CRITICAL CARE ALERT®

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INSIDE

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Use of Corticosteroids in Persistent ARDS

ABSTRACT & COMMENTARY

By James E. McFeely, MD

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Dr. McFeely reports no financial relationship to this field of study.

Synopsis: *A prospective randomized trial carried out over a 6-year period of time enrolled 180 patients with ARDS of at least 7 days duration, and randomized them to receive either methylprednisolone or placebo. There was no significant difference noted in mortality at 60 days, though there was some improvement in ventilator-free and shock-free days during the first 28 days in patients treated with steroids. Steroids were also associated with an increased risk of death if started more than two weeks after the onset of ARDS.*

Source: Steinberg KP, et al. *N Engl J Med*. 2006;354:1671-1684.

Corticosteroids have been studied in various phases in the treatment of Acute Respiratory Distress Syndrome (ARDS), which is characterized by an inflammatory injury to the lung resulting in acute hypoxemic respiratory failure. Four trials of steroids in early ARDS failed to show any improvement. However, several reports in small case series showed a possible benefit from moderate-dose steroids in patients with persistent ARDS, including a single-center study involving a small number of patients that suggested an improvement in lung function and survival. On this basis, the ARDS Network undertook a larger, multi-center, placebo-controlled randomized study of steroids in patients with persistent ARDS.

Patients were enrolled between August 1997 and November 2003 at 25 hospitals in the ARDS network. Out of 4,000 patients screened (3,464 of whom were eligible), 180 (5%) enrolled between day 7 and 28 after the onset of ARDS and were randomly assigned in a double-blind fashion to receive either methylprednisolone or placebo. The initial demographic variables were similar between the two study groups except for gender (more men were assigned

placebo). Methylprednisolone was administered as a single dose of 2 mg/kg of predicted body weight, followed by a dose of 0.5 mg/kg every 6 hours for 14 days. The dose was subsequently reduced to 0.5 mg/kg every 12 hours for 7 days, then tapered. Tapering occurred more rapidly if fungal disease or septic shock developed, or if the patient improved to the point of having been extubated for at least 48 hours.

The study's primary end point was mortality at 60 days. Secondary end points included the number of ventilator-free and organ failure-free days, infectious complications, and markers of inflammation and fibroproliferation. The trial was initially designed to enroll 400 patients, but two years into the study sample size was changed based on low enrollment as well as results of the contemporaneous low tidal volume ARDS net study.[1]

Based on an intention-to-treat analysis, there was no significant difference in mortality between the 2 treatment groups, either at the 60-day time interval (28.6% placebo, 29.2% methylprednisolone) or at 180 days. The steroid group experienced significantly more ventilator-free days than the placebo group during the first 28 days (14 days vs 24 days); they also had more shock-free days and showed improvements in oxygenation and respiratory system compliance as compared with the placebo group. However, patients in the steroid group were more likely to require reintubation (28% vs 9%). Further, patients among the steroid group who had ARDS for more than 13 days before enrollment showed a significantly increased mortality rate.

COMMENTARY

The ARDS Network is to be commended for their perseverance in attempting to answer the question of steroid use in late ARDS. However, while the results of this paper might suggest that steroids (at least at the dose and timing used in the study) are unfortunately not going to be of use for the fibroproliferative phase of ARDS, problems with recruitment and the length of time it took to complete enrollment raise questions about the applicability of this result.

This study was open for enrollment at 25 hospitals for 2,296 days. During this time, the practice of critical care medicine was in rapid evolution. While the study was initially conducted in parallel with the ARDS low-tidal-volume study, subsequent results from the latter study[1] led researchers to decrease enrollment and include additional covariate analyses. In addition, many changes in critical care practice have had a direct impact on the primary and secondary end points of the study, including the use of vasopressin for shock, tight glycemic control, early goal-directed therapy, use of activated protein C (Xigris) for sepsis, and development of protocols for weaning and use of sedatives. Each of these could be expected to have an effect on overall mortality of similar magnitude to steroid use in ARDS. Moreover, only 5% of patients who were eligible for the study (180/3464) were actually enrolled. While there were appropriate reasons for this, the exclusions do raise a question regarding the applicability of this result to a larger population.

