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SPECIAL FEATURE

Ethics in the ICU: Negotiating Requests for Inappropriate Treatments

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In today's world of technology and constant advancement in medicine, critical care practitioners are often asked to provide more, to provide miracles, to keep loved ones alive. We even may feel like we are asked to bring loved ones back to life. These complex situations lead us to pause and ask: What is appropriate and what is not? What is beneficial, what causes more harm than benefit, what is futile? When asked to provide treatments and therapies that may be inappropriate, how should we respond?

FUTILE OR POTENTIALLY INAPPROPRIATE?

In medicine, the word "futile" is challenging and emotionally laden. Strictly speaking, futile interventions cannot accomplish the intended physiologic goal.[1] Because people often transfer their own interpretation of quality of life onto what therapies might be considered "futile," there have been efforts by ethicists and critical care clinicians to avoid this term, replacing it with "potentially inappropriate" instead.[2,3]

When considering potentially inappropriate medical treatments, it is important for clinicians to reflect on the physiologic intent, transference of values, laws and legal precedents, and scope of practice. Some therapies may offer some short-term or even medium-term benefit; however, long-term impact remains less clear. We question the cost/benefit ratio, the extent of suffering the patient will endure, and the quality of life that the patient may experience, if they survive, projecting our values onto the patient and family.

An example of a potentially inappropriate intervention could include requesting amputation of the left leg as treatment for a pneumonia; this would not be considered appropriate because it is not indicated and would cause harm. Similarly, why would it be acceptable to give chemotherapy to a patient in whom it would almost be guaranteed to shorten life? Performing cardiopulmonary resuscitation (CPR) on a body in rigor mortis would be absolutely

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futile. Thus, I would propose that CPR on a person on maximal vasopressor support and mechanical ventilation would also be considered physiologically futile. Some would argue that this could be a slippery slope of describing when CPR would be futile and favor the term "legally discretionary," where there exist specific laws that allow physicians to say no to treatments and procedures which are generally accepted to have minimal benefit and legal precedent.[3,4] For example, a patient has worsening septic shock and escalating vasopressor need, but oxygenation and ventilation are maintained. In more of a palliative care setting, a patient with advanced metastatic cancer may have terminal delirium but acceptable hemodynamics and respiratory status. Would it be appropriate to withhold intubation and CPR in these patients? Many, but not all, clinicians would agree that would be appropriate given a known irreversible cause, but physiologically, short-term life prolongation might possibly be achieved with resuscitation. The laws vary from location to location, but they may involve foregoing CPR in situations when there is a reasonable certainty that it will not have its intended effect.

In contrast, consider the actively drinking patient with cirrhosis whose family requests liver transplantation and asks the team to override organ allocation protocols, which is illegal. Requests of this nature can be described as "legally proscribed," or treatments and protocols that are not legal for clinicians to provide. Assuming documentation of laws and policies can be provided to the family, a simple statement that the request is against the law would be a clear and appropriate response.

Alternatively, a patient with anoxic encephalopathy but normally functioning organs is protecting their airway. The family does not desire to pursue artificial nutrition or hydration, signs a do not resuscitate/do not intubate/physician orders for life-sustaining treatment (DNR/DNI/POLST) order, and asks the team to give the patient an extra-large dose of opioid to allow the patient to die more quickly. Although comfort medications are ethically appropriate in end-of-life situations by the principle of double effect, the intention and dose must be for symptom management and not to hasten death.[5] If the goal is for hastening of death, this is ethically inappropriate and, in fact, illegal in this context.

Requests for potentially inappropriate treatments in the intensive care unit (ICU) often occur near the end of life and may have the intention of prolonging life or hastening death. Responding to these requests can be challenging, unpleasant, or even fear-inducing. To help clinicians navigate these situations, the American Thoracic Society, in collaboration with several other professional societies, created a policy statement for responding to requests for potentially inappropriate treatments in intensive care units.[4]

THE IMPORTANCE OF COMMUNICATION

At the heart of many challenging end-of-life situations is the family's love for the patient. Good communication in the ICU is essential to ensure that the care delivered aligns with the patient's, or surrogate's, goals of care, and to maintain a firm line when faced with requests for therapies that are inappropriate.[6-9] Often these requests for inappropriate treatment are simply cries for help, a desire to be heard and valued.

