Quality, patient safety, and culture: ‘We have met the enemy and he is us’—Pogo (Walt Kelly, 1971)*

The director of every intensive care unit is constantly faced with the task of improving the quality and efficiency of the care delivered to the critically ill patients in his or her charge. The very concept of “quality” has always been problematic: defining and measuring “quality” health care has always been difficult, while improving it, or, for that matter, effecting any change in medicine, has historically been easier said than done. The quality movement in medicine was initiated by Florence Nightingale when she undertook the first audits of hospital mortality rates and began a campaign to collect uniform hospital and surgical statistics so that the “laws which regulate diseased action would become better known, the results of particular methods of treatment, as well of special operations, would be better ascertained than they are at present.” (1) Although her pioneering work was championed by the International Statistical Congress of London, the medical community was less than impressed and change came slowly and belatedly. After all, she was a woman and not a physician.

Fifty years later, Ernest Amory Codman, an innovative Boston surgeon who was as confrontational as Nightingale was reclusive, dedicated his career to the challenge of improving quality. In 1910, he went public with his “End Results Idea.” As Codman stated, this “was merely the common-sense notion that every hospital should follow every patient it treats, long enough to determine whether or not the treatment has been successful, and then to inquire ‘if not, why not’ with a view to preventing similar failures in the future” (2). This concept proved to be spectacularly unpopular within the medical community. In 1914, shortly after proposing an even more radical program for evaluating the performance of surgeons, the Massachusetts General Hospital revoked his staff privileges and he was expelled from the Massachusetts Medical Society. Codman himself predicted that several generations of physicians would come and go before his efforts would be recognized and translated into meaningful improvements in patient care and outcomes (3). He was, of course, incorrigibly optimistic (4).

Many efforts to implement quality measures have met with stubborn resistance from even the most well-intentioned practitioners and there has been little to show in the way of substantial improvements. As the cost of health care has risen, numerous studies began to point out the financial cost of low-quality care and medical errors (5). Indeed, the business case for quality has been made repeatedly, a prime example being the formation of the Leapfrog Group by the Business Roundtable in November 2000 (6). A major shift in the quality movement took place in 1999 with the publication of “To Err Is Human: Building a Safer Health System” by the Institute of Medicine (7). This report estimated that as many as 98,000 Americans died annually of preventable medical errors. This ushered in the era of patient safety. Spurred on by this report and the growing awareness of the immense human and financial costs of medical errors and less than optimal quality care, governmental agencies, accrediting bodies, nonprofit organizations, and hospitals poured substantial resources into efforts to improve patient safety. Whether these efforts have made a difference is unclear. A recent study by the Office of the Inspector General for the Department of Health and Human Services (8) found that one of every seven Medicare beneficiaries who is hospitalized is harming as a result of systemic problems with healthcare delivery. Unexpected adverse events added some $4.4 billion to annual healthcare costs and contributed to some 180,000 deaths per year. The study also noted that in the month of October 2008, 134,000 Medicare patients experienced at least one adverse event with at least 44% of them being preventable. This study is depressingly similar to the retrospective study of 2341 admissions in ten hospitals in North Carolina from 2002 through 2007, which found that there were 25 harmful events per 100 admissions. Over this 7-yr period, there were no significant reductions in either the overall event rate or the preventable event rate (9). Although medicine has been notoriously famous for resistance to change, the lack of progress on the quality front is astounding. Robert H. Brook, one of the founders of the modern academic quality movement, recently acknowledged this and declared “the end of the quality improvement movement” as we know it (10).

In the face of this resounding lack of progress, what are the physician and nurse directors of intensive care units to do? Why is change so difficult to implement? The problem, of course, lies within our own environments, or as Pogo said, we have met the enemy and he is us. We need to examine ourselves and our own unique cultures. Although organizational psychology and culture are not taught in medical schools, we are fortunate in that we have colleagues in the social sciences who have taken an interest in our world and examined it (11). Indeed, although there is a substantial body of literature regarding corporate cultures and behaviors, there has been growing interest in the unique culture of medicine and hospitals, which proves to be significantly more complex, if not more interesting. Edgar Schein, who is generally credited with creating the phrase “corporate culture,” defines organizational culture as: “A pattern of shared basic assumptions that was learned by a group as it solved its problems of external adaptation and internal integration, that has worked well enough to be considered valid and, there-

*See also p. 934.

Key Words: culture; quality; climate; patient safety; medical errors

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fore, to be taught to new members as the correct way you perceive, think, and feel in relation to those problems” (12). Schein goes on to state that culture is the most difficult organizational attribute to change, outlasting organizational products, services, founders, and leadership and all other physical attributes of the organization. Finally, he notes that “the bottom line for leaders is that if they do not become conscious of the cultures in which they are embedded, those cultures will manage them.”

Culture, however, is not the same as climate. The quality literature is replete with references to patient safety climate and patient safety culture. Although organizational culture includes deeply held values, beliefs, and assumptions, organizational climate, on the other hand, is often defined as the recurring patterns of behavior, attitudes, and feelings that characterize life in the organization. Organizational climate has also been described as a way of quantifying the “culture” of an organization, a measurable set of properties of the work environment, perceived directly or indirectly by the employees, which can be a major force in influencing employee behavior. Organizational theorists have suggested that culture is like the personality of an individual, something difficult if not impossible to change, whereas climate is similar to mood, more easily modifiable. It may well be that long-term modification of climate may well result in a change in culture. Culture in turn influences climate.

In this issue of Critical Care Medicine, Sexton and colleagues (13), already extensively published in the fields of safety, quality, and medical error reduction, present evidence that the perception of patient safety climate can in fact be modified. This is just one of many papers by these authors regarding the use of a specific tool, the CUSP—comprehensive unit-based safety program, for the improvement of the patient safety climate. In this particular study, the CUSP was used in 71 intensive care units with surveys assessing the perception of patient safety taken in 2004 and again in 2006. The results show that it is indeed possible to change the perception of the patient safety climate, a significant step forward in realizing a durable positive change in unit safety culture. The CUSP is already used throughout the United States and in many other countries. Although there have been studies demonstrating the relationship between a climate of patient safety and safety performance (14), it is the change in culture that has been the most difficult to effect and assess. Whether this will translate into meaningful and lasting improvements in clinical outcomes remains to be seen.

The lessons for directors of intensive care units are that climate and possibly culture can be both measured and modified and that validated tools to effect that change are now available. Equally important is that the directors and managers of units must take time to understand the cultures and climates of their units. The lack of progress over the past decade in reducing preventable errors must not be allowed to persist. The study by Sexton and colleagues holds out the hope that climate change may be the means to move forward.

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Beta-blockers: Essential heart failure therapy*

Beta-blocker therapy was first successfully used for the treatment of left ventricular systolic dysfunction in the late 1970s (1). Since then, many large randomized, prospective, controlled trials have demonstrated the benefits of β-blocker therapy after acute myocardial infarction, in heart failure resulting from ischemic and non-ischemic cardiomyopathy, and in patients with class III and IV heart failure (2–5). These studies have resulted in strong recommendations in current heart failure management guidelines for the use of the β-blockers metoprolol succinate, carvedilol, and bisoprolol in patients with symptomatic and asymptomatic left ventricular dysfunction.

What is the best approach regarding β-blockers in patients who experience significant decompensation in their heart failure status? Small studies support the use of β-blockers after acute heart failure resulting from left ventricular systolic dysfunction, were felt to require inotrope therapy, and received a course of levosimendan or dobutamine. The use of β-blockers was determined by the treating centers, not mandated by study protocol. Patients receiving β-blockers at entry and also at hospital discharge had shorter hospitalization times and better survival at 30 and 180 days postdischarge than patients who did not receive β-blockers or who had them withdrawn (although the latter was not statistically significant after an adjustment for age and comorbid conditions). Interestingly, patients who were not on β-blockers at entry but who were discharged on therapy also had poorer outcomes, possibly because they had yet to accrue the benefit of longer-term β-blockade before hospitalization.

The beneficial effects of β-blockers in the setting of left ventricular systolic dysfunction are in large part mediated through attenuation of catecholamine-mediated stimulation of cardiac β-receptors and cardiac and vascular α receptors (carvedilol has β- and α-blocking properties). Sympathetic nervous system activation is a key mediator of cardiac remodeling in heart failure, and β-blocker-mediated reductions in heart rate, oxygen consumption, vasoconstriction, and cell necrosis result in reverse remodeling, often with significant improvement in left ventricular geometry and systolic performance.

Heart failure practice guidelines emphasize continuation of chronic oral heart failure medical therapy during acute heart failure hospitalizations. Reducing β-blocker doses or withholding therapy is only to be considered if marked volume overload is present, because up titration of β-blockers while patients are still congested may reduce the effectiveness of therapies to relieve congestion (11). European Society of Cardiology guidelines agree that β-blockers should only be stopped if patients are unstable with signs of low output or if there is severe bradycardia, advanced heart block, bronchospasm, or cardiogenic shock (12). Heart Failure Society of America guidelines also concur. Temporary dose reduction by 50% could be considered in patients with severe heart failure exacerbations, and abrupt discontinuation should be avoided except in life-threatening circumstances (13). There is also widespread recognition that patients are far more likely to continue on recommended heart failure therapies if these are prescribed at the time of hospital discharge rather than assuming they will be resumed when patients are “more stable” at some time after discharge.

There is solid support for prescribing β-blockers, titrating to maximal tolerated doses, and continuing therapy even during acute exacerbations in patients with heart failure. Our patients will benefit as we understand these principles and consistently apply them in practice.

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*See also p. 940.

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n this issue of Critical Care Medicine, Maraví-Poma and colleagues (1) describe the impact of the 2009 pH1N1 pandemic on pregnant women admitted to 148 Spanish intensive care units from April 2009 to February 2010. Using a voluntary registry, the authors describe the impact of the viral infection on the prevalence, morbidity, and mortality of women of childbearing age (pregnant or nonpregnant) admitted to intensive care units in Spain. This study confirms several important pieces of information and presents a strong message to the critical care community.

If any doubts existed after the publication of the first series of cases arising in the United States (2, 3) and Australia and New Zealand (4), the associated article (1) demonstrates just how fast a scientific society can, with the enthusiasm and motivation of intensive care professionals, set up the structures and negotiate the processes necessary to perform real-time data collection on new diseases. This is not a minimal task with the burgeoning bureaucracy that has developed after recent legislation in Europe that has impacted significantly on health-care research. Perhaps the most important part of these processes, however, is the ability for these registries to acquire and assess the data and provide feedback to the clinical community that enables diagnostic algorithms to be honed and practice guidelines developed. One of the more impressive feats of the Spanish study was their ability to look at the data and provide weekly reports from the Spanish Society of Intensive Care Medicine to the local clinicians. Not only was this a reassurance for the hard-pressed workforce, but also provided valuable insights that certainly improved treatments and probably saved lives. It must be remembered that this current pandemic is barely 1 yr old and the data that are now available are changing the way we look at the presentation and treatment of this disease before it has been confined to the textbooks of history. This is an opportunity that our predecessors never had. These processes are similar to those described during the Severe Acute Respiratory Syndrome epidemic in Toronto in 2003 (5).

Since the early reports described the demographic characteristics of the populations affected by the 2009 pH1N1 virus, it has been suggested that pregnant women have a disproportionately higher risk for hospitalization and death than nonpregnant women (2). This fact has been suggested in several different populations that include the United States (2, 3) and Australia and New Zealand (4). The study from Spain has a similar finding with a six-fold increase in intensive care unit admission rate and a sevenfold increase in the likelihood of dying when comparing pregnant with nonpregnant women of potential childbearing age. These increases in prevalence and risk of death have been described in previous influenza pandemics as far back as 1918 (6, 7). The reasons behind this, however, are not well understood with several immunologic mechanisms linked to the selective immunosuppression existent during pregnancy being hypothesized as being a likely important risk factor (8). The interesting finding in this study, however, is that although the risks are greater, pregnancy per se is not an independent risk factor for mortality with only the severity of illness and the presence of obesity being related to death. This raises the question as to what it is about the pregnant patients that renders them more liable to this disease if it is not the pregnancy on its own.

Mortality attributed to the influenza pH1N1 infection has been shown to be related to a number of factors that include time to presentation, delays in appropriate treatment, the development of viral pneumonia, and also the existence of a number of comorbidities, perhaps the most well known being obesity and asthma. A further factor that affects the likelihood of acquiring the infection is whether the patient has been vaccinated. Despite knowing these data, the absolute mortality remains worryingly high (5%) in the United States despite the fact that Siston et al [2] analyzed a sample of all cases reported to the Centers for Disease Control and Prevention.
Putting intensive care unit data into the public domain—And using it effectively*

Saeed et al (1) report in this issue on the creation of a robust deidentified intensive care unit (ICU) database that they have made publicly available to other investigators. The Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC-II) database has the potential to be an important facilitator of ICU research. However, there are several aspects of the data set that investigators should consider when planning studies. First, the authors used data entered into an operational ICU clinical information system (CIS). Use of ICU CISs has increased significantly over recent years, driven by governmental incentives and the belief that electronic data systems can improve patient outcomes. Operational CISs are considerably different from traditional research databases. In the former, trained data collectors expend considerable energy to ensure that data are complete and accurate. In contrast, real-world documentation oftentimes is viewed as a necessary task, but not one requiring primary focus. Data may not be entered in a timely fashion; physicians vary in their attention to detail and the completeness of their documentation, typographic errors occur, and erroneous assessments can be immortalized. There also is the potential for information bias. For example, despite recommendations calling for routine assessment of patients for delirium, few ICUs do this in a structured manner; as a result, delirium scores tend to be documented only in patients with agitation. Attempting to determine the incidence of delirium from such data would likely underestimate the true incidence.

What most distinguishes the MIMIC-II database is its open access, which allows

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*See also p. 952.

Key Words: critical care research; clinical databases; ICU clinical information systems

Dr. Breslow is an employee of Philips VISICU and is co-creator of an ICU research database.
interested investigators to independently use the data. One hopes that this will increase the number of studies that will be generated from the data set. However, most clinicians lack the requisite technical skills to perform research with complex databases, and a database analyst familiar with large clinical databases will be a necessary part of the study team. Preliminary queries oftentimes will be required to assess the feasibility of performing a given study (eg, are there sufficient numbers of patients with the problem to be studied). Investigators will need to evaluate data quality and develop strategies for handling missing and bad data. Are missing data assumed to be normal (eg, does the absence of a pH result imply that the clinical team had no concern about acid-base disturbances), or should that patient be excluded from the analysis? What strategies will be used when nonphysiological values are encountered? These efforts take considerable time and experience, and investigators must be careful to avoid drawing inappropriate conclusions. Open access to the data also places greater concern on data deidentification procedures. Although the MIMIC-II database was stripped of obvious identifiers, the known source of the data increases the risk of patient identification. For example, it might be fairly easy to associate a medical event described in the Boston Globe (eg, gunshot wound of a 22-yr-old morbidly obese woman pregnant with twins) with a patient in the database. The creators of the MIMIC-II database chose to include free-text documents after stripping out obvious identifiers. Despite assurances that this methodology is reliable, investigators should be aware that apparently benign text can increase the number of studies that will be generated from the MIMIC-II database (2, 3) and highlight additional potential uses. Despite the power of such studies, investigators considering using the MIMIC-II database need to appreciate several important limitations of database studies. Sophisticated and complex risk adjustment methodologies must be used to compensate for the diversity of diseases and variability in chronic health status and severity of illness. Most validated ICU scoring systems have focused on admission risk (4–6) and thus are not useful when evaluating events that occur later in the ICU stay. As mentioned previously, questions focusing on specific diagnoses or therapies may not be feasible because of inadequate numbers of patients in the database. Finally, research should be limited to identifying previously unrecognized associations rather than attempting to establish causality.

Other organizations have recently reported on the use of ICU CIS databases for research. The Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC) data mart contains ICU CIS data from 204 ICU beds at the Mayo Clinic hospitals (7). The METRIC data mart is used for clinical reporting, real-time clinical decision support, and clinical research (8). Our group (Philips VISICU) aggregates deidentified ICU CIS data from >500 U.S. ICUs with remote ICU care programs and has made these data available to investigators from the sites contributing data through the self-governing eICU Research Institute (9). Research proposals are prioritized by the eICU Research Institute publications committee (comprised of investigators from participating institutions), and all analytic work is performed by an independent designated academic research team. The issues raised about the MIMIC-II data apply to these latter two databases as well. The availability of the MIMIC-II database promises to generate valuable insights into ICU care. The authors are to be congratulated for making this important resource available to all.

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REFERENCES
Passing the bug—Translocation, bacteremia, and sepsis in the intensive care unit patient: Is intestinal decontamination the answer?*

Sepsis is common and a cause of significant mortality in the intensive care unit (ICU) patient (1); the frequent isolation of enteric-type Gram-negative organisms from such cases understandably led to the incrimination of the gastrointestinal tract as the source of such grave infections. An enthusiasm for “decontaminating” the intestine followed and, although this strategy did result in a decline in bacteriologically confirmed episodes of bacteremia, clinically relevant end points proved more resistant to change and concerns regarding the risks of such widespread antibiotic use persisted, resulting in reluctance to adopt this approach (2, 3). Recent studies and the very large Dutch multicentered randomized controlled trial, in particular, have, revived interest in decontamination by showing, in the latter case, a modest but statistically significant reduction in day 28 mortality in comparison to standard care for those randomized to selective decontamination of either the oropharynx or gastrointestinal tract (number needed to treat to prevent one death at day 28: 19 and 24, respectively) (4).

In that same study, ICU-acquired bacteremia was less common among those randomized to intestinal decontamination (4); the aim of the study reported by Oostdijk and her colleagues (5) in this issue of Critical Care Medicine was to further define relationships between intestinal decontamination and Gram-negative bacteremia. For this study, an additional 1042 patients from a single center were added to the 5939 patients from the original multicentered study. Oropharyngeal decontamination involved the application of a paste containing colistin, tobramycin, and amphotericin B; intestinal decontamination involved the additional administration of a suspension containing the same three antimicrobials through a nasogastric tube, also for the duration of ICU stay, and intravenous cefotaxime for the first 4 days. Gram-negative organisms were detected by cultures of daily rectal swabs and bacteremia by blood cultures. In pooled data from both populations, ICU-acquired bacteremia, at 6.2% and 4%, respectively, was more common among those who received standard care or oropharyngeal decontamination than among those who received intestinal decontamination, at 1.9%. Based on the temporal association between positive rectal swabs and bacteremia with the same organism as well as their estimates of the contribution of oropharyngeal bacterial contamination, the authors concluded that gastrointestinal carriage of Gram-negative bacteria was responsible for at least 36% of all episodes of ICU-acquired Gram-negative bacteremia. One could logically assume that the successful elimination of intestinal Gram-negatives would reduce or eliminate these episodes of bacteremia and benefit the patient.

Not so fast! Although the sheer size of the study population tends to minimize the effects of confounding factors, there are some noteworthy methodologic limitations. First, although the addition of the single-center cohort augmented numbers further, these subjects were not randomized in the same manner as the original group; second, rectal samples were not obtained from all study groups; third, blood cultures were obtained, not according to a set and uniform protocol, but as clinically indicated; and, finally, clinical outcomes are not provided. One could assume, based on the results of the original randomized controlled trial (4), that bacteremia did not influence clinical end points and mortality, in particular. In this article, the authors concede this point by calculating a number needed to treat of 50 for intestinal decontamination to prevent Gram-negative bacteremia, not to mind significant sepsis or death (5). Elsewhere they have reported on a trend toward an increased risk for nosocomial infections in treated patients after their transfer from the ICU to hospital wards (6) and on the potential for promoting antibiotic resistance with these strategies (7).

The concept of intestinal translocation of enteric bacteria and their association with Gram-negative sepsis was established decades ago in animal models (8) and its occurrence linked with a number of disorders that are likely to be encountered in the ICU: major surgery, shock, burns, liver cirrhosis, and portal hypertension (9), to name but a few. Indeed, the critically ill ICU patient would appear to be primed for its occurrence given the high prevalence of intestinal dysmotility, ileus, increased intestinal permeability, impaired intestinal blood flow, local and systemic immunosuppression, and alterations in the gut microbiota in this context (10, 11). However, clinically relevant translocation has been more difficult to demonstrate in humans and direct correlations among enteric organisms, gut dysfunction, bacteremia, and sepsis more elusive (12, 13). Many factors contribute to this dichotomy between laboratory animals and humans and are especially relevant to the ICU patient. First and foremost is the clinical scenario; this is a highly heterogeneous population (a factor that should have been diminished by the sheer weight of numbers in the study by Oostdijk and colleagues) with varying comorbidities and subjected to a host of potentially confounding interventions (as exemplified by the frequent use of other antibiotics in all arms of this study). It is

*See also p. 961.

Key Words: intestinal decontamination; Gram-negative sepsis; intensive care unit; bacterial translocation; bacteremia; microbiota

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nigh impossible to control for such a multiplicity of variables.

Enter next the chicken and the egg! Are the proposed changes in intestinal permeability and resultant translocation mere epiphenomena and resultant translocation in a severely ill patient and not independent variables predictive of outcome? This remains a possibility until more direct evidence to incriminate translocation as a primary phenomenon is extant. Indeed, mindful of these issues, the very definition of translocation has been questioned. Originally coined by Berg and Owens to refer to the passage of viable bacteria from the gut through the epithelium to the lamina propria and thence to mesenteric lymph nodes and possibly other organs (8), and subsequently modified by Alexander to refer to the movement of viable and nonviable microbes or their toxic products across an intact intestinal barrier (14), Tsujimoto and colleagues (13) have proposed a radical revision that includes translocation of pathogen-associated molecular patterns. In support, they draw on an extensive literature associating a variety of pathogen-associated molecular patterns such as lipopolysaccharide on Gram-negative organisms and lipoteichoic acid on Gram-positive organisms as potent activators through their relevant Toll-like receptors of an intense inflammatory response akin to that seen in overwhelming sepsis and the sepsis-induced systemic inflammatory response syndrome (11, 13).

Oostdijk and her colleagues are to be congratulated on grasping with both arms the nettle that is sepsis in the ICU; they have convincingly shown that their strategies for decontamination of the oropharynx and gastrointestinal tract can reduce mortality (4), but I would suggest that the evidence that intestinal decontamination exerts its benefits through the reduction or elimination of clinically relevant Gram-negative bacteremia remains precariously circumstantial and, taken together with the associated risks (15), the case for adoption of this approach, over the more limited strategy of oropharyngeal decontamination, for example, in clinical practice, not proven.

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REFERENCES

Palliative care makes intensive care units intensive care and intensive caring units*

“Where will ‘usual care’ in advanced illness be ‘palliative care’?”
—Meg Campbell (1)

No where is palliative care more imperative than it is in critical care. The potential for both patient and family suffering is great. Most patients experience pain, discomfort, fear, and confusion. Approximately 20% of deaths in the United States occur during or shortly after an intensive care unit (ICU) admission (2). For many critical care practitioners, there used to be a blurring in the distinction between palliative care and end-of-life care. Today the blurring is between palliative care and usual care. Some of our patients are at the end of their lives but most of them are suffering.

During 45 yrs of critical care practice, I have seen several phases. In the 1970s and 1980s, the science of critical care medicine developed quickly and led to an increased ability to save lives. However, by the late 1980s, intensive care was described as an arena for punitive survivalists. Patients were being asked to suffer through more and more interventions.

We had not developed the knowledge and skills needed to administer narcotics and sedatives safely. In the 1990s, with the intention of reducing suffering, we overcorrected and some of our patients spent part of their ICU stay in drug-induced comas. Recently, we have come to understand that this practice increases the patient’s length of stay and potential for developing the complications of critical illness. We struggle to limit the use of narcotics and sedatives while monitoring patients for discomfort and distress.

Palliative care refers to interventions that reduce the severity of disease symptoms rather than treating the disease itself. Because we have always wanted to reduce patient suffering, palliative care has always been an integral part of our practice although we have not labeled it as such.

In the past decade, there has been a tremendous increase in the emphasis on palliative care. Eighty percent of hospitals with >250 beds and 55% of those with >50 beds now have palliative care programs. The prevalence of hospital programs increased 125% between 2000 and 2008 (3). Membership in the American Association of Hospice and Palliative Medicine increased from 2100 in 2004 to 4000 in 2010. In the same period, membership in the Hospice and Palliative Care Nurses Association increased from 6850 to 9800 (4) The National Priorities Partnership convened by the National Quality Forum has set palliative care as one of the six health care priorities for the United States (4). Since January 2011, Medicare regulations provide for payment of time spent advising patients about options for end-of-life care, a discussion that should also include descriptions of palliative care. This policy may help eliminate one barrier to palliative care: the limited time practitioners have to spend communicating with patients and their families.

Quality improvement cannot occur in palliative care without assessment tools. In this issue of Critical Care Medicine, Ho et al (2) describe an effort to develop a tool to determine clinicians’ perceptions of palliative care in their ICU. Based on seven domains of palliative care recently developed by the Robert Wood Johnson Foundation’s Critical Care End-Of-Life Peer Work Group (5), a ten-question survey was developed. Their study takes a step toward determining the items’ content validity. Although the ultimate goal for palliative care programs is improved patient and family outcomes, it is important to evaluate the structures and processes that lead to those outcomes. Clinicians are positioned to assess these aspects. Future studies could compare patient and family assessments with those of physicians, nurses, and social workers, a third key member of the palliative care team (6).

The authors used the survey tool to evaluate the quality of palliative care in 13 ICUs from the perspectives of 289 nurses and 188 physicians. Because it was a convenience sample, their results cannot be generalized to other units. It was not surprising that significant differences were found in the perceptions of these two groups. Differences are frequently found between nurse and physician perceptions of the care provided critically ill patients. Why would perceptions of two professions with unique roles and responsibilities be expected to be the same? In fact, identifying differences can lead to a richer discourse and more creativity in process improvement.

The demand for palliative care is expected to continue to increase (7). Several tools are being created to help units meet this demand. Professional organizations have published recommendations for end-of-life and palliative care in intensive care (8–10). Studies have evaluated the impact of palliative care programs on the cost of care (10–12). A format for comparing and contrasting consultative vs. integrated models of palliative care delivery in the ICU is available (13). Triggers for palliative care consults (14) and a “bundle” of palliative care quality measures have been developed for ICUs (15).

Some aspects of palliative care are difficult to quantify but easy to recognize. They involve the art of compassionate care practices. At our best, we are keenly aware of patients and families as individuals, we use frequent touch and eye contact, we tell them what we are doing, we act with tenderness, we minimize discomfort and anxiety, we seek out interactions with families, and we acknowledge and address conflict. At our worst, we are more concerned about devices than patients, we are not gentle with patient care.

*See also p. 975.

Key Words: palliative care; intensive care; critical care; quality improvement; clinicians’ ratings; end-of-life care

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and interventions, we avoid family contact, and we ignore or disguise conflict.

Socrates said that the best way to live with honor in this world is to be what we pretend to be. As critical care practitioners, we have stepped up to society and offered our service in the zone between life and death. We promise to do our best to save lives and, when that is not possible, to focus on comfort and dignity in death. In either case, we commit to providing care in a compassionate, caring, gentle, and respectful way. Palliative care is a core part of critical care. Maureen A. Harvey, RN, MPH, FCCM Consultants in Critical Care, Inc Glenbrook, NV

REFERENCES


Biomarkers in fever and neutropenia: A solution in search of a problem?*

The management of febrile neutropenia has not changed all that much since the studies almost 40 yrs ago that showed that empiric treatment of fever with broad-spectrum antibiotics active against Pseudomonas aeruginosa was superior to the previous practice of initiating antibiotics after documenting infections (1). Current guidelines continue to support this strategy: start broad-spectrum agents and continue them until both the fever and the neutropenia have resolved (2). The overall mortality of an episode of febrile neutropenia is 3–10% (3), suggesting that the empiric approach is successful. A persistent problem, however, is that fever may be the result of multiple factors, and in fact bacterial infection is documented in less than half of the episodes (3). This suggests that exposing all patients with febrile neutropenia to antibiotics is wasteful and, in this era of increasing bacterial resistance, even dangerous. In this context, several biomarkers with the potential to discriminate between infected and noninfected patients have been studied (4–6). In this issue of Critical Care Medicine, Lin et al (7) publish their investigation of soluble triggering receptor of myeloid cells (sTREM-1) alone or combined with procalcitonin to identify patients with febrile neutropenia without infection. Other investigators have just published their findings on the same topic in pediatric patients (8). Both articles have some methodologic problems, but even if one accepts their results at face value, the conclusion is fairly consistent: sTREM-1 determination is not sensitive or specific enough to be useful in neutropenic patients with fever. sTREM levels were significantly higher in patients with infection only in the Lin et al study, but as Figure 4 of their article shows, only one-fourth of the patients identified as “low risk for infection” were indeed infected. The results in the article by Miedema et al (8) are even less supportive of a role for sTREM in this setting. Given that TREM-1 is upregulated in neutrophils and monocytes during bacterial infection (9), it may come as no surprise that detection of its soluble form has limited value when the neutrophil count is low.

After some very promising initial investigations (10, 11), the record of sTREM as a useful marker for infection is

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*See also p. 993.

Key Words: febrile neutropenia; fever; granulocytopenia; sTREM-1; interleukin 8; procalcitonin; biomarkers

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mixed, and recent studies suggest the discriminating power of the test is not good enough (12–14). After the results from Lin et al and Miedema et al, it would seem prudent to refrain from advocating its use as a marker of infection during neutropenia.

Regarding the general use of biomarkers in febrile neutropenia, it would be desirable to define exactly what the problem is that needs to be addressed. There is no question that patients with fever and neutropenia are a heterogeneous group in terms of risk of infection and death, and targeted management seems very appealing. (In fact, they are so heterogeneous that any study of biomarkers may not be generally applicable.) In any case, one must weigh the risk of overuse of antibacterials against the risk of withholding antibiotics in neutropenic patients in whom bacterial infection may progress most quickly. The general problem with any test applied to patients with fever and neutropenia is that it must be at least as sensitive as fever itself and more specific: false-negatives (infected patients misidentified by the test as noninfected) are unacceptable. In particular, to discontinue antibiotics in a neutropenic, febrile, critically ill patient in the intensive care unit, a test with a nearly 100% negative predictive value would be required. It should be kept in mind that the persistent mortality of febrile neutropenia is seldom caused by using too many antibiotics for too long; rather, it is the result of antibiotics being started too late. Even if an ideal biomarker or combination were found that allowed 100% accurate identification of infected patients and early discontinuation of antibiotics, the bulk of the mortality of febrile neutropenia would remain untouched. This is not to imply that decreasing cost and inconvenience are not worthy goals; it is just to put the problem into perspective. It is perhaps ironic that a well-established method to decrease costs, and possibly reduce mortality, is to administer antibi-

What should the intensive care medicine practitioner know about all these tests? It seems fair to say that, as yet, they are for research only. The currently available data suggest interleukin-8 and procalcitonin are the most promising (6, 8). Interleukin-8 was used to discontinue antibiotics in low-risk patients in a proof-of-concept study (5). Procalcitonin seems to be also a sensitive marker, and it might be useful combined with others (6, 8, 18).

In general, any study of biomarkers in fever and neutropenia should formulate a feasible strategy to use the biomarker in question and ideally explain in detail how (or by how much) the proposed approach would improve on our current practice.

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The family experience with intensive care unit care: More than mere satisfaction*

Qualitative analysis of an intensive care unit family satisfaction survey" by Dr. Henrich and colleagues (1) in this issue of Critical Care Medicine is an excellent multisite study that evaluates the intensive care unit experience directly through feedback from family members. The study analyzed the write-in comments returned on a validated survey of satisfaction with intensive care unit care. An excellent response rate was achieved. The purpose of this qualitative analysis was to identify themes of family member experiences. The themes that emerged were both positive and negative, depending on whether the situation was handled well. The six most frequently recounted themes were quality of staff, overall quality of medical care, compassion and respect shown to the patient and family, communication with doctors, waiting room, and patient room. The selection of themes was well-supported through rich description (1). In the future, these themes could be considered essential elements within evaluations of intensive care unit family satisfaction. Physician and staff educational programs could focus on these themes to form discrete items within family-centered care competency.

After reading the article, I was left wondering whether there was any difference in the responses of family members of survivors vs. nonsurvivors. Also, although results were presented in text and in tabular format, it would have been helpful, as is typical within qualitative work, to generate a concept map visually depicting the inter-relationships between constructs forming the themes. These two suggestions could provide context for ad hoc analyses.

Due to the multisite nature of the research, the results are more generalizable than those of most qualitative studies. The site-specific issues were appropriately minimized by the weighting of the scores. However, administrators may learn from this report to use the technique of sorting survey comments into themes to identify site-specific concerns within a performance improvement program. In fact, in my own organization we have purchased NVivo (QSR International, Doncaster, Victoria, Australia) for just this purpose, with the plan to analyze themes in patient as well as in staff surveys. It stands to reason that negative comments occurring in themes without prompting are fertile areas for improvement. For example, in a previous study including an analysis of family needs (2, 3), as in this one by Dr. Henrich and colleagues (1), the issue of parking was repeatedly found in the write-in comments. One participant even stated, [paraphrased from transcript] "I stay all day to be with my husband and I am exhausted by the evening but the cost of the parking is so high. The staff told me if I wait until after 10:00 when the attendant goes home, I would not have to pay. So, I stay and it drains me." Another participant commented, “Finding a spot starts the day with a lot of stress. I barely have enough energy to cope as it is. The added stress of parking is enough to tip me over the edge.” Parking is a modern-day concern not found in the older literature and should be considered in urban environments. The stress imposed by inadequate parking services may affect the overall experience and further the development of anxiety in an already unbearable situation (3). This example of parking, a previously unattended issue in the medical literature, is not just a matter of keeping our customers happy, but instead it is a factor in maintaining the family member’s strength to cope while minimizing the incidence of anxiety.

Dr. Henrich and colleagues provide further validation of the recommendations within the Society of Critical Care Medicine/American College of Critical Care Medicine guideline for family support (4). Since the publication of the guideline in 2007, more than 40 research studies have been published on family support, with none refuting and all adding to validate various recommendations within the document (Web of Science, Journal Citation Reports, Davidson 2007). In particular, the findings of Dr. Henrich and colleagues support flexible visiting, the need for frequent visiting, and the family desire to participate in rounds. Again, meeting these family needs is more than just a nice thing to do, it creates a relationship with family health.

The negative family experience is related to adverse psychological outcomes such as anxiety, depression, posttraumatic stress, and complicated grief that may last at least 4 yrs after discharge or death (5–10). Because of the growing concern regarding long-term effects to the patient and family in response to critical illness, the Society of Critical Care Medicine recently convened a task force to address the issue. The task force, led by past president Maureen Harvey, RN, FCCM, and I proposed a new term to describe the cluster of events experienced by patients and their families long after discharge: postintensive care syndrome. The patient response includes physical, psychological, and cognitive components. The family psychological response is referred to as postintensive care syndrome—family (see Critical Connections, December 2010).

This new study by Dr. Henrich and colleagues (1) provides insight into a new approach for evaluating the family experience so that deficits in the environment and quality of care can be addressed proactively. Most importantly, Dr. Henrich and colleagues highlight issues that are of most importance to families, validated through the voice of the family. If action were taken to assure a program of family-centered care inclusive of the six essential
Making progress with the egress*

Would P.T. Barnum make a good hospital administrator?

The legendary showman P.T. Barnum operated a museum in New York during the mid-19th century that was a cross between a circus sideshow and a venue for unusual artifacts and animals. The museum was popular but Barnum realized that he was losing money because visitors were staying too long. To reduce the length of stay, he posted a sign pointing to a door that said “This Way to the Egress.” Patrons followed the sign to what they thought was another exhibit only to be led outside because the word egress is synonymous with exit (1). If only reducing length of stay in the intensive care unit (ICU) was so simple!

Kramer and Zimmerman (2) have conducted an important multicentered study on length of stay (LOS) in this issue of Critical Care Medicine. Their two main conclusions are that hospital and ICU LOS are strongly correlated and that some hospitals were more efficient (had shorter mean hospitalizations than expected after adjusting for case mix) than others (2). Although these findings are not unexpected, their article raises many issues that warrant comment.

How to Model Length of Stay

First, hospital LOS is measured here as time between ICU admission and discharge in an attempt to better capture the role ICU LOS has on subsequent LOS. This novel approach is valid because time before ICU admission was an independent predictor in the regression models. However, it is unclear how the more traditional LOS measure of time from admission to discharge would affect which hospitals appear efficient.

Like in most studies, LOS is right-skewed rather than “bell”-shaped (ie, a small number of patients had very long hospitalizations, whereas many had short stays) and this needs to be addressed statistically (3). Like some researchers, the authors truncated extreme LOS values before running various regression models (4). This improves fit but prevents the analyst from seeing how hospitals handle patients with long hospitalizations. They ultimately adopted a simple, traditional ordinary least squares model because it was similar in explanatory power to other more complex models that either took random effects at the hospital level into account or a generalized linear model with a gamma distribution (which prevents predicted LOS from being nonnegative) and logarithmic link (which accounts for the skew). The models’ similarities in performance were in part the result of the inclusion of a myriad of detailed diagnoses, sample size, and the outlier truncation. Liu et al (5) performed a comparable study in which raw, trimmed, and transformed LOS values were estimated with similar models as done here and also found that all their models had notably low but similar $R^2$ values at the patient level.

That said, ordinary least squares regression models may yield biased estimates because they are sensitive to outliers and can produce negative predictions, which are not valid in this context. Theoretically, the generalized linear model structure should perform better in most LOS applications (although the benefit may be slight), does not require data truncation, but is more complex. Generalized linear model models also have the advantage of not requiring a smearing factor, whereas...
Do Not Let the Tail Wag the Dog

The authors also found that the time after ICU discharge was brief and conclude that reductions in LOS after ICU discharge would be difficult (2). However, given the mechanical ventilation example, reducing the “tail end” of ICU LOS may not reduce costs appreciably either. To reduce costs, having the “right” patients in the ICU is key. The authors have published an innovative model identifying patients who may be too “well” to benefit from ICU care (16). This research should complement the more established analyses of factors that indicate when patients are too sick to benefit from ICU care (eg, patients with metastatic cancer with hypercalcemia, pleural effusion, and brain metastasis).

Furthermore, if future clinicians exclude from the ICU more patients who are too well (and these patients survive with short LOS) or too sick (and these patients die with short LOS) to benefit from ICU care, paradoxically this would cause an increase in the hospitals’ mean ICU LOS but ICU mortality would decrease. This can be misinterpreted as a decline in efficiency unless the proper quantitative analyses are used for benchmarking.

What Should Be Done Now?

Following evidence-based best practices has consistently reduced mortality, costs, and LOS (17). The two biggest barriers to implementing evidence-based best practices are a dysfunctional multidisciplinary team and the failure to use statistical quality control methods to track evidence-based best practices use (17). Decisions on ICU patient discharge are intrinsically team-based with communication between the physicians and nurses and between the healthcare team and families crucial (18). LOS and LOS variation among patients will be reduced when we make sure medical teams give the right care to the right patients at the right time. When that happens, even P.T. Barnum would be impressed, because our ICUs would become the greatest show on earth.

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Mortality prediction in adult respiratory distress syndrome: Get real*

One of the main barriers to the adherence of clinicians to evidence-based medicine is its reliance on strictly designed and carried-out randomized controlled studies in which the healthcare process may seem far removed from “real-life” healthcare (1). Indeed, to ensure analysis and interpretability, patient inclusion follows strict criteria and studied therapies obey strict protocols. Therefore, conclusions regarding study cohorts may not transpose to real-life patient groups in real-life healthcare. This is why clinicians increasingly expect follow-up studies to determine whether study findings can be transposed to less restrictive groups and settings closer to real-life critical care.

In this issue of Critical Care Medicine, Damluji et al (2), following up on a study by Cooke et al (3) previously published in Critical Care Medicine establishing a “simple” score predictive of mortality in acute lung injury (ALI) and adult respiratory distress syndrome (ARDS) derived from data in the ARDS Network trial low tidal volume ventilation study patient cohort (4), provide the first step in transposing it closer to “real life”: its application to an external validation cohort from another multicenter clinical study of ALI.

Several concepts are at stake with mortality prediction scores. First and foremost, such scores established by discriminating between groups with different mortality rates are appropriate for stratifying patients included in subsequent studies into groups with similar predicted mortality rates to decrease group inhomogeneity that may otherwise lead to study bias. Therefore, reliable mortality scores are valuable tools for clinical research, particularly in ALI/ARDS, a case-in-point for both patient and disease inhomogeneity, although patient stratification in such a complex disease cannot be limited to mortality risk. Second, in diseases in which management and/or specific therapies are tailored to mortality risk, predictive scores are indispensable even though predictive scores are not designed to determine individual prognosis and only provide an estimate. This is precisely the case in ALI/ARDS. Indeed, in these pages, Diaz et al (5) recently reviewed the practical clinical management of severe ARDS and proposed a rational stepwise strategy based on mortality risk assessment through another simple score: the lung injury score. Likewise, emerging invasive but potentially lifesaving therapies in ARDS, such as extracorporeal membrane oxygenation, require identifying patients at high risk of death warranting their use albeit early enough to increase survival (6). Last, managing patients with severe ARDS also involves communicating with surrogates who want physicians to disclose their prognostic estimates (7) in which scores may be taken into account.

In their study, Damluji et al (2) show that applying the predictive score to their external validation cohort does not outperform a general intensive care unit mortality score: Acute Physiology and Chronic Health Evaluation (APACHE) II. This is similar to the fact that when Cooke et al (3) internally validated their score in another ARDS Network study cohort from the Assessment of Low tidal volume and elevated End-expiratory volume to Obviate Lung Injury study (8), not only did it not outperform APACHE III, a refined version of the APACHE score, but it performed worse. In the accompanying editorial, Scales and Gattas (9) had already underlined that the score required validation in a follow-up study on an external cohort while expecting that the score would perform even poorly. Unexpectedly, Damluji et al find that it fares better, not worse, but in comparison to APACHE II not APACHE III. The findings of Damluji et al are strengthened by this choice of APACHE II as a comparator since APACHE II is a simpler version of the APACHE score and has been found to outperform APACHE III (10, 11). However, they also show that while the score discriminated patients with the highest or lowest mortality risks, it behaved inconsistently across the mortality risk spectrum, showing poor calibration: for intermediate risk (score of 1 or 2) patients, observed mortality was higher than predicted (25.3% vs. 16.5% and 40.6% vs. 31.0%, respectively).

What one might conclude from this important follow-up study, for which the authors must be commended, is that the score performs better than initially in an external cohort in predicting high mortality, which is the main use for a predictive score in ARDS. However, