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ABSTRACT & COMMENTARY

A New Paradigm in the Management of Massive and Submassive Pulmonary Embolism

By Elaine Chen, MD

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

SYNOPSIS: A multidisciplinary pulmonary embolism (PE) response team is a sustainable option to improve care for severe PE.

SOURCE: Kabrhel C, Rosovsky R, Channick R, et al. A multidisciplinary pulmonary embolism response team: Initial 30-month experience with a novel approach to delivery of care to patients with submassive and massive pulmonary embolism. *Chest* 2016;150:384-393.

Pulmonary embolism (PE) remains a common condition with high morbidity and mortality. Most cases are treated with systemic anticoagulation alone, but many other treatment options can be considered for severe cases. Real-time multispecialty discussion is required to integrate these treatments into clinical care.

To meet this need, a rapid response team was developed specifically for pulmonary embolism management, called the Pulmonary Embolism Response Team (PERT). The team included specialists in cardiology, cardiac surgery, echocardiography, emergency medicine, hematology, pulmonary/critical care, radiology, and vascular medicine. Upon activation, the team reviewed clinical data and conferred online in real time. After reaching a consensus, the team relayed the decision to the referring provider and mobilized recommended resources for interventions.

This report describes 30 months of data following initiation of the PERT. Confirmed PEs were characterized as massive (sustained hypotension or pulselessness), submassive (right ventricular dysfunction or myocardial necrosis without hypotension), or low

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risk (not meeting criteria for massive or submassive). Treatments recorded included anticoagulation, systemic IV thrombolysis, catheter-directed thrombolysis, suction thrombectomy, surgical thromboembolectomy, extracorporeal membrane oxygenation (ECMO), or inferior vena cava (IVC) filter placement that were delivered within three days of activation. In 30 months of measurement, the PERT was activated 394 times, increasing by 16% in each six-month measurement period. Most activations originated from the ED (58%), with the next most frequent from an ICU (20%). Three hundred fourteen (80%) patients had PE confirmed within three days of PERT activation. One hundred forty-three (46% of 314) were characterized as submassive, and 80 (25%) were characterized as massive. The majority of patients (69%) were treated with anticoagulation alone. Catheter-directed thrombolysis was utilized in 28 patients (9%), systemic IV thrombolysis in 14 (5%), surgical thrombectomy in eight (3%), and suction thrombectomy in one (0.3%).

Of the 80 patients with massive PE, 52 did not have a contraindication to thrombolysis, but 32 (62%) did not receive systemic, catheter-directed, or surgical thrombus removal. Bleeding complications occurred in 25 (8%) patients by day seven, and 11 (6%) patients between days eight and 30. More bleeding occurred in the IV thrombolysis group, but bleeding complications in the catheter-directed thrombolysis group were similar to those who received anticoagulation alone. Overall 30-day mortality was 12% (31/265) for those with confirmed PE, with higher mortality for those with massive PE compared with either submassive ($P < 0.001$) or low risk ($P = 0.04$). Those without confirmation of PE had the highest 30-day mortality of 49%.

This report represents the first longitudinal assessment of a new PE management paradigm. Adoption was immediate and sustained, and other national centers also have developed similar programs. Acknowledging differences between clinical data and registry data, the authors made a few comparisons. In the EMPEROR registry, 2% of PEs overall and 9% of PEs with hypotension were treated with thrombolysis, and in the ICOPER registry, 13% of PEs were treated with thrombolysis. At the current institution, prior to PERT initiation, 3% of PEs were treated with thrombolysis or thromboembolectomy. During the study period, 14% of patients overall and 23% of patients with massive PE were treated with some form of thrombolysis or thromboembolectomy, representing an increase in use of advanced therapies as a result of this formal process.

Establishing a PERT is an organizational process, requiring significant clinician effort and dedication as well as a high level of clinical service with 24-hour availability of rapid response teams, catheterization lab, and operating room services. The authors proposed that the PERT paradigm may come to represent a new standard of care for patients with PE.

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While systemic anticoagulation alone is an appropriate treatment for low-risk PE, deciding on the most appropriate therapy for massive or submassive PE remains unclear. With availability and evolution of advanced interventions with possibly as much clinical benefit but significantly lower risk compared with systemic thrombolysis, the decision is becoming more challenging. Novel catheter-directed therapies continue to be tested and refined, and there remains no gold standard of therapy. Institutional experience with these therapies also can have a significant effect on outcomes.[1,2]

This process has been widely copied, though probably in varying forms, at both large academic centers as described in this report, as well as in community hospitals.[3] In our institution, a similar program was established several years ago, because of recurrent retrospective discussions regarding the challenges to managing massive and submassive PE. Referring providers often had uncertainties about which consultant(s) to call, which therapies to request, managing multiple recommendations from different consultants, and coordinating next steps. With the initiation of our multidisciplinary team, the process of calling a

consulting team has been standardized, resulting in a streamlined process for the referring provider.

Many of the benefits of a PERT are intangible and difficult to measure. Optimal treatment is difficult to define, as so many therapies are simultaneously evaluated in clinical practice, with new techniques constantly evolving. Myriad clinical variables dictate which therapies can be offered to each patient.

The gold standard for diagnosis of PE has evolved recently from pulmonary angiogram to CT PE. Will the standard for treatment of massive and submassive PE similarly evolve? As yet, we have no standard for optimal treatment for acute submassive PE, so multidisciplinary, expert consensus, clinical decision making is perhaps the best substitute for now. ■

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ABSTRACT & COMMENTARY

Rehabilitation in the ICU: More Questions Than Answers

By Kathryn Radigan, MD

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

SYNOPSIS: In patients with acute respiratory failure, standardized rehabilitation therapy consisting of passive range of motion, physical therapy, and progressive resistance exercise did not decrease hospital length of stay compared to usual care.

SOURCE: Morris PE, Berry MJ, Files DC, et al. Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: A randomized clinical trial. *JAMA* 2016;28;315:2694-2702.

Patients who survive acute respiratory failure often endure impaired physical function for years after their critical illness. Physical therapy in the ICU may improve the outcomes of patients with acute respiratory failure. To evaluate the benefits of physical therapy, Morris et al conducted a single-center, randomized clinical trial at Wake Forest Baptist Medical Center in North Carolina. From October 2009 through May 2014, adult patients who were admitted to the ICU with acute respiratory failure requiring mechanical ventilation (PaO_2/FiO_2 < 300) were randomized to standardized rehabilitation therapy (SRT) or usual care and followed for six months. Exclusion criteria included inability to walk without assistance prior to ICU admission, cognitive impairment prior to admission to ICU, body mass index > 50 kg/m^2, neuromuscular disease that may impair ventilator weaning, acute hip fracture/unstable cervical spine fracture, mechanical ventilation > 80 hours or existing hospitalization > 7 days, patients with do-not-intubate (DNI) orders, or moribund state. For the duration of their admission to the hospital, SRT patients received daily therapy, including passive range of motion, physical therapy, and progressive resistance exercise. Usual care patients received weekday physical therapy when ordered by the clinical team. If the patient was unconscious, the sessions consisted of passive range of motion. The median days of delivery of therapy for the SRT group was 8.0 (IQR 5.0-14.0) for passive range of motion, 5.0 (IQR 3.0-8.0) for physical therapy, and 3.0 (IQR 1.0-5.0) for progressive resistance exercise. For the usual care group, the median days of physical therapy was 1.0 (IQR 0.0-8.0). Patients underwent blinded assessment at ICU discharge, at hospital discharge, and at two, four, and six months. The primary outcome was hospital length of stay (LOS) with secondary outcomes including ventilator days, ICU days, Short Physical Performance Battery (SPPB) score, Functional Performance Inventory (FPI) score, Mini-Mental State Examination (MMSE) score, handgrip and handheld dynamometer strength, 36-item Short-Form Healthy Surveys (SF-36) for physical and mental health, and physical function scale score.

Three hundred patients were randomized with no difference in median hospital LOS between the SRT group (median 10 days, IQR 6-17) and usual care

group (median 10 days, IQR 7-16; median difference 0; 95% confidence interval [CI], -1.5 to 3; *P* = 0.41). There also was no difference in duration of mechanical ventilation or ICU care and no effect at six months for handgrip (difference, 2.0 kg; 95% CI, -1.3 to 5.4; *P* = 0.23) and handheld dynamometer strength (difference, 0.4 lb; 95% CI, -2.9 to 3.7; *P* = 0.82), SF-36 physical health score (difference, 2.4; 95% CI, -1.2 to 6.0; *P* = 0.19), and MMSE score (difference, 0.6; 95% CI, -0.2 to 1.4; *P* = 0.17). At six months, the SRT group scored higher on the SPPB (difference, 1.1; 95% CI, 0.04-2.1; *P* = 0.04), SF-36 physical function scale (difference, 12.2; 95% CI, 3.8-20.7; *P* = 0.001), and the FPI (difference, 0.2; 95% CI, 0.04-0.4; *P* = 0.02). In summary, SRT consisting of passive range of motion, physical therapy, and progressive resistance exercise did not decrease hospital length of stay compared to usual care.

■ COMMENTARY

Approximately 50% of critically ill patients with sepsis, multi-organ failure, or prolonged respiratory failure exhibit protracted muscular weakness that often persists after hospital discharge.[1] Within the last decade, the practice of placing critically ill patients on bed rest, often in a medication-induced coma, has been transformed to seeing mechanically ventilated patients ambulating around the ICU, all in an attempt to transform long-term outcomes in this patient population. A number of studies have addressed both the benefits and safety of physical therapy in the ICU. However, these same studies have raised questions about the timing, quantity, and type of rehabilitation that would be most beneficial for specific groups of ICU patients. To further investigate the benefits of rehabilitation in the ICU setting, Morris et al conducted a randomized, clinical trial comparing early daily delivery of a structured, multifaceted ICU and hospital rehabilitation program to usual care. Unfortunately, the researchers found there were no differences in hospital length of stay, ventilator-free days, or ICU-free days. Furthermore, functional-related and health-related quality of life outcomes were similar for both the SRT and usual care groups at discharge.

Despite no differences in outcomes between the two groups, there was substantially more exercise delivered and performed in the SRT group vs. the usual care group. The usual care group received physical therapy for only 12% of the study days while the SRT group received passive range of motion for 87% of the study days, physical therapy for 55% of the study days, and progressive resistance exercise for 36% of the study days. Although the benefit of this therapy was not obvious at hospital discharge, there were differences in physical function measures (SPPB, SF-36 PFS, and FPI) at six months. Perhaps, outcomes of critically ill patients who undergo physical rehabilitation in the ICU should be measured at six months or even one year after their critical illness. Of course, following patients for longer periods of time would have to be tempered by the possibility of higher dropout rates, which already were higher than expected for this study, with 24% lost to follow-up or withdrawals.

Unfortunately, a significant limitation of this study was the lack of a standardized sedation protocol. Within the intervention group, 30% of the patients' ventilator days were associated with continuous drip medications, and for 15% of the ventilator days, the patients were unarousable. It has been well described how difficult it is to institute a successful mobility program without a significant change in culture, including an aggressive sedation protocol addressing treatment of delirium and limitation of sedative medications. Although a culture change may be initiated in a variety of ways, the ABCDE Initiative has been successful and outlines straightforward tenants to be aggressive and successful with this culture change. The ABCDE bundle includes implementing the Awakening and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility (ABCDE) bundle on a daily basis.[2] Compared to a control group, patients who underwent the ABCDE bundle spend more days breathing without mechanical ventilation, experience less delirium, and increase their odds of mobilizing out of bed at least daily compared to pre-bundle patients. It remains a concern that the patients in the Morris et al study underwent no sedation protocol. A different trial by Schweikert et al highlighted this concern as they were able to show that interruption of sedation along with physical and occupational rehabilitation is most important during mechanical ventilation, specifically within a median of 1.5 days after intubation.[3] Despite the same amount of daily physical therapy after mechanical ventilation, the intervention group received an average of 19 minutes of physical therapy per day during mechanical ventilation while the control group received no physical therapy until after extubation. Although the Morris et al study does not reveal at what time point the patients received physical therapy, it appears there was a delay that was more than ideal, with patients receiving physical therapy on average five days into their 10-day hospital stay.