Good communication also is paramount to build trust and negotiate the conflict that often is associated with requests for inappropriate treatment. Initial establishment of strong trust and good communication between the medical team and the family can temper requests for inappropriate treatments.[10] Improving communication requires time and effort, with tools that most clinicians already have; most significant is a listening ear.

To start, take some extra time to listen to the family. Ask about the patient as a human, ask what they love to do. Ask if they have ever talked to the patient about end-of-life issues or life-prolonging therapies. Ask what the family is hoping for, what they expect, and what they are worried about. Then, align the medical team with the patient and family rather than antagonizing. I have heard members of the clinical team tell me that the family "doesn't understand" or "has unrealistic expectations." Rather,

understand that families are using hope and optimism as a coping mechanism. Acknowledge that loss and change are hard, and emphasize that the medical team's goal also is to preserve and recover life. The "I wish" statement is a tool that can be employed effectively in these situations: "I wish we could make her better," "I wish we had additional treatments to offer," "I wish things were different."[11] Offer support to the family, validate and normalize the emotions they are feeling, empathize, and allow silence. Table 1 summarizes some take-home communication pearls.

Tailoring communication to the preferred decision-making style of the family also can improve communication. The spectrum of shared decision-making ranges from an autonomous style, driven by the patient and family, to a more paternalistic or parentalistic style, where patients and surrogates cede authority to providers.[9,12-15] Most patients and families will fall somewhere in the middle of this continuum in the decision-making process. Clinicians should adapt the decision-making model to the needs and preferences of the patient or surrogate. However, in the setting of requests for inappropriate treatments, the physician has a firm obligation to offer only clinically and ethically appropriate options.

When treatment alternatives are not being offered, particularly in the case of CPR, common communication approaches include the concepts of informed non-dissent or informed assent.[16-20] With informed non-dissent, a family is notified of a decision (such as a DNR order) that will be put in place if they do not object. With informed assent, a family is notified, for example, that CPR will not be performed because it will not work, and given an opportunity to acknowledge understanding. In this model, the family is not given an option to object. These methods of communication may ease the burden on families who feel they are being tasked with a difficult or impossible decision.

The discussion of appropriate or inappropriate CPR is a subject of ongoing evolution. I once interacted with an awake patient who repeatedly requested "one round of CPR" at the time of cardiac arrest or death. She was alert and fully cognizant; she worked in healthcare with a partial understanding of the nature of CPR. She had advanced metastatic cancer and was near death, but it was not imminent. Our medical team had multiple discussions about the ethics of providing partial CPR and the moral distress associated with being asked to inflict unnecessary and non-beneficial suffering to honor the patient's explicit wishes.

In contrast, I spoke with the mother of a young patient with a very new and devastating diagnosis of hematologic malignancy, who rapidly required escalating mechanical ventilation and vasopressors. She strongly emphasized that she wanted "everything" done to save her son. We gave him everything we possibly had, counseled his mother as such, and told her we would not perform CPR. She very gratefully but tearfully assented to the DNR order. If assent cannot be obtained, unilateral DNR policies can be considered, depending on the policies and laws of the hospital and state.

Table 1: Communication Pearls

- Take extra time to listen.
- Ask about the patient as a person.
- Ask about hopes, expectations, and fears.
- Align the medical team with the family.
- Acknowledge that loss and change are hard.
- Use statements such as, "I wish things were different."
- Tailor communication to the decision-making style of the family.
- Use informed assent or informed non-dissent when not offering alternatives.

