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SPECIAL FEATURE

ICU Outcomes and Triage in Patients with Old Age and Advanced Cancer

By Elaine Chen, MD

Assistant Professor, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Section of Palliative Medicine, Rush University Medical Center, Chicago

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

Intensive care use is increasing worldwide. The total number of available ICU beds is increasing as well. In one report, the total number of adult ICU beds in the United States was estimated to have increased from 67,000 to 77,000 between 2000 and 2009 (about 15%), mirroring population growth. In contrast, acute care beds have changed little.[1] ICU bed occupancy in the United States is estimated at approximately two-thirds, but varies based on type of ICU, hospital type, and hospital size.[2] Worldwide practices for admission into ICUs vary; in areas with high ICU beds per capita, such as the United States, ICU admission criteria may be more lenient than in Europe and Asia, where ICU bed availability is much lower.[3,4] In developing nations, ICU beds are scarce and in extremely high demand.[3,4] When beds are insufficient, ICUs employ triage strategies to select patients most likely to benefit from ICU admission, excluding those who are considered too well or too sick to benefit.[5] The triage process is complex, affected by factors such as reasons for requesting ICU admission, evaluation and decision about appropriateness by the intensivist, and bed availability.[6] Objective triage criteria have been developed and validated; these criteria include myriad parameters, such as age, diagnosis, comorbidities, vital signs, lab values, and others.[7] They have not been widely adopted and may be too cumbersome to calculate in routine clinical decision-making.

Two patient populations to consider when contemplating ICU triage include the elderly, particularly the very old (age > 80 years), and those suffering from advanced cancer (either solid tumor or hematologic). Historically, these two populations often were excluded from consideration of intensive care due to their poor prognosis. Older guidelines described metastatic cancer patients unresponsive to chemotherapy as "generally not appropriate for ICU admission," and prior to the mid-1990s, any use of life-sustaining treatment in cancer patients

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was associated with high mortality rates greater than 70%.[8,9] What are the outcomes and benefits of ICU admission for very old patients and those presenting with advanced cancer?

ELDERLY PATIENTS

The proportion of the population that is > 80 years of age is growing rapidly, as are their healthcare needs. Indeed, the number of patients ≥ 80 years of age admitted to the ICU in recent decades has increased rapidly, and they are sicker than in the past. Elderly patients present with more comorbid conditions and less physiologic reserve, which may worsen their prognoses.[10] In Australia and New Zealand in 2005, patients > 80 years of age represented 14% of total ICU admissions; based on growth patterns, by 2015, 25% of admissions to the ICU were predicted to be ≥ 80 years of age.[11] In France, a cohort comparison study reported that a three-year cohort that concluded in 2004 demonstrated significantly higher severity of illness than a cohort that concluded in 1995.[12] Despite similar mortality, the more recent cohort received significantly higher intensity of treatment that resulted in a much higher chance of survival when adjusting for disease severity

Weighing the risks and benefits of ICU admission for elderly patients includes many potential considerations. Admission to an ICU following planned surgery in an appropriate surgical candidate results in good outcomes. A French review reported that elderly patients who required an ICU stay after planned surgery experienced 12% ICU mortality, 25% hospital mortality, and 72% of survivors discharged.[13] However, those with unplanned ICU stays for a medical indication or emergency surgery experienced much higher mortality (38-64% ICU mortality, 45-55% hospital mortality, and one-year mortality of 60-90%) with poor long-term quality of life.[13] Several international studies found that among older patients with a high severity of illness, age alone was associated with higher mortality, whereas comorbidities and pre-hospitalization functional status were poor predictors of outcome.[11-13] Elderly patients are more prone to ICU-related complications such as nosocomial infection, iatrogenic complications, imposed bed rest, sleep deprivation, delirium, and increased length of stay; thus, rapid discharge from the ICU is recommended when possible. However, studies have shown that despite hesitance to admit elderly patients to the ICU, elderly patients may experience a greater mortality benefit from an ICU stay compared with their younger counterparts.[10]

Also consider post-discharge quality of life when deciding on ICU admission of critically ill elderly patients. Despite the mortality benefit of admission, this may not translate into improvement in quality of life of quality-adjusted life-years. In fact, studies have shown that elderly survivors experience poorer quality of life and quality-adjusted life-years compared to younger patients.[10] Therefore, take into consideration patient and family preferences before admission to an ICU.