Although the exact prescription of rehabilitation and the best time to measure outcomes may still be in question, it makes sense that patients would benefit from physical therapy in the ICU setting. This study was helpful in highlighting the need for cul-

ture change in our ICUs with an aggressive sedation protocol. It also highlighted the benefit of measuring longer-term outcomes in our patients. However, this study also should challenge us to continue to ask questions, namely, which critically ill patient should receive what type of rehabilitation at what stage in his or her illness and for what period of time? ■

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ABSTRACT & COMMENTARY

Should We Use Non-invasive Ventilation to Treat Acute Respiratory Distress Syndrome?

By Richard Kallet, MS, RRT, FCCM

Director of Quality Assurance, Respiratory Care Services, San Francisco General Hospital

Mr. Kallet reports no financial relationships relevant to this field of study.

SYNOPSIS: Managing acute respiratory distress syndrome (ARDS) with non-invasive ventilation was associated with increased failure as the severity of ARDS increased.

SOURCE: Bellani G, Laffey JG, Pham T, et al. Non-invasive ventilation of patients with ARDS: Insights from the LUNG SAFE study. *Am J Respir Crit Care* Med 2016 Oct. 18 [Epub ahead of print].

This study was a subset analysis from a larger multinational observational study of adult patients presenting with acute hypoxemic respiratory failure. Those meeting the Berlin definition of acute respiratory distress syndrome (ARDS) within two days of acute hypoxemia onset and who received non-invasive ventilation (NIV) during the first two days of ARDS were studied. Patients who required invasive mechanical ventilation (MV) on ARDS day one were classified as invasive MV only. NIV failure was defined as those requiring invasive MV after day two of NIV for ARDS. Data were collected once daily during a reference period. Patients were followed until death or hospital discharge. Analysis was restricted to those without imposed care limitations prior to initiating NIV or invasive MV.

Only 18% of ARDS patients received NIV on day one, and 15.5% were managed with NIV on both ARDS days one and two. Of these, 28% were managed with continuous positive airway pressure only. Those initially managed with NIV were older and had a higher prevalence for comorbidities (e.g., chronic renal failure, congestive heart failure, chronic obstructive pulmonary disease) that coincided with delayed recognition of ARDS compared to those managed with invasive MV. Moreover, NIV was associated with lower positive end-expiratory pressure (PEEP), higher tidal volume (V_T), and higher respiratory frequency.

NIV failure occurred in 37.5% of patients and was independently associated with increased non-pulmonary organ failure scores, lower arterial oxygen partial pressure to inspired oxygen fraction (PaO_2/FiO_2) and increased arterial carbon dioxide partial pressure ($PaCO_2$). When compared to those successfully managed with NIV, those who failed NIV had a substantially higher mortality (10.6 vs. 42.7%, $P < 0.001$). Although there were no differences in either ICU or hospital mortality between those managed with NIV vs. invasive MV, Cox regression modeling adjusting for comorbidities demonstrated an independent association between NIV and ICU mortality. Moreover, matched comparisons between cohorts according to a PaO_2/FiO_2 cutoff < 150 mmHg found a significantly higher mortality in those receiving NIV vs. invasive MV (36.2% vs. 24.7%, $P = 0.033$).

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In this study, NIV was attempted in < 20% of ARDS patients with an approximately 62% success rate, suggesting clinician bias favoring conservative application. Similar studies found lower NIV success rates (39%, 54%, 56%).[1-3] NIV success also decreased with increasing ARDS severity from 78% to 58% to 53% (for mild, moderate, and severe forms, respectively). Similar studies also have reported that increasing ARDS severity corresponds with decreasing NIV success rates of 81%, 27%, 17% and 69%, 38%, 16% for mild, moderate, and severe forms, respectively.[1-3]

That those with moderately severe to severe ARDS (i.e., PaO_2/FiO_2 < 150 mmHg) failing NIV had a substantially higher mortality than those managed on invasive MV reinforces previous concerns about utilizing NIV for ARDS. The effectiveness of NIV in self-limiting, readily reversible forms of acute respiratory failure does not necessarily translate to ARDS, which can rapidly progress and require weeks of mechanical ventilation. In addition, the difficulty in applying higher levels of PEEP and precisely controlling V_T in NIV likely increases the susceptibility to ventilator-induced lung injury. Moreover, the relatively prolonged course of ARDS raises other concerns with long-term use of NIV: severe skin ulceration (now publicly reportable), maintaining adequate nutritional intake, and increased aspiration risk associated with discoordinated swallowing during elastic loading of the respiratory muscles.[4]

In summary, previous recommendations regarding NIV in ARDS remain highly relevant; it should be restricted to milder manifestations and abandoned quickly in favor of invasive MV if it fails to stabilize gas exchange and reverse respiratory distress within a few hours. ■

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ABSTRACT & COMMENTARY

High-flow Nasal Cannula vs. Noninvasive Ventilation in Postextubation Failure: Does It Matter?