What can be concluded from this study is that starting steroids more than two weeks after the onset of ARDS is probably a bad idea and likely increases the risk of death. This paper also documented high incidences of neuromyopathy. While there was no difference in frequency between the 2 groups, patients on steroids seem to have more severe myopathy. This was perhaps complicated by the increased frequency of hyperglycemia, also seen in the corticosteroid group. Fortunately, no significant increase in infectious complications was identified.

Reduction in the excessive inflammatory response to ARDS still seems to be a promising therapeutic target in ARDS. It may be that corticosteroids, however, are too blunt an instrument in this situation. In the 10 years since this trial was first designed, we've come a

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long way in identifying inflammatory and anti-inflammatory genes and mediators. This trial helps narrow the time window for optimal anti-inflammatory therapy. Hopefully, the next trial will be performed with a more targeted therapy applied over a broader range of patients, and will be brought to conclusion more quickly. ■

Reference

1. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342:1301-1308.

Does Early Enteral Feeding Improve Outcomes in Medical ICU Patients?

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In a retrospective analysis, medical ICU patients requiring mechanical ventilation for 2 days or more had lower ICU and hospital mortality (but more ventilator-associated pneumonia) if they were begun on enteral feeding during that time than if they were not.*

Source: Artinian V, et al. *Chest*. 2006;129:960-967.

Artinian and colleagues performed a retrospective analysis on a large prospectively acquired database from ICUs across the United States to examine the effect of initiating early enteral feeding on outcomes in non-surgical, mechanically ventilated ICU patients. They used patient data from Project IMPACT CCM, Inc (www.cerner.com/piccm/about.html), a proprietary ICU data collection and management system. After exclusion of patients who were weaned or died within 48 hours, or were predicted to have a contraindication to enteral feeding (such as those with gastrointestinal bleeding, ileus, or pancreatitis), data from 4,049 patients who were ventilated for at least 2 days were used in the study. Patients in whom the records showed that enteral feeding was begun within the first 48 h of commencement of ventilatory support (n = 2,537) were compared to those without such documentation (n = 1,512). The investigators determined associations between early feeding status and ICU and hospital mortality, ventilator-free days, ICU length of stay, and the incidence of ventilator-associated pneumonia (VAP), using a standardized definition. They also attempted to adjust for imbalances in the patient groups by matching a subset of 1,264 of the early feeding patients with an equal number of non-fed patients by means of a propensity score.

The 63% of patients who received early feeding were significantly older, more likely to be white, and to have been admitted to the ICU for respiratory reasons. Early feeding patients were also less seriously ill as measured by MPM-0 and SAPS II scores. ICU and hospital mortality were lower in the early feeding patients (18% vs 21%; $P = 0.01$, and 29% vs 34%; $P = 0.001$, respectively). The mortality differences were primarily among the most seriously ill quartile of the early feeding group, and these persisted in the secondary analysis using propensity score. Early feeding patients had longer ICU lengths of stay (10.9 vs 10.2 days; $P = 0.01$), and also had an increased risk of VAP in all adjusted analysis, but there was no difference in 28-day ventilator-free days. In the several prediction models used, early enteral feeding was associated with an approximately 20% decrease in ICU mortality and a 25% decrease in hospital mortality. The authors recommend early enteral feeding for medical ICU patients, based on their conclusion that such an approach to nutritional support reduces ICU and hospital mortality primarily because of improvements in the sickest patients.

■ COMMENTARY

The clinical importance of early nutritional support in the ICU remains controversial. Food is good, and it would seem to be self-evident that feeding critically ill patients would be good for them, yet this has been surprisingly difficult to establish convincingly. Poorly nourished patients do less well than those with better nutritional status, but this is not the same as saying that early, aggressive feeding across the board will improve outcomes. A systematic review of studies in critically ill patients with abdominal surgery, hip fracture, trauma, and burns concluded that early enteral feeding was beneficial in those groups.[1] However, the only previous study[2] in mechanically ventilated medical ICU patients—a single-center randomized controlled trial—found that early institution of full enteral nutritional support was associated with increases in the rates of VAP and *Clostridium difficile*-associated diarrhea, longer stays in the ICU and in the hospital, and no differences in mortality. The results of this study differ strikingly from those of the latter.

In the hierarchy of evidence-based medicine, the findings of appropriately powered randomized clinical trials—or better yet, of meta-analysis of several

such trials—carried out with patients similar to those of present interest and using clinically relevant end points, are at the top of the list. The results of smaller clinical trials and prospective studies with surrogate end points, data from retrospective studies, and the findings of studies on animals are placed progressively lower on the list. This is not to say that a retrospective study can't get it right or that the results of such a study should not be taken seriously. A retrospective analysis with findings at variance with those of a randomized clinical trial does present the clinician with a dilemma, however,

As the authors acknowledge, the present study has several limitations. The only thing in the database about the nutritional management of the patients is whether enteral feeding was initiated in the first 48 hours of mechanical ventilation; how much was given or whether it was tolerated is unknown, as are the nutritional formula used and whether the tube was gastric or postpyloric. Perhaps more importantly, as in any retrospective analysis it is not possible to know for sure why early enteral feeding was done in some patients and not others. Although the authors went to great lengths to eliminate confounding by indication, the possibility remains that something important about the early feeding patients that was not included in the database was different. As one of my colleagues likes to remind me, sicker patients don't do as well as patients who are less sick. Or perhaps there was something different about the medical ICU physicians who started their patients on early enteral feeding as compared with those who did not.

These issues notwithstanding, this study provides evidence for improved outcomes among medical ICU patients who require mechanical ventilation for 2 days or more—especially those who are more seriously ill—if they are begun on enteral feeding during that time. In the absence of contraindications, it would be reasonable to attempt enteral feeding under such circumstances, although the state of the evidence at present is that we do not know for sure whether this is really in our patients' best interests. ■

References

1. Marik PE, Zaloga GP. *Crit Care Med.* 2001;29:2264-2270; Erratum in: *Crit Care Med*. 2002;30:725

2. Ibrahim EH, et al. *JPEN J Parenter Enteral Nutr*. 2002;26:174-181.

Cost-Effectiveness of BNP Measurement in Acute Dyspnea

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *This study in patients presenting to the emergency department with acute dyspnea showed that rapid BNP testing is cost-effective during the initial hospital encounter as well as at 180 days.*

Source: Mueller C, et al. *Arch Intern Med*. 2006;166:1081-1087.

MUELLER AND COLLEAGUES AT THE UNIVERSITY Hospital in Basel, Switzerland, investigated the clinical utility and cost-effectiveness of immediately measuring the serum level of B-type natriuretic peptide (BNP) in patients presenting to the emergency department with acute dyspnea. The clinical results of the BNP Acute Shortness of Breath Evaluation (BASEL) study, a randomized single-blind clinical trial of 452 patients, were published in 2004.[1] This paper presents a prospectively identified cost-effectiveness analysis from that study.

Patients presenting with acute dyspnea who did not have trauma, severe renal disease, or cardiogenic shock, were randomized to have immediate measurement of BNP using a point-of-care assay or to receive conventional assessment and management without BNP measurement. The patients were generally elderly (mean age, 71 years). About half of them had known coronary artery disease, and slightly fewer had known obstructive lung disease. Heart failure was considered unlikely if the BNP level was < 100 pg/mL (36% of patients), most likely if the level was > 500 pg/mL (36%), and uncertain if the level was between 100 and 500 pg/mL (28%).

Patients in the BNP group had appropriate therapy initiated more rapidly (median time, 63 vs 90 min; P = 0.03) and were less likely to be admitted to the hospital (75% vs 85%; P = 0.008), than patients in the conventional care group. In addition, patients in the BNP group were less likely to be admitted to the ICU (15% vs 24%; P = 0.01). BNP-assigned patients had shorter hospital lengths of stay, both initially (median, 8 vs 10 days; P = 0.02) and during the 180-day observation period (10 vs 14 days; P = 0.005). The diagnosis of COPD exacerbation was made more often in the BNP group than in the control group (23% vs 11%, respectively; P = 0.001).

Total initial treatment costs were less in the BNP group ($5410 vs $7264; $P = 0.006$), as were total treatment costs at 180 days ($7930 vs $10,503; $P = 0.004$). All-cause mortality initially and at 180 days (about 20%) was not different in the 2 groups.

COMMENTARY

BNP testing has become widespread in the assessment of patients with dyspnea, as well as in suspected heart failure and for following the course of patients with known heart failure. Its utility seems to be greatest when there is diagnostic uncertainty—when the patient does not have clear features of heart failure or another, non-cardiac cause for acute dyspnea.