PATIENTS WITH ADVANCED CANCER

As with the elderly, there may be hesitance to admit those with cancer, particularly advanced cancer, to the ICU because of the high potential mortality. In the past, those with metastatic disease or neutropenia often were automatically rejected from the ICU.[8] Considering advances in critical care with improvements in mortality, give thoughtful consideration to each cancer patient regarding the potential benefit of ICU admission.

The use of ICU care for patients presenting with advanced cancer is increasing. A Brazilian and French study both reported that cancer was present in approximately 20% of all ICU admits.[14,15] Although the incidence of new cancer diagnoses each year has increased gradually, improved treatment has led to improved survival and, thus, more patients living with cancer.[16] Additionally, of those with cancer, the proportion who are admitted to the ICU are increasing as well. One U.S. database analysis of older adults suffering from advanced lung cancer demonstrated an increase in ICU admissions from 17.5% to 24.7% between 1993 and 2002, even while hospice use increased from 28.8% to 49.9%.[17] Another U.S. review of 848,303 Medicare

Table 1: Factors Predictive of Higher Mortality
• Older age • Progressive or active cancer • Higher severity of illness scores • Degree of organ failure at the time of admission • Degree of organ failure on day three of ICU admission • Need for mechanical ventilation • Need for vasopressors • Presence of sepsis or septic shock • Poor performance status • Late or delayed ICU admission

patients revealed an increase in ICU use during the last month of life from 24.3% in 2000 to 29.2% in 2009, and a Canadian study reported an increase in ICU admissions for patients presenting with cancer within 30 days of death from 3.06% in 1993 to 5.39% in 2004.[18]

Although worldwide mortality rates for cancer patients vary widely, they have been improving overall. A U.S. academic center reported a general MICU mortality of 20-30%, but 41% mortality for those with cancer, and 67% mortality for cancer patients with more than two organs in failure.[19] In a Turkish study, overall ICU mortality for cancer patients was reported to be 55%, and a Brazilian study reported 53% ICU mortality for non-scheduled ICU admissions in those with cancer.[14,20] As with the elderly, cancer patients with scheduled surgeries requiring postoperative ICU care experienced a mortality of only 11%. With mechanically ventilated cancer patients, mortality remains extremely high at 78%.[15] Worldwide mortality differences may be related to bed availability, ICU triage practices, and severity of illness of those admitted; presumably, those treating lower acuity patients would experience lower mortality. Regardless, with improvements in critical care, overall mortality rates have decreased for critically ill patients with cancer from more than 80% in the 1980s to approximately 50% in the late 2000s.[21,22]

Prognostic factors for mortality in critically ill cancer patients have been described in various studies (*see Table 1*). The Turkish study referenced previously found that four variables were independent predictors for ICU mortality: 1) progressive cancer, as opposed to limited stage or in remission, 2) higher Acute Physiology and Chronic Health Evaluation II scores at the time of admission, reflecting higher severity of illness, 3) sepsis or septic shock during the ICU stay, and 4) use of vasopressors.[20] The Brazilian group also found that mortality was influenced by higher severity of organ failure at the time of ICU admission, active cancer, as well as poor performance status and need for mechanical ventilation.[14] One French study observed that mortality, as related to organ failure, was more correlated with severity of organ failure at day three rather than at the time of admission.[21] Type of malignancy and presence of neutropenia (including neutrophil count or duration of neutropenia) were found by multiple recent studies to have no effect on short-term mortality.[9,14] Delayed admission to the ICU also was associated with higher mortality, so early admission is strongly recommended. Among cancer patients, one special group includes patients with stem cell transplants; those with autologous transplants were found to demonstrate no difference in mortality rates than other cancer patients, but those with allogeneic stem cell transplants did experience higher mortality.[9,19]