A RECOMMENDED PROCEDURAL RESOLUTION PROCESS

If communication fails to resolve a conflict, American Thoracic Society guidelines recommend the following procedural resolution process.[4] The first step in this process is to involve expert consultation. This could be an ethics consultation or a palliative care consultation, if they are not yet involved. These guidelines also recommend informing the surrogates in writing when this process is started. Consultation from ethics committees may vary among institutions, depending on the scope, makeup, and availability of the committee members. These members of ethics committees may include physicians from various specialties, chaplains, attorneys, ethicists, psychologists, or nurses. Unlike medical consultation, which a provider must request, ethics consultation often can be requested by any member of the healthcare team, a patient, or a family member. An ethics consultation generally will involve gathering medical information and applying it to an ethical framework. Potential benefits and risks to involved parties should be weighed. The four box or four topic approach is a common ethical framework that may be applied.[21,22] The four topics to be considered are medical indications, patient preferences, quality of life, and contextual features. Using this framework, an ethics team may consider core principles, frame an ethics question, and offer a list of ethical options. An ethics consultation may be beneficial even if the family members and physician have come to consensus to help staff who may be struggling with moral distress or compassion fatigue to better understand the issues and decisions.

If, after expert consultation, consensus has not been reached, the next step is to obtain a second opinion. This

should be an independent clinician with appropriate expertise in the patient's condition and prognosis. Practically, I might consult with another clinician in my institution, or the family might request that medical records be sent to another institution or ask that I speak with an outside team and solicit their recommendations.

The next step detailed in the guidelines is to perform a review by an interdisciplinary hospital committee. This committee should not include treating clinicians and should offer clinicians and family members an opportunity to share their perspectives. In the fast-paced clinical environment of the ICU, this is not common.

Requesting transfer to a different institution is the next step and is pursued more commonly. The transfer process can vary in practice between institutions and also may depend on the type of institution. If families obtain the name and contact information of a physician or hospital who has accepted the case, our hospital transfer center will facilitate the transfer. Sometimes, families may obtain the name and contact information of a physician or hospital who would be willing to hear about the case from me, and I discuss the case to see if they are willing to accept. Surrogates should be informed of their right to pursue an extramural appeal, such as through the judicial system. After this full process has been completed, the decision then can be implemented. If the committee agrees with the clinician, then the disputed treatments may be withheld or withdrawn, with a care plan to include ongoing provision of indicated treatments as well as comfort to the patient.

CONCLUSION

In summary, a proactive approach should be taken to handle requests for potentially inappropriate treatments in the ICU. Communication with the patient and family should begin at the time of ICU admission to gain trust and develop rapport. When requests for potentially inappropriate treatments occur, the initial steps include increasing communication and improving mutual understanding to find a path that is ethically and legally appropriate while honoring the goals and concerns expressed by patients and their families. If requests persist and conflict develops despite these communication strategies, clinicians should seek external assistance in a stepwise fashion. These steps may include obtaining a second opinion from colleagues, institutional ethics consult, external review, extramural appeal, and seeking transfer to another facility. ■

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ABSTRACT & COMMENTARY

Prone Positioning May Improve Outcomes for Patients on ECMO for Severe ARDS

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SYNOPSIS: In patients on venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome, prone positioning is safe and feasible. Prone positioning appears to improve survival but increases length of stay.

SOURCE: Giani M, Martucci G, Madotto F, et al. Prone positioning during venovenous extracorporeal membrane oxygenation in acute respiratory distress syndrome. A multicenter cohort study and propensity-matched analysis. *Ann Am Thorac Soc* 2021;18:495-501.

Prone positioning (PP) has shown benefits in patients with refractory hypoxemia from acute respiratory distress syndrome (ARDS).[1] The EOLIA trial demonstrated extracorporeal membrane oxygenation (ECMO) can be used for patients with progressive hypoxemia or hypercarbia despite PP and other therapies for ARDS.[2] The current paper is a retrospective, multicenter cohort study to assess the feasibility and efficacy of PP in patients on venovenous ECMO (VV-ECMO). The authors compared patients from four centers where PP is performed routinely on VV-ECMO patients with patients from two other centers where VV-ECMO patients remain supine. All patients underwent lung protective ventilation with driving pressures < 10 cm H_2O to 12 cm H_2O, respiratory rate < 20 breaths/minute, and moderate positive end-expiratory pressures (PEEP).