By Betty Tran, MD, MSc, Editor

SYNOPSIS: In this multicenter, randomized, clinical trial of critically ill adults at high risk for reintubation, high-flow conditioned oxygen therapy was not inferior to noninvasive mechanical ventilation with regard to preventing reintubation and postextubation respiratory failure within 72 hours of extubation.

SOURCE: Hernandez G, Vaquero C, Colinas L, et al. Effect of postextubation high-flow nasal cannula vs noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: A randomized clinical trial. *JAMA* 2016;316:1565-1574.

This was a multicenter, randomized, noninferiority trial in Spain between 2012-2014 in which patients from three ICUs were screened for inclusion in the study if they were ready for extubation with at least one risk factor that deemed them high risk for reintubation: age > 65 years, heart failure as the primary indication for mechanical ventilation, moderate-severe COPD, an Acute Physiology and Chronic Health Evaluation II (APACHE II) score > 12 on extubation day, body mass index > 30 kg/m^2, airway patency problems (e.g., high risk of developing laryngeal edema), inability to deal with respiratory secretions, difficult/prolonged weaning, failing first attempt at extubation, more than two comorbidities, and mechanical ventilation for more than seven days. Patients who passed their spontaneous breathing trial and underwent extubation were randomized to receive noninvasive ventilation (NIV) or high-flow conditioned oxygen to begin immediately after extubation for a duration of 24 hours before switching to conventional oxygen therapy, if needed. NIV was delivered via full face mask with settings adjusted to target a respiratory rate of 25 breaths/minute and adequate gas exchange (arterial oxygen saturation [SpO_2] of 92%, pH 7.35). Notably, sedation to help increase tolerance to NIV was not allowed. High-flow oxygen was initiated with a flow of 10 L/minute and titrated up by 5 L/minute steps until patients experienced discomfort; FiO_2 was adjusted to maintain an SpO_2 of 92%. The primary outcomes were reintubation after extubation and postextubation respiratory failure within 72 hours defined by any of the following: pH < 7.35 with $PaCO_2$ > 45 mmHg, SpO_2 < 90% or PaO_2 < 60 mmHg at FiO_2 > 0.4, respiratory rate > 35 breaths/minute, decreased level of consciousness, agitation, or clinical signs of respiratory fatigue or increased work of breathing. Secondary outcomes included respiratory infection, sepsis, or multiple organ failure, ICU and hospital length of stay, and

mortality, and the reason for failure of the assigned treatment, if applicable (e.g., patient discomfort requiring withdrawal of the therapy for more than six hours, nasal septum, or skin trauma). Noninferiority was established if the between-group difference in treatment failure rates was < 10%.

After screening 1,211 adults on mechanical ventilation for > 12 hours, 604 were randomized: 290 to high-flow oxygen and 314 to NIV. There were only two dropouts in each group. Both groups were similar except for a lower incidence of heart failure in the high-flow oxygen group and a higher incidence of surgical diagnoses in the NIV group. High-flow oxygen was noninferior to NIV, with reintubation occurring in 60 patients (19.1%) in the NIV group compared to 66 patients (22.8%) in the high-flow oxygen group (risk difference, -3.7%; 95% confidence interval [CI], -9.1% to infinity). More patients in the NIV group experienced postextubation respiratory failure within 72 hours than in the high-flow oxygen group (39.8% vs. 26.9%; risk difference, 12.9%; 95% CI, 6.6% to infinity). Median time to reintubation was not significantly different in the two groups. In terms of secondary outcomes, median ICU length of stay was lower in the high-flow oxygen group compared to the NIV group (3 days vs. 4 days; IQR, 2-9; $P = 0.048$), but other secondary outcomes were similar between the two groups.

■ COMMENTARY

This study adds to the growing literature on the role of noninvasive approaches to reducing the need for reintubation in respiratory failure. The benefits of avoiding reintubation if possible include shorter ICU stays and reduced morbidity and mortality, mainly attributable to nosocomial infection.[1] The role of NIV in postextubation respiratory failure has been debated, with some studies showing no benefit or even harm with regard to delaying reintubation and others reporting improved outcomes in patients specifically with COPD and hypercapnia.[2-4] A more recent study by Jaber et al found that NIV use reduced the seven-day reintubation rate compared to standard oxygen therapy in a population of patients undergoing major abdominal surgery, although the NIV group contained more COPD patients, which may have skewed the findings.[5] With regard to high-flow oxygen therapy, the same group led by Hernandez et al previously reported that compared to standard treatment with oxygen, high-flow nasal cannula reduced the risk of reintubation within 72 hours among a group of patients at low risk for reintubation.[6]

The question of whether to use one modality over the other, however, remains unanswered. In addition to the current study, Stephan et al reported that high-flow nasal cannula was not inferior to NIV in a population of postoperative cardiac surgery patients in reducing the rate of reintubation, crossover to the other study therapy, or early discontinuation of treatment.[7] It seems intuitive that high-flow nasal cannula may be the easier alternative with regard to patient comfort, tolerability, and longer-term continuous use (to avoid facial skin breakdown and allow for oral intake), although whether it can be used with similar effect with NIV will need to be evaluated in different patient populations.

There are several other issues to keep in mind. First, these studies are randomized, but it is impossible to blind them; specific, predefined clinical criteria with regard to postextubation failure does help reduce bias. Second, these studies are conducted in experienced centers, and the results may not be reproducible in the community at large. Finally, based on the data we have, we still do not know the optimal settings and durations of use for NIV and high-flow oxygen in the postextubation setting. The two groups in this study contained patients on these therapies for no more than 24 hours, and in the NIV group, the total time under NIV was only 14 hours (IQR, 8-23). As the authors noted, although longer usage of these modalities may improve extubation success, it may run the risk of delaying reintubation when necessary. At this time, it is difficult to make specific recommendations or guidelines for the use of either high-flow oxygen or NIV as a part of the management of postextubation respiratory failure given these uncertainties. ■

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CME/CE QUESTIONS

1. For patients with confirmed pulmonary embolism characterized as massive, a Pulmonary Embolism Response Team resulted in:
a. an increase in use of systemic thrombolysis to 50% of patients without any contraindication.
b. an increase in use of some form of thrombolysis or thrombectomy to 23%.
c. a decrease in hemorrhagic complications in 30 days to 3%.
d. a decrease in 30-day mortality from 49% to 12%.
e. a decrease in one-year incidence of persistent right heart strain to 15%.

2. To execute a successful critical care rehabilitation program, the hospital should implement:
a. an aggressive protocol to minimize sedation use.
b. a standardized physical therapy prescription with the same plan of care for every patient.
c. aggressive inhaler therapy.
d. Both a and b.
e. None of the above

3. Which of the following statements is true regarding the Bellani study?
a. Less than 20% of patients were managed with noninvasive ventilation (NIV).
b. The overall NIV success rate was 85%.
c. NIV was associated with higher positive end-expiratory pressure and lower tidal volume delivery.
d. Hospital mortality was similar between those managed with NIV and invasive mechanical ventilation.
e. Both a and d

4. Which of the following is true in the study by Hernandez et al?
a. High-flow nasal cannula is noninferior to noninvasive ventilation in patients at high risk for postextubation respiratory failure.
b. In patients at high risk for postextubation respiratory failure, noninvasive ventilation is preferred if they have chronic hypercapnia.
c. High-flow nasal cannula is superior to noninvasive ventilation in patients requiring these therapies for longer than 24 hours.
d. Patients in the high-flow nasal cannula group demonstrated more delayed times to reintubation compared to the noninvasive ventilation group.
e. None of the above

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify relevant topics in the practice of critical care medicine;
- utilize recommendations from current clinical guidelines; and
- manage common critically ill patient and ICU administration scenarios.

Critical Care [ALERT]

Authoritative, evidence-based summaries for the critical care clinician

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