Multiple models have been proposed for determining admission or rejection into the ICU or for setting initial duration of time-limited trials (*see Table 2*). In France, one ICU reported a standard policy of refusing admission to bedridden patients and those in whom no cancer-directed treatment was available.[15] This same center recommended unrestricted admission to those with a new diagnosis of malignancy that had not yet been treated, acute tumor lysis syndrome, bulky or infiltrating tumors at the earliest phase of treatment, or patients in complete remission, as well as a five-day, time-limited trial of full intensive care services for those who do not fit the criteria.[15] A later study by the same group suggested that patients with a history of allogeneic stem cell transplant with graft-versus-host disease, age > 70 years, and altered performance status should not be recommended for ICU admission. A U.S. simulation model also recommends time-limited trials of one to four days of ICU care for those with poor prognosis from solid tumors with very high severity

Table 2: Criteria for ICU Admission or Rejection
Admission • Post-procedure complication • Recent diagnosis of cancer within one month or not yet treated • Good functional status (ECOG 0-1) • Life expectancy of greater than six months • Acute tumor lysis syndrome • Bulky or infiltrating tumor in early phase of treatment • Cancer in remission **Rejection** • Bedridden for past three months • No cancer-directed treatments available • Allogeneic stem cell transplant with graft-versus-host disease • > 70 years of age

of illness, citing that longer trials did not result in improved survival; those with hematologic malignancy and less severe illness may benefit from longer trials of intensive care.[23] Due to the unreliability of triage models, many sources recommend at least a three-day trial of full ICU care before deciding to withdraw life support.

FAMILY PERSPECTIVES

In addition to considering the risk of morbidity and mortality when deciding on admission of elderly patients or those with advanced cancer to an ICU, consider the perspectives of family members. This is important because family members may bear the brunt of decision-making, grief, and post-discharge caregiving. One study of families of patients with advanced cancer found lower satisfaction with end-of-life care in those who experienced an ICU admission within 30 days of death and higher satisfaction among those who died at home and who received hospice care for more than three days.[24] Another study of family members of elderly patients reported high levels of stress, anxiety, and depression related to decision-making in the ICU.[25] These studies clearly underscore the benefits of trying to avoid unnecessary ICU admission in terminal situations and the importance of advance care planning to help these patients meet their end-of-life goals.

There is no question that the provision of early comprehensive palliative care is important in the elderly and those suffering from cancer. A landmark study in 2010 showed that early outpatient palliative care in patients presenting with metastatic lung cancer resulted in improved quality of life, decreased aggressive care, and even longer survival.[26] The palliative care group experienced significantly fewer hospital admissions than the standard care group (36.7% vs. 53.6%), hence fewer ICU admissions.[26]

Although improving palliative care efforts is important, these interventions do not always result in decreased admissions to the ICU at the end of life. A Canadian survey of family members of patients > 80 years of age who were admitted to the ICU found that despite 24% of family members preferring comfort measures only, 84% of those patients received life-sustaining treatments during their ICU stay, and 20% of them for more than seven days.[25] One U.S. study found that 47% of patients who died in an ICU with advanced cancer, poor functional status, and poor prognosis had completed advance care planning discussions with their physicians prior to ICU admission.[18]

Make efforts to assess for preference and avoid the unnecessary stress, burden, and cost of ICU admission in those whose families would prefer palliative measures. Less than 60% of families of elderly patients in the ICU reported that a physician had spoken with them about choosing between treatment options for their family member within 24 hours of admission; they also reported a poor understanding of both their role in decision-making and what the doctors told them.[25] This stresses the importance of continued efforts on the part of physicians to improve communication with families of critically ill patients in the ICU.