Although the BASEL study looked only at patients presenting to the emergency department, it is tempting to assume that BNP testing would also be both clinically useful and cost-effective in evaluating hospitalized patients who develop acute dyspnea (although this has not been studied). In an editorial on BNP and cost-effectiveness analysis accompanying the paper by Mueller et al, Hlatky and Heidenreich[2] conclude by stating, "In patients with neither clear evidence of heart failure nor an extremely low suspicion of heart failure, it is reasonable to expect that BNP testing will lead to a definitive diagnosis more rapidly and will pay for itself with more efficient clinical management." Based on the findings of Mueller et al in the BASEL study, I agree.

References

1. Mueller C, et al. *N Engl J Med.* 2004;350:647-654.
2. Hlatky M, Heidenreich P. *Arch Intern Med.* 2006;166:1063-1064.

Special Feature

End-of-Life Care in the ICU: Perspectives on Surrogate Decision-Making and Managing Conflicts

By Leslie A. Hoffman, RN, PhD

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Dr. Hoffman reports no financial relationship to this field of study.

One in 5 Americans dies in or shortly after discharge from an intensive care unit (ICU), an outcome that exposes critical care clinicians to frequent discussions that concern end-of-life care.[1] This essay focuses on 4 topics of importance to end-of-life care in the ICU: 1) accuracy of surrogate decision-making; 2) dealing with conflicts; 3) surrogate willingness to endorse genetic research; and 4) opportunities for improving end-of-life care.

Accuracy of Surrogate Decision-Making

Prior to the 1980s, medical decision-making was generally paternalistic. Physicians, guided by ethical principles, decided what treatment was the most appropriate, with little input from the patient or family.[1,2] Since 1980, there has been an increasing emphasis on allowing patients to make their own decisions, including the right to choose what medical care they do and do not want to receive.[2] In 2004, strong support emerged for a shared decision-making approach.[3] In this model, the physician works with the patient and family to determine health care values, beliefs, and preferences. The physician not only provides information, but also recommends the treatment that is viewed to be the most consistent with the patient's values and goals. This model blends the opposing forces of patient self-determination and the patient's need for guidance regarding complex management decisions.[1] Because most patients who are near death in the ICU are unable to voice their preferences, a surrogate is typically asked to assume the role that would normally be assumed by the patient and make decisions that best fit with the patient's wishes or best interests.[1]

Surrogate decision-making is viewed as extending patient autonomy by allowing the preferences of patients to guide their care, even if they cannot make these decisions themselves. However authors of a recent meta-analysis concluded that surrogates incorrectly predict end-of-life treatment preferences in approximately one-third of cases.[4] From a systematic literature search, 16 studies were identified that involved 151 hypothetical scenarios, 2,595 surrogate-patient pairs, and 19,526 patient-surrogate paired responses. Twelve studies assessed whether surrogates were more likely to favor or reject treatment the patient might want. Three studies found that surrogates tend to err in favor of approving interventions that the patient did not want and one found the opposite. Eight studies reported mixed results with no consistent trend in surrogates' mistakes. In 5 studies, investigators assigned the patient's surrogate based on the relevant state's relationship hierarchy and in 6 studies patients designated who they wished to be their surrogate. Patient designated surrogates were cor-

rect 69% of the time and legally assigned surrogates 68% of the time. There are also indications that surrogates and patients view consequences of treatment differently, which may preclude greater uniformity in opinion. In a study in which agreement occurred 70% of the time, patients selected "burden on the family" and "time left to live" as the most important factor to guide decision-making, whereas surrogates identified "pain" as the most important factor.[5]

Several studies have evaluated the potential of using a community standard for reference. In this model, the "community" consists of patients possessing experience with specific health states, diseases or treatments and the "standard" represents the preferences of these patients.[6] The argument for using a community standard is based on the belief that groups of people share core values that can used analyzed to identify end-of-life treatment choices in various situations. In a study comparing the accuracy of such a model and decisions of surrogates, surrogates who had known the patient 47 ± 6 years were unable to predict preferences more accurately than the model. Both surrogates and the model had an average accuracy rate of 74-75%.[6] This form of decision making has several advantages. If preferences are unknown, modal preferences can be used to guide the discussion.[6] Preferences derived in this manner can be particularly helpful because they describe the choices of individuals who had actual experience with a specific disease or treatment.

Of interest, the rate of surrogate-patient agreement appears to be slightly higher when the choice involves whether to participate in a clinical research trial. Patients scheduled for elective cardiac surgery were asked to evaluate two study protocols (one low risk and one high risk). The patients and surrogates were then asked to indicate if they would consent to study participation. The surrogate's prediction was incorrect in 15% of cases for the low-risk study and 20% of cases for the high-risk study.[7]

Despite these findings, four studies have indicated that surrogates are more accurate in predicting treatment preferences than physicians.[4] Therefore, in the absence of alternate methods, current reliance on surrogates or a community standard can be defended as the best available method for implementing the substituted judgment standard.[1-7]

Dealing with Conflicts

Interpersonal conflicts regarding complex decisional issues are inevitable in the high-pressured work of health care.[8] Poorly managed, conflict saps productivity and spawns additional disputes. Well-managed conflict can enhance the self-esteem of all involved parties and engender creative solutions beyond expectations. Just as thoughtful differential diagnosis precedes optimum treatment, management of conflict involving different preferences is greatly enhanced when preceded by careful assessment.[8]

Conflicts commonly arise in the context of end-of-life treatment decisions. A common cause of such conflicts arises from family demands for care that the health care team believes is futile.[9] When conflicts occur, the option exists to deal with the issue promptly and directly or delay action. Both choices can be appropriate.[9] The most important pitfall in dealing with conflicts is to begin negotiations when you are angry, defensive, or preoccupied with emergent issues that make it impossible to devote sufficient time to resolving the conflict.[9] Additional pitfalls and useful communications strategies are summarized in Tables 1 and 2.

Several authors have developed a step-wise approach to resolving conflicts which involve issues related to end-of-life decision-making that involves surrogates.[9,10] The first step involves acknowledging that a conflict exists. The second step involves preparing for discussion by reviewing known issues, what has been done, and selecting a time to address the issue when there are a minimum of distractions. Stone[10] recommends approaching such situations with curiosity directed toward eliciting the "real" issues which are prompting the conflict. In such situations, affective issues are likely more important than the facts. Mediation experts recommend that, rather than ignoring emotions, one should openly acknowledge these on the part of both parties in the dispute.

Opportunities for Improving End-of-Life Care

Evidence from a number of studies suggests that families of critically ill patients are not satisfied with the amount and clarity of information they receive from health care providers.[1] From focus group discussions, surrogates identified six domains of information that they believed would assist in patient-centered decision-making in the setting of critical illness.[11] These 6 domains were:

a. the nature of the patient's illness and treatment;
b. prognosis for outcomes, including ventilator independence, survival, functional recovery and an acceptable quality of life;
c. potential for pain and other distressing symptoms;
d. potential complications of treatment;
e. expected care needs after hospitalization; and
f. alternatives to continuation of treatment into the chronic phase of critical illness.

Table 1

Behaviors to Avoid When Dealing with Conflicts

Behavior	Consequence
Avoiding or denying the conflict exists	Problem escalates Not addressing issue impacts leadership credibility
Assuming you know the entire story	Views not expressed may be the real source of problem Missed opportunity to hear others viewpoint
Assuming conflict will resolve on its own	If this were the situation, the conflict would not exist Resolution may become more difficult over time
Attempting to solve the problem based on "evidence"	Ignores factors/emotions that created the problem
Labeling the family as dysfunctional	Makes it more likely the conflict will escalate
Ignoring your own beliefs and emotions	Open acknowledgement of issues and problems, tends to diffuse emotions and encourage a solution
Attempting to solve the conflict when distracted	Prevents full attention to the problem Suggests lack of concern and tends to escalate issue

Adapted from: Beck AL, Arnold RM. Dealing with conflict in caring for the seriously ill. JAMA 2005;293:1374-1381.

Participants observed that the transition from acute to chronic critical illness passed without focused discussion of the potential for future recovery (functional capacity, quality of life) or alternative plans of care (withholding or withdrawing treatment). When discussions took place, participants observed that they typically occurred when treatment was prolonged and death was imminent.[11] The participants all shared that they felt it was relevant and important to discuss possible options, including termination of mechanical ventilation and other life-sustaining treatments earlier in the course of illness.

Surrogate Consent for Genetic Research

Several clinical trials have examined or are actively recruiting patients for studies involving gene-based therapeutics.[12] Studies that involve genetic research pose unique challenges in the critical care environment because patients are unlikely to have discussed their wishes with their surrogate decision-maker, the surrogate may have no personal knowledge about this treatment option and the surrogate may need to make a quick decision because the therapy must be administered promptly after diagnosis of a complication, eg, sepsis.[12] Requests to participate in clinical trials that involve genetic testing introduce complex issues into the patient-provider relationship, due to concerns about potential loss of confidentiality, economic discrimination, and stigmatization.[13]

To explore how surrogates might react to a request for genetic samples, Freeman and colleagues[12] interviewed surrogate decision-makers for 117 critically ill patients admitted to medical and surgical ICUs. The surrogates were 48.4 ± 1.2 years of age, 33% male, and 21% African-American. One-third (37.6%) had 12 or fewer years of education. Surrogate decision-makers were willing to permit genetic testing to aid diagnosis (95%), guide drug prescription (97%), or explain familial or ethnic disease predisposition (90%), without apparent concern that findings would be stigmatizing. Genetic testing was not perceived to be a barrier to participation in clinical trials, with 91.4% indicating they would be "very willing or somewhat willing" to give consent. Few (7.7%) indicated that availability of a small honorarium would make them "much more likely" to give consent. However, a majority were reluctant to permit testing if employers (79.5%), health insurers (76.9%), or life insurers (78.6%) could access results.

The subject of safeguarding clinical trial participants has received extensive coverage in the literature and media. In

Table 2

Useful Tools for Addressing Conflict

Tool	Useful Phrases
Active listening	"What I'm hearing you saying is…." "It sounds to me as if you are concerned about…."
Realistic goal setting	"Despite our best efforts, it may not be possible to…" "Miracles do happen, but in my experience, it does not appear that…."
Explaining	"My view of the situation is that [example] would give her, at best, a less than 50% chance of improving."
Empathizing	"I can see that you care a great deal about …." "I think anyone would feel concerned in this situation"
Reframing	"What would [name] want in this situation?"
Brainstorming	"Lets' discuss several different choices and their consequences."

Adapted from: Beck AL, Arnold RM. Dealing with conflict in caring for the seriously ill. JAMA 2005;293:1374-1381.

this discussion, limited attention has been given to exploring preferences toward enrolling in such studies in the setting of critical illness. Genetic research presents unique ethical challenges not encountered in other studies enrolling critically ill patients. This study, one of the few to address this issue, suggests that surrogate decision-makers are willing to support such studies providing that data are collected anonymously. Future studies are needed to more fully understand how patients and surrogate decision-makers view this treatment option.

Summary

Dealing with end-of-life decision making is a critical, but difficult, skill to master. Recognizing and actively dealing with such issues can improve dialogue, and help guide surrogates and other health care providers through difficult decisions in a manner that results in a solution acceptable to all parties. The effort is time-consuming and challenging but the rewards justify the effort. As new insights evolve, it is likely that ability to provide appropriate support will continue to improve. ■

References

1. White DB, Curtis JR. *Curr Opin Crit Care*. 2005;11: 610-615.
2. Emanuel EJ, Emanuel LL. *JAMA*. 1992;267: 2067-2071.
3. Thompson BT, et al. *Crit Care Med*. 2004;32: 1781-1784.
4. Shalowitz DI, et al. *Arch Intern Med*. 2006;166: 493-497.
5. Hare J, et al. *Arch Intern Med*. 1992;152:1049-1054.
6. Smucker WD, et al. *Med Decis Making*. 2000;20: 271-280.
7. Coppolino M, Ackerson L. *Chest*. 2001;119:603-612.
8. Siders CT, Aschenbrener CA. *Physician Exec.* 1999;25: 32-37.
9. Back AL, Arnold RM. *JAMA*. 2005;293:1374-1381.
10. Stone D, et al. *Difficult conversations: How to discuss what matters most*. New York, NY: Viking Penguin Books; 1999.
11. Nelson JE, et al. *J Crit Care*. 2005;20:79-89.
12. Freeman BD, et al. *Crit Care Med*. 2006;34:986-994.
13. Lapham EV, et al. *Science*. 1996;274:621-624.

CME / CE Questions

15. Starting methylprednisolone more than two weeks after the onset of ARDS may have which effect?
a. increase the risk of death
b. decrease time on the ventilator
c. decrease time in shock
d. decrease mortality at 28 days
e. decrease mortality at 60 days

16. As compared with placebo, steroids given to patients with late-phase ARDS had which of the following effects?
a. increased risk of infectious complications
b. increased rate of neuromuscular weakness
c. decreased mortality at 28 days
d. decreased mortality at 60 days
e. decreased length of hospitalization

17. Immediate BNP testing in patients presenting to the emergency department with acute dyspnea, as compared to usual assessment and management without BNP testing:
a. reduced the number of patients admitted to the hospital
b. reduced the number of patients admitted to the ICU
c. reduced total treatment costs
d. all of the above
e. none of the above

18. Studies indicate that surrogates:
a. incorrectly predict patient preferences approximately one-third of the time.
b. are more accurate in their predictions if the patient and surrogate discus preferences.
c. are more accurate in their predictions than a "community" standard
d. refuse study participation for 50% of critical care protocols.
e. are less accurate in predicting treatment preferences than physicians.

Answers: 15 (a); 16 (b); 17 (d); 18 (a)

CME / CE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

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Capping Drug Benefits—Will it Help Control Healthcare Costs?

Controlling healthcare costs is tricky business, and sometimes the best intentions have adverse outcomes, as pointed out in a new study in the June 1 *New England Journal of Medicine*. Financial caps on Medicare drug benefits were reviewed in a large group of Medicare + Choice beneficiaries in northern California (over 150,000 individuals) who had $1,000 annual drug benefit cap compared to those who did not have a limit on their drug benefits (41,904 individuals). The cap on pharmacy costs was effective at reducing pharmacy costs by 31% (95% CI, 29 to 33%), but the capped group had total healthcare costs that were only 1% lower overall (95% CI, -4 to 6%). Those with capped benefit were more likely to visit the emergency department (RR, 1.09 [1.04 to 1.14) and were also more likely to be hospitalized for non-elective admissions (RR, 1.13 [1.05 to 1.21]). The death rate was also higher in the capped group (RR, 1.22), with a difference of 0.68 per hundred person-years [0 .30 to 1.07]. Patients on chronic medications for hypertension, hyperlipidemia, or diabetes were more likely to be nonadherent to drug therapy if they had a capped benefit and, for each of those diagnoses, physiologic outcomes were worse for subjects with capped drug benefits, including systolic blood pressure over 140 mm Hg, serum LDL greater than 130, and a HbgA1c over 8 (respective risk ratios 1.05 [1.00 to 1.09], 1.13 [1.03 to 1.25], 1.23 [1.03 to 1.46]).

The authors conclude that a cap on drug benefits was associated with lower drug consumption and unfavorable clinical outcomes. In patients with chronic diseases, the benefit cap was associated with nonadherence to drug therapy and poorer clinical outcomes. Overall, any savings realized by a drug cap was offset by an increase in the rate of hospital admissions and emergency department visits (*N Engl J Med*. 2006;354:2349-2359). An accompanying editorial states, "Effective strategies for reducing the level and growth of spending will need to rely on tools other than high-deductible plans and limits on benefits" such as preventative care and dealing with the obesity epidemic, as well as improved information systems (*N Engl J Med*. 2006;354:2385-2386).

The STAR Trial (Tamoxifen and Raloxifene)

Results from the long awaited STAR trial (the National Surgical Adjuvant Breast and Bowel project Study of Tamoxifen and Raloxifene) have been published as an early release article on the *JAMA* website. This multicenter trial of nearly 20,000 women mean age 58.5 years with an increased 5-year breast cancer risk was designed to compare the incidence of invasive breast cancer, uterine cancer, noninvasive breast cancer, bone fractures, and thromboembolic events in those treated with oral tamoxifen 20 mg per day or raloxifene 60 mg per day over 5 years. Tamoxifen has been used to treat early and advanced breast cancer for more than 30 years, and has also been shown to reduce the risk of invasive and non-invasive breast cancer in women who were at increase risk.

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The STAR was designed to see if the second-generation selective estrogen receptor modulator (SERM) raloxifene would also be effective in this role. Raloxifene is currently approved for the prevention and treatment of postmenopausal osteoporosis. After 5 years, there were 163 cases of invasive breast cancer in the tamoxifen group and 168 in the raloxifene group (incidence, 4.30/1000 vs 4.41/1000; RR, 1.02; 95% CI, 0.82 to 1.28). Noninvasive breast cancers were slightly more common in the raloxifene group (1.52 vs 2.11 cases per 1000; RR, 1.40; 95% CI, 0.98 to 2.00). The rate of uterine cancer was lower in the raloxifene group (RR, 0.62; 95% CI, 0.35 to 1.08). No differences were found for other invasive cancers, ischemic heart disease, stroke, or osteoporotic fractures. Thromboembolic events were more common in the tamoxifen group (RR, 0.70 nickel and 95% CI, 0.54 to 0.91). Cataracts and cataract surgery were also less common in the raloxifene group. The overall death rate and the causes of death were the same in both groups.

The authors conclude that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer, and has a lower risk of thromboembolic events and cataracts but is associated with a nonsignificant higher risk of noninvasive breast cancer (*JAMA* early release, posted online June 5, 2006 jama.ama-assn.org). This study is important because although there was no control group, tamoxifen is proven to reduce breast cancer incidence and is approved for this indication, but with a higher incidence of endometrial cancer, thromboembolic events, DVT, and stroke. Previous studies have shown that raloxifene reduces the risk of estrogen receptor-positive invasive breast cancer by up to 66% over 8 years of treatment compared to placebo (MORE and CORE trials [*JNCI* 2004;96:1751-1761]). Quality-of-life issues have been a concern with SERMs, and was hoped that raloxifene would be the better tolerated than tamoxifen.

An accompanying article also published online focused on patient reported symptoms and quality of life issues in participants in the STAR trial. There was no significant differences between tamoxifen and raloxifene in patient reported outcomes for physical health, mental health, and depression, although the tamoxifen group reported better sexual function (age-adjusted repeated measure odds ratio 1.22%; 95% CI, 1.01 to 1.46). Women in the raloxifene group reported more musculoskeletal problems ($P = .002$), dyspareunia ($P < .001$), and weight gain ($P < .001$). Women in the tamoxifen group reported greater severity of gynecological problems ($P < .001$), vasomotor symptoms ($P < .001$), leg cramps ($P < .001$), and bladder control symptoms ($P < .001$). Overall, mean symptom severity was low among women in both groups (*JAMA*. early release, posted online June 5, 2006 jama.ama-assn.org).

An accompanying editorial points out that tamoxifen is rarely used as an agent for protection against breast cancer in women at risk, and it had been hoped that raloxifene would provide an alternative with equal efficacy for breast cancer and less adverse effects. Unfortunately, the STAR trial does not clearly demonstrate this. Both drugs are effective at preventing breast cancer but both carry increased risk of endometrial cancer and thromboembolic events. Raloxifene has an advantage of being approved for reduction of osteoporotic fractures, but whether this will convince primary care physicians to prescribe the drug for women at risk of breast cancer is unknown (*JAMA*. early release, posted online June 5, 2006 jama.ama-assn.org).

FDA Actions

Merck has received approval to market a vaccine to prevent human papilloma virus (HPV) infections. The vaccine received a priority review, and is seen as a major advance because of the association between HPV and cervical cancer. The vaccine targets HPV types 16 and 18, which are responsible for 70% of cervical cancers and types 6 and 11, which are the most common cause of genital warts. HPV vaccine is given in 3 separate IM injections over 6 months and will cost $120 per dose, $360 for the entire course. It is approved for use in females age 9 to 26. Merck will market the HPV vaccine as Gardisil.

Merck has also received approval to market its live zoster vaccine for the prevention of herpes zoster in individuals aged 60 and older. The vaccine, which is a live attenuated varicella-zoster virus, is given as a single-dose subcutaneous injection. The vaccine has been shown to significantly decrease the rate of varicella-zoster (shingles) in older adults and decrease the rate of postherpetic neuralgia in those who developed shingles despite the vaccine. Merck will market the live zoster vaccine as Zostavax. ■