Of the 240 patients on VV-ECMO studied, 107 underwent PP and 133 remained supine. Patients were mostly male (65%) with an average age of 48-49 years. Pneumonia was the predominant cause of ARDS (91% to 92.5%). The partial pressure of oxygen to fraction of inspired oxygen (P/F) ratio of patients before ECMO in the PP and supine groups was 73 and 76, respectively, and each group had undergone an average of two days of mechanical ventilation before being placed on ECMO. The PP group first underwent proning on average four days from the start of ECMO. Notable differences between the two groups included a higher rate of acute kidney injury requiring dialysis in the PP group (15.9% vs. 6.8%), while the supine group had higher rates of hypertension (34.6%), immunodeficiency (22.6%), and asthma-chronic obstructive pulmonary disease (12.78%) than the PP group (20.6%, 14%, and 6.4%, respectively).

The study endpoints included evaluation of the safety of PP in ECMO patients as well as effects on gas exchange, respiratory mechanics, mortality, and length of stay. In the 107 PP patients, there were 21 reported complications, including eight desaturations, four bleeding episodes, and four decreases of ECMO blood flows, as well as one episode each of thigh swelling, face swelling, and vomiting. The most notable changes in respiratory and hemodynamic parameters with PP included improvements in P/F ratio and partial pressure of arterial oxygen (PaO_2), and a decrease in pulmonary shunt fraction. Plateau pressure (Pplat), driving pressure, and PEEP were not statistically different before and after prone positioning, although tidal volumes increased 12 mL and respiratory system compliance (Crs) increased from 23 ± 14 mL to 25 ± 15 mL/cm H_2O ($P = 0.038$). Mortality at hospital discharge decreased significantly in the PP group compared with supine patients (34% vs. 49.6%; $P = 0.017$). In contrast, the median duration of ECMO support and intensive care unit (ICU) length of stay (LOS) increased in patients in the PP group compared with supine patients (six days vs. nine days, respectively).

■ COMMENTARY

When considered in the context of other studies, this report adds to our understanding of the optimal management of patients with severe ARDS. The interpretation of this study by itself is limited by its retrospective and multicenter cohort design. As discussed by the authors, patients in the PP and supine groups were located in separate institutions. While all belonged to the Italian National Network for the Treatment of Acute Respiratory Failure, there were no strict ventilatory protocols within the trial, which raises the potential for confounding variables. The two groups differed in important parameters, as discussed earlier, including large differences in the rates of immunosuppression and active malignancy. To reduce this confounding, the authors performed a propensity-matched analysis of a smaller cohort of patients within the trial and re-demonstrated a mortality benefit of PP vs. supine position (30% vs. 53%; $P = 0.024$). The rates of complications were low, and the use of PP in VV-ECMO patients appears safe.

Other studies have evaluated the effect of PP on mortality and LOS in patients with severe ARDS with mixed results. One retrospective analysis of 158 patients failed to demonstrate significant differences in hospital survival or rates of ECMO weaning.[3] This study had significantly higher rates of fungal and pneumocystis infection within the PP group, implying differences in immunosuppression that might confound the analysis. Early prone positioning (within 17 hours of ECMO) was associated with improved outcomes in this study, although the PP group tended to be on mechanical ventilation longer before ECMO than the supine group. Retrospective re-analysis of the randomized EOLIA trial comparing outcomes of patients on VV-ECMO who underwent PP demonstrated significantly improved 30- and 60-day survival compared to patients who remained supine (43% vs. 71%; $P < 0.001$; and 40% vs. 62%; $P = 0.004$, respectively).[4] Most recently, a retrospective study of patients with SARS-CoV-2-induced ARDS showed a mortality benefit of PP vs. supine position (56% vs. 78.6%, respectively; $P = 0.02$).[5] None of these studies reported significant changes in Pplat, driving pressures, or Crs, raising the question of how PP improves mortality. However, a growing body of retrospective evidence supports the use of PP in ARDS patients treated on VV-ECMO.

Overall, this study suggests PP may be safe for patients undergoing VV-ECMO for the treatment of ARDS. Mechanistically, the reason for improved outcomes with PP remains unclear. The apparent improvement in mortality in patients proned on VV-ECMO for ARDS must be weighed against the clear increase in ECMO resource utilization and hospital LOS that would increase strain on the healthcare system as a whole. ■

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ABSTRACT & COMMENTARY

The Effect of Antiviral Drugs on COVID-19 Outcomes and Mortality

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SYNOPSIS: The WHO Solidarity Trial Consortium found that remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had "little or no effect" on relevant outcomes.

SOURCE: WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed antiviral drugs for COVID-19 — Interim WHO Solidarity Trial Results. *N Engl J Med* 2021;384:497-511.

The Solidarity Trial Consortium sponsored by the World Health Organization (WHO) randomized inpatients with COVID-19 equally among one of the following five drug regimens and the local standard of care: remdesivir (2,750 patients), hydroxychloroquine (954 patients), lopinavir alone (1,411 patients), interferon beta alone (2,063 patients), and lopinavir plus interferon beta (651 patients). The patients were randomized in 405 hospitals and in 30 countries. The trial was open-label, and no placebos were used. The controls were assigned to the local standard of care where the drug that was being randomized was available. The only exception was lopinavir plus interferon beta, where the control group was lopinavir alone. Some institutions had multiple drugs available, and in these institutions, patients assigned to the control group served as controls for each of the drug groups available. Written informed consent was provided by patients or their designees. National monitors were in place to resolve questions about trial strategy or drug adverse effects. One-third of total patients randomized were younger than age 50 years, and 19% were older than age 70 years. One-third were not receiving any oxygen at the time of study entry, and only 8% were mechanically ventilated; the rest received varying amounts of supplemental oxygen. Overall, 62% were male.

The primary outcome was in-hospital mortality for each intervention/control group, in addition to analyses of in-hospital mortality stratified by age and use of mechanical ventilation. Prespecified secondary outcomes included the need for mechanical ventilation among those not requiring support at the start of randomization, duration of mechanical ventilation, and hospital length of stay. All treatments lasted a maximum of 14 days. The results were mostly disappointing, with no drug (or drug combination in the case of lopinavir plus interferon beta) associated with either a reduction in mortality or a favorable outcome with respect to the secondary outcomes. Importantly, none of the trial interventions reduced the need for mechanical ventilation.

■ COMMENTARY

This ambitious worldwide trial failed to demonstrate any mortality reduction of antiviral therapy (remdesivir, lopinavir, or interferon beta) or treatment with drugs repurposed to treat COVID-19 infection (hydroxychloroquine). The lack of benefit was consistent across age groups and disease severity (i.e., including requirements for oxygen, mechanical ventilation, or extracorporeal membrane oxygenation). The trial consortium also found no impact on the need for mechanical ventilation among those who were not intubated at randomization. The authors performed a meta-analysis of randomized trials for remdesivir (Solidarity [n = 5,451 randomized], the Adaptive COVID-19 Treatment Trial, or ACTT-1 [n = 1,062 patients randomized]) and found no mortality benefit. Similarly, meta-analyses for all trials for hydroxychloroquine and lopinavir, including the Solidarity cohort, showed no mortality benefit.

The European Respiratory Society (ERS) recently published guidelines for the management of hospitalized adults with COVID-19 infection.[1] The guidelines were developed by a task force using the GRADE methodology (Grading of Recommendations Assessment, Development, and Evaluation), wherein the quality of evidence is rated from very low to high, and recommendations based on the quality of evidence are rated as strong or weak. With respect to drugs evaluated by the Solidarity consortium reviewed here, the ERS recommends not offering remdesivir to hospitalized patients with COVID-19 infection requiring invasive mechanical ventilation (conditional/weak recommendation, moderate quality of evidence), but it makes no recommendations regarding the use of remdesivir in hospitalized patients not requiring invasive mechanical ventilation. The panel recommends against the use of lopinavir to hospitalized patients with COVID-19 infection (strong recommendation with moderate quality of evidence). The panel also recommends against the use of interferon beta for inpatients with COVID-19 infection (weak recommendation based on very low quality evidence).

A recent randomized controlled trial compared tocilizumab (a monoclonal antibody against the interleukin-6 receptor) to placebo in patients admitted to a hospital with COVID-19 infection and evidence of a hyperinflammatory state (at least one of the following: D-dimer level higher than 1,000 ng/milliliter, ferritin level higher than 500 ng/milliliter, C-reactive protein [CRP] level higher than 50 mg/liter, or a lactate dehydrogenase [LDH] level higher than 250 U/liter).[2] The study found no benefit with respect to preventing intubation or death among inpatients with COVID-19, albeit with wide confidence intervals for efficacy implying the "possibility of some benefit or harm." A recent propensity-matched analysis assessing the effect of tocilizumab on outcomes in COVID-19 critical illness found a mortality benefit among those patients who received tocilizumab compared with those who did not.[3] Accordingly, the ERS guidelines suggest "offering interleukin-6 receptor antagonist monoclonal antibody therapy to hospitalized patients with COVID-19 requiring oxygen or invasive ventilatory support" (weak recommendation/low quality of evidence). Therefore, tocilizumab may be considered for inpatients with COVID-19 infection requiring oxygen or undergoing noninvasive mechanical ventilation who worsen while on dexamethasone after 48 hours AND are receiving high-flow nasal cannula oxygen at > 30 L/minute and FiO_2 > 0.4 with CRP ≥ 75 mg/L per institutional guidelines. Among inpatients who are mechanically ventilated or undergoing ECMO, tocilizumab may be considered as adjunctive therapy to dexamethasone for patients without improvement or with worsening respiratory function within 24 hours and accompanying worsening inflammatory markers. Tocilizumab typically is dosed at 8 mg/kg (single intravenous dose) rounded to 400 mg (for 40 kg to 65 kg of body weight), 600 mg (for 66 kg to 90 kg of body weight), and 800 mg (> 90 kg of body weight). Considered contraindications to the use of tocilizumab include the following:

- hospitalization > four days;
- duration of mechanical ventilation > 24 hours;
- active tuberculosis;
- pregnancy or breast-feeding;
- suspected or confirmed viral, fungal, or bacterial infection other than SARS-CoV-2.

Results of the ACTT-2 trial were reported recently.[4] Baricitinib is an oral Janus kinase 1 (JAK-1) and JAK-2 inhibitor and was hypothesized to modulate the immune response to the virus by inhibiting the signaling pathway of cytokines that are upregulated in COVID-19 infection. Baricitinib and remdesivir were compared to remdesivir alone. Hospitalized adults with COVID-19 infection receiving either high-flow

oxygen or noninvasive ventilation were randomized. "Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status." There was no difference with respect to 28-day mortality rates. A minimal incremental benefit of baricitinib alone over dexamethasone alone is likely. Institution-specific guidelines may recommend the combination in the defined population studied in the trial. Anti-spike neutralizing monoclonal antibodies have been approved for use in outpatients with COVID-19 infection, but none have been approved for hospitalized patients with more severe disease.

The landscape of drug therapy for severe COVID-19 infection has evolved since the start of the pandemic. Unfortunately, only a single therapy (dexamethasone) has clearly been shown to affect mortality in the setting of severe COVID-19 infection. Multiple clinical trials are ongoing. ■

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CME/CE QUESTIONS

1. **When obtaining an ethics consultation to discuss requests for potentially inappropriate treatments, ethicists may use a framework called the four topic approach. Which of the following concepts is one of the topics in this four topic approach?**
   a. Non-maleficence
   b. Patient preferences
   c. Futility
   d. Paternalism
2. **In the article by Giani et al, which of the following is true regarding prone positioning for patients on venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome?**
   a. It is contraindicated.
   b. It increases hospital length of stay.
   c. It increases intensive care unit mortality.
   d. It increases plateau pressure (Pplat).
3. **Tocilizumab therapy is contraindicated in which of the following?**
   a. Worsening hypoxia within 48 hours after dexamethasone therapy
   b. Day 4 of hospitalization
   c. Previously treated tuberculosis
   d. Duration of mechanical ventilation > 24 hours

CME/CE INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.

2. Log on to **ReliasMedia.com** and click on My Account. First-time users must register on the site. Tests are taken after each issue.

3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.

5. Once the completed evaluation is received, a credit letter will be emailed to you.

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.