SUMMARY

The very elderly and those with advanced cancer should not be excluded from admission to the ICU based on those qualities alone. The number of patients with advanced age and advanced cancer is on the rise, and ICU use among those populations is increasing. Although ICU bed availability may dictate some triage decisions, these at-risk patient populations may benefit from earlier admission to an ICU if this is consistent with their goals of care. Early palliative care, advance care planning prior to the terminal phase, and comprehensive communication efforts while in the ICU are recommended for the elderly and those with advanced cancer. Extremely moribund patients may not benefit from aggressive ICU care, but at the time of triage it is difficult to predict those patients. Thus, prognostic factors and family preference should be considered when deciding on ICU admission, but early admission with a time-limited trial of at least three to five days often is warranted regardless of clinical status to patients who were not previously moribund. Continue improving clinical management, communication, and decision-making to improve outcomes as well as patient and family satisfaction for the very old and those with cancer in the ICU. ■

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ABSTRACT & COMMENTARY

How Good Is Passive Leg Raise at Predicting Fluid Responsiveness?

By Eric Walter, MD, MSc

Pulmonary and Critical Care Medicine, Northwest Permanente and Kaiser Sunnyside Medical Center, Portland, OR

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

SYNOPSIS: In a meta-analysis of 23 clinical trials, passive leg raise was shown to be an excellent predictor of fluid responsiveness.

SOURCE: Cherpanath TG, Hirsch A, Geerts BF, et al. Predicting fluid responsiveness by passive leg raising: A systematic review and meta-analysis of 23 clinical trials. *Crit Care Med* 2016:44:981-991.

Fluid resuscitation is a fundamental procedure in critical care medicine. At first, this appears easy: If blood pressure is low, give more fluids. Time has taught clinicians that this is not such a simple decision. In some patients, more fluids are lifesaving. For others, fluid resuscitation increases morbidity and mortality. Determining who will respond to fluids is now one of the principle questions in critical care. Passive leg raise (PLR) is a simple bedside test used to assess fluid responsiveness. The patient raises both straightened legs 45 degrees and holds the pose for approximately one minute. PLR acts as a reversible fluid bolus, rapidly, yet transiently increasing preload and cardiac output.

PLR has been well studied in small clinical trials. Cherpanath et al summarized the predictive value of PLR in various clinical situations. They presented a meta-analysis of 23 studies that compared PLR to a true fluid challenge (the gold standard). Studies defined a positive response to a fluid challenge differently, but in general an increase of more than 15%

in blood flow was defined as a positive response. Techniques used to measure blood flow included esophageal doppler, transthoracic echocardiography, calibrated pulse contour analysis, and bioreactance. The meta-analysis included 1,013 patients, although individual studies were small (17-102 patients). The majority of patients were septic (57%) and required vasopressor support (56%).

The pooled sensitivity for PLR was 86% (95% confidence interval [CI], 79-92%) with a specificity of 92% (95% CI, 88-96%). The area under the receiver operating curve was 0.95. PLR diagnostic performance did not differ between spontaneously and mechanically ventilated patients. Using changes in pulse pressure as a measure of fluid responsiveness was less predictive (sensitivity 58% [95% CI, 44-71%]; specificity 83% [95% CI, 68-92%]) than the use of flow variables such as cardiac output, stroke volume, or aortic blood flow. Researchers could not assess the utility of PLR in patients in atrial fibrillation because most patients were in normal sinus rhythm.

■ COMMENTARY

PLR works by creating an "auto transfusion" that reversibly moves an estimated 250-350 mL of blood into the chest cavity. Cardiac preload increases, and if patients are fluid responsive, an increase in cardiac output occurs. Clinicians observe the maximal effect in about one minute and it disappears when the legs are lowered. The reported sensitivity of 86% and specificity of 92% is remarkable (almost too good to be true). Furthermore, PLR is easy, requires minimal training, and has few complications. This sounds like the perfect test. So should medical professionals use PLR as part of a routine clinical exam?

Maybe, but several questions remain. First, for most of these studies the assessment of whether a patient responded to PLR required measurements of cardiac output was not easily available to many ICU clinicians. Although echocardiography is used more commonly in the ICU, few clinicians will have the expertise to measure cardiac output, let alone differentiate between a change in cardiac output of 15%. Esophageal doppler and bioreactance are not commonly available. Pulse contour analysis is more widely available but requires equipment and arterial access.

Second, what does fluid responsive really mean? This was defined as an increase in cardiac output of ≥ 15%. Is this a clinically relevant definition? The goal of fluid resuscitation is not just to improve cardiac output but to improve perfusion and ultimately patient outcomes. The lessons learned from the pulmonary artery catheter remind one that simply knowing how to measure physiologic variables does not automatically translate into better care. Researchers must conduct more studies showing that a PLR-informed fluid strategy leads to better outcomes compared to other approaches. ■

ABSTRACT & COMMENTARY

Proportional Assist Ventilation and Lung Protection in Acute Respiratory Distress Syndrome: A Way Forward

By Richard Kallet, MS, RRT, FAARC, 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: A post-hoc analysis found that once patients were allowed to control their breathing pattern on high-level proportional assist ventilation, they continued to maintain an estimated driving pressure remarkably close to that measured during lung protective ventilation.

SOURCE: Georgopoulos D, Xirouchaki N, Tzanakis N, Younes M. Driving pressure during assisted mechanical ventilation. Is it controlled by patient brain? *Respir Physiol Neurobiol* 2016;228:69-75.

A post-hoc analysis of a 2008 study that compared proportional assist ventilation (PAV+) to pressure support ventilation in patients with acute respiratory failure examined 108 patients in the PAV+ arm (59% of whom had acute respiratory distress syndrome or ARDS).[1] Preclinical studies have shown that animals with acute lung injury (who possess an inherently strong Hering-Breuer inspiratory-inhibitory reflex) instinctively adopt a lung-protective breathing pattern. Because the Hering-Breuer reflex is weaker in humans, the study inquired whether animal model findings are

generalizable to patients with ARDS. Baseline chest mechanics were measured during both controlled mechanical ventilation (CMV) and during PAV+. The focus was plateau pressure (P_{PLAT}) and the elastic driving pressure ($\Delta P = P_{PLAT}$ – positive-end expiratory pressure or PEEP), which was recently shown to be a robust mortality predictor.[2] Although patients increased their tidal volume (V_T) on PAV+, they maintained almost identical P_{PLAT} and ΔP as during CMV. When chest compliance measured on PAV+ was lower than on CMV, patients modestly increased their V_T (~ 0.6-0.8 mL/kg). Moreover, a higher ΔP during CMV was associated with subsequent decreased PAV+ support (and vice versa), signifying decreased breathing effort at higher loads and suggesting neuromuscular load adaptation.

■ COMMENTARY

Beyond these intriguing results is their application to the practical problem regarding the management of patients recovering from ARDS. That is, how best to manage competing, often contradictory, issues that negatively affect patient outcomes. These include maintaining lung protection, preventing respiratory muscle fatigue, and ameliorating dyspnea and asynchrony, while minimizing sedation to expedite weaning. This study suggests that PAV+, a closed-loop, within-breath form of pressure support ventilation, may provide the best approach to solve this conundrum.

PAV+ provides a clinician-set level of the total work of breathing performed by the patient, based on instantaneous measurements of flow and volume change integrated with real-time estimations of total elastic and resistive ventilatory work. It can be thought of as "pressure support with power steering," such that increases or decreases in muscle pressure is met with a proportional increase or decrease in pressure support. Therefore, this mode is contraindicated both in those with respiratory muscle weakness and in those in the acute phase of severe respiratory failure. The patients in this study were clearly in the recovery phase (i.e., median PEEP, fraction of inspired oxygen [FiO_2], and minute ventilation of 6 cm H_2O, 0.40, and 9.9 L/minute, respectively). In addition, the median chest compliance on CMV, P_{PLAT}, and PaO_2/FiO_2 ratio were 44 mL/cm H_2O, 18 cm H_2O, and 215 mmHg, respectively.

Nonetheless, PAV+ with relatively higher PEEP remains a plausible strategy in stable patients with ARDS who remain ventilator dependent, particularly those with abnormal chest wall compliance. Often, these patients have stable gas exchange on reasonable settings (e.g., PEEP/FiO_2 ~ 10 cmH_2O/ < 0.60), yet they cannot tolerate pressure support ventilation low enough to limit stretch-related injury and avoid acute muscle fatigue, nor can they tolerate CMV with a protective V_T without requiring generous sedation to control asynchrony and dyspnea.

Finally, it's unclear whether apparent autoregulation of ΔP actually signifies neural control of stretch in this setting. During brief periods of unassisted breathing, ventilator-dependent ARDS patients generate muscle pressures approximating the cutoff point for increased mortality risk (16.5 vs. 15 cm H_2O, respectively) while limiting V_T to 4-5 mL/kg.[2,3] However, this merely may reflect an adaptive strategy to avoid respiratory muscle injury when chest elastance is high as originally proposed by Otis' theory of minimal work. Both inspiratory muscle fatigue and dyspnea occur when inspiratory muscle pressure exceeds approximately 50% of maximal force generating capacity. Thus, this level of muscle pressure or ΔPAV+ may only reflect adaptation in the face of incipient muscle fatigue. Regardless, PAV+, if not misapplied, may become an important tool in the armamentarium in managing ARDS and should be studied in prospective clinical trials. ■

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CME/CE QUESTIONS

1. Which of the following is recommended when considering triage of the elderly and those with cancer into the ICU?
a. Patients with a stem cell transplant and neutropenia are not recommended for ICU admission.
b. Bedridden patients with poor prognosis solid tumors should receive a time-limited trial of at least seven days of full code ICU care.
c. Patients with more than four organs in failure at the time of ICU evaluation should not be admitted due to extremely high mortality.
d. Those patients who are admitted for planned surgical procedures have a low mortality and should be admitted to the ICU if needed.
e. None of the above.

2. Which of the following is not associated with higher mortality in cancer patients?
a. Degree of organ failure at the time of admission
b. Degree of organ failure on day three of ICU admission
c. Duration of neutropenia
d. Need for mechanical ventilation
e. None of the above

3. In the meta-analysis of clinical trials assessing passive leg raise:
a. passive leg raise is a very sensitive test but has poor specificity.
b. passive leg raise is a very specific test but has poor sensitivity.
c. fluid responsiveness was generally defined as an increase in cardiac output > 15%.
d. the effect of a passive leg raise requires transthoracic echocardiography to be measured.
e. a strategy using passive leg raise to assess fluid responsiveness has been shown to decrease mortality among patients with sepsis.

4. Which of the following statements is true with respect to passive leg raise?
a. Passive leg raise can accurately differentiate patients who are likely to respond to fluid resuscitation.
b. A change in systolic blood pressure can be used to assess the effect of a passive leg raise.
c. Passive leg raise decreases preload.
d. Passive leg raise is not an accurate predictor of fluid responsiveness in patients who are mechanically ventilated.
e. The peak effect of passive leg raise occurs after five minutes.

5. Which of the following statements is *false* regarding PAV+?
a. PAV+ is sometimes referred to as "pressure support with power steering."
b. PAV+ is a within-breath, closed-loop form of ventilation.
c. PAV+ works by adjusting the number of mandatory breaths delivered by the ventilator as patient work of breathing increases or decreases.
d. PAV+ measures instantaneous flow and volume change with real-time estimations of both elastic and resistive work.
e. The clinician can set the percentage of total work of breathing he or she wishes the patient to perform.

6. Which of the following statements is true regarding the study by Georgopoulos et al?
a. The study was a post-hoc analysis of a 2008 study comparing PAV+ to pressure support.
b. All study patients had acute respiratory distress syndrome.
c. All study patients required PEEP levels above 10 cm H_2O.
d. The PAV+ level was close to the driving pressure measured during CMV.
e. Both a and d