relatively short (average one to 12 days), and not surprisingly, each of the single case reports survived. Of the three studies involving ≥ 10 patients, survival was 62% (n = 21), 83% (n = 12), and 70% (n = 10). These single-center reports likely also included some selection bias related to each center's comfort with emergent cannulation for acute pulmonary embolism, changing medical therapies over this period of time (e.g., embolectomy, catheter embolectomy, thrombolysis), and patient selection. There was no difference in mortality among the various treatment modalities for pulmonary embolism (surgical embolectomy, catheter embolectomy, thrombolysis).[39]

CONCLUSION

The indications for ECMO continue to expand in patients with severe ARDS. Timely recognition of patients failing to respond to standard rescue therapies should prompt early evaluation for ECMO support. Minimizing days on mechanical ventilation prior to instituting ECMO is associated with better outcomes. As ECMO outcomes continue improving, it is important for clinicians to feel comfortable with the range of etiologies of respiratory failure for which ECMO may be beneficial. ■

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ABSTRACT & COMMENTARY

Surviving Critical Illness: Who Returns to Work?

By Elaine Chen, MD

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Dr. Chen reports no financial relationships relevant to this field of study.

SYNOPSIS: Three months after surviving critical illness due to respiratory failure or shock, more than 60% of survivors experienced a decrease in employment. At 12 months, almost half of survivors still experienced a decrease in employment.

SOURCE: Norman BC, et al. Employment outcomes after critical illness: An analysis of the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors cohort. *Crit Care Med* 2016;44:2003-2009.

Critical care use is increasing, and ICU survival rates are improving. Survivors of critical illness may experience post-intensive care syndrome, characterized by impaired cognitive, physical, and psychological function. Returning to employment marks an important milestone in recovery.[1] An earlier study of health-related quality of life of general ICU survivors reported that approximately half of patients returned to school or work one year after discharge.[2] This prospective cohort study is nested within a larger study, the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) study at Vanderbilt University and Saint Thomas Hospital. Subjects were adults admitted to an ICU with respiratory failure, cardiogenic shock, or septic shock. Patients were evaluated via survey for employment level at three and 12 months after discharge. Primary independent risk factors examined included in-hospital duration of delirium and cognitive function at follow-up. The primary outcome was self-reported decrease in employment level compared with prior employment level. Decrease was defined as going from full-time employment to unemployed or part-time employment, or part-time employment to unemployed. Physical health status, depressive symptoms, and severity of illness were measured with well-validated tools. Of 636 patients in the three-month follow-up cohort, 113 were identified as employed prior to illness. Of these, 100 (88%) were employed full time, and 13 (12%) were employed part time. At three months, 67 (58%) were unemployed, nine (8%) were employed part time, and 39 (34%) were employed full time; of these, 70 (62%) reported decreased employment. At 12-month follow-up, available data on 94 patients revealed that 45 patients remained unemployed (47%), 7% were employed part time, and 45% had returned to full-time employment. Overall, 46 patients (49%) reported a decrease in employment at 12 months. Adjustment for covariates revealed no association with duration of in-hospital delirium, cognitive function at three months, or severity of illness. However, better cognitive function at 12 months was marginally associated with lower odds of decreased employment at 12 months. The authors cited three key findings. First, rates of unemployment for survivors of critical illness remained high at one year after discharge. Second, there was no significant relationship between delirium during hospitalization or cognitive function with decreased employment at three months. Third, better cognitive function at 12 months was associated with a trend toward lower odds of decreased employment ($P = 0.07$).

■ COMMENTARY

As intensivists, we don't always know how our patients fare after they leave our care. Some return to the ICU repeatedly. Those who improve and stabilize often don't return to our clinics after their ICU stay, but rather return to their primary care providers. Many studies have evaluated physical, psychological, and cognitive function but fewer have evaluated employment. One longitudinal study of acute respiratory distress syndrome (ARDS) survivors found that six years after discharge, approximately 25% of patients remained unemployed due to health conditions, with high rates of cognitive dysfunction and disability.[3] This study reported that at one year, about half of ICU survivors will be working at a decreased level of employment compared to before their illness. In this article, the authors proposed that at three months, the physical and clinical factors related to the ICU still play a stronger role than cognition in decreasing re-entrance into the workforce, but at 12 months those factors have largely resolved. I am reminded of two patients who experienced prolonged ICU stays due to critical illness who have returned for follow-up with me over the past three years. The first patient is a 30-year-old woman who was hospitalized with a lupus flare and subsequently developed severe ARDS and sepsis. At her three-month follow-up visit, she could not walk from her wheelchair to the examining table and required oxygen at rest. After about one year, she returned to work part time and now works full time while caring for two children. The second patient is a bone marrow transplant recipient who was cured of his hematologic malignancy but suffered from a severe central nervous system infection. He experiences residual cognitive deficits, and while his physical function is nearly back to baseline, he has been unable to return to work after three years.

These two patients left a profound impression on me, and have led me to question what is the "normal" trajectory after ICU survival? The ideal would be to recover to baseline function rapidly, such that the sequelae of illness are not significantly noticeable. A friend of mine who received therapeutic hypothermia after a post-surgical cardiac arrest returned to full function and employment as a pharmacist within one year. Although this article will not change practice, it spurs reflection for critical care providers.

Although this study focused on delirium and cognition, other factors in the database potentially could be studied with regard to their effects on recovery. This study can help us counsel our younger, previously very functional patients and their families during their time of critical illness that regardless of how sick they are now, if they survive, long-term outcomes can be very positive. ■

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ABSTRACT & COMMENTARY

Hyperoxia in ICU Patients May Cause Harm

By Samuel Nadler, MD, PhD

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Dr. Nadler reports no financial relationships relevant to this field of study.

SYNOPSIS: Patients randomized to maintain oxygen saturation between 94-98% experienced better outcomes than patients allowed to receive partial pressure of oxygen > 150 mmHg.

SOURCE: Girardis M, et al. Effect of conservative vs. conventional oxygen therapy on mortality among patients in an intensive care unit. *JAMA* 2016;316:1583-1589.

Supplemental oxygen is a ubiquitous therapy in the ICU, although precise targets for oxygen saturation (SpO_2) and arterial partial pressure of oxygen (PaO_2) are unclear. Although it is clear that hypoxia can lead to harm, data showing that hyperoxia produces harmful effects are more limited. The OXYGEN-ICU trial was a single-center, randomized, clinical study that examined the effects of oxygen delivery on mortality in patients in the ICU. Adult patients with an expected stay in the ICU of > 72 hours were randomized to either conservative or conventional oxygen therapy. Patients in the conservative group received supplemental oxygen titrated to maintain SpO_2 between 94-98% or PaO_2 between 70-100 mmHg. Patients in the conventional control group received supplemental oxygen according to standard ICU protocols targeting SpO_2 97-100% and allowing PaO_2 values up to 150 mmHg. Patients who were pregnant, immunosuppressed, or transitioned to comfort measures only were excluded. This study was meant to enroll 660 patients for adequate power to detect a 6% mortality difference but was terminated early due to an earthquake, limiting further enrollment and an unscheduled interim analysis demonstrating significant benefit with the conservative protocol. Overall, this study enrolled 480 patients, with 236 randomized to conservative oxygen therapy and 244 to conventional therapy. Although the two groups were randomized, some important differences in each group are notable. Fewer patients in the conservative arm presented with COPD, chronic liver disease, respiratory failure, mechanical ventilation, shock, liver failure, renal failure, and documented infections overall, leading to a lower Simplified Acute Physiology Score II (SAPS II) in the conservative group compared to the conventional arm (37 vs. 39, respectively). Trial conductors used a modified intention-to-treat model was used that censored patients enrolled in the trial who left the ICU within 72 hours. Thus, 216 patients were included in the conservative analysis and 218 in the conventional group. With these caveats, conservative therapy led to an absolute risk reduction in ICU mortality of 8.6% (11.6% vs. 20.3% in the conservative vs. conventional groups, respectively; $P = 0.01$). With conservative oxygen therapy, there also were improvements in many secondary outcomes, including hospital mortality, shock, bacteremia, and mechanical ventilation-free hours. A subgroup post-hoc analysis of only patients on mechanical ventilation also demonstrated mortality benefit (absolute risk reduction 5%; 95% confidence interval, 0-9%).

■ COMMENTARY

At first, this study seems to indicate that targeting more modest SpO_2 goals of 94-98% may be beneficial to ICU patients. However, several caveats deserve mention. First, this study was terminated early due to factors beyond the control of the investigators, but early termination predisposes to overestimation of effect size. The study was not terminated due to pre-specified futility criteria as might affect other trials terminated due to safety concerns. While randomized, the conservative therapy arm clearly contained lower-acuity patients, and this could certainly influence the outcomes. Overall, there were few events in each arm, which also can affect the reliability of these data. However, this study shows trends similar to other studies of conservative vs. conventional oxygen delivery. The AVOID investigators demonstrated that supplemental oxygen administered to patients with acute ST-segment elevation myocardial infarction without oxygen desaturation led to larger infarct size and may increase early myocardial injury.[1] The PROXI trial demonstrated that higher FiO_2 during anesthesia for abdominal surgery led to an increased likelihood of infection.[2] In contrast, a smaller pilot study from the CLOSE and ANZIC inves-

tigators failed to show significant effects on mortality in mechanically ventilated patients.[3]

This study adds to the body of evidence that supplemental oxygen delivery without regard to need can be harmful. More importantly, this study seems to indicate that there is no strong indication to supplement SpO_2 levels close to 100%, and that patients with SpO_2 of 94% may not need supplemental oxygen in the ICU. Targeting more modest SpO_2 and PaO_2 goals clearly is not harmful and may lead to certain benefits. ■

REFERENCES

1. Stub D, et al. Air versus oxygen in ST-segment elevation myocardial infarction. *Circulation* 2015;131:2143-2150.
2. Meyhoff CS, et al. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery. *JAMA* 2009;302:1543-1550.
3. Panwar R, et al. Conservative versus liberal oxygenation targets for mechanically ventilated patients. *Am J Respir Crit Care Med* 2016;193:43-51.

CME/CE QUESTIONS

1. Each of the following patients with respiratory failure has an appropriate indication for ECMO support *except*:
a. an 80-year-old patient with stage IV lung cancer with metastatic disease, intubated for three weeks.
b. a 25-year-old patient with acute hypoxemic respiratory failure due to influenza.
c. a 40-year-old cystic fibrosis patient, listed for lung transplant, with acute hypercarbic respiratory failure.
d. a 50-year-old patient undergoing knee arthroscopy with acute intraoperative hypoxemia unresponsive to aggressive recruitment maneuvers, PEEP escalation, and prone positioning.
e. a 34-year-old motor vehicle accident patient with acute respiratory failure due to blunt chest trauma and pulmonary contusion.

2. Which of the following is an advantage of the bicaval dual lumen internal jugular ECMO cannula?
a. Facilitates mobility
b. Facilitates prone positioning
c. Facilitates ambulation
d. Can achieve 5-6 L blood flows
e. All of the above

3. In the BRAIN-ICU study, which of the following factors was found to be associated with decreased employment in survivors of critical illness?
a. Duration of ICU stay
b. Duration of delirium during ICU stay
c. Cognitive function at 12 months post-discharge
d. Cognitive function at three months post-discharge
e. Physical function at three months post-discharge

4. Which of the following is true of previously employed survivors of critical illness as described in the BRAIN-ICU study?
a. About half will return to prior levels of employment at 12 months after discharge.
b. Decreased physical function severely impairs ability to return to work at 12 months after discharge.
c. Good cognitive function at the time of discharge significantly increases one's ability to return to work.
d. Depression decreases an ICU survivor's ability to return to work.
e. A longer duration of delirium during the ICU stay predicts a lower likelihood of returning to work at 12 months.

5. The Oxygen-ICU study demonstrated that:
a. PaO_2 > 150 was beneficial.
b. PaO_2 of 100-150 improved mortality.
c. higher oxygen delivery was associated with increased bacteremia.
d. Both b and c
e. All of the above

6. When compared with patients administered conventional oxygen supplementation, patients with goal SpO_2 94-98% experienced:
a. longer ICU length of stay.
b. improved ICU mortality.
c. decreased surgical site infections.
d. increased hospital length of stay.
e. All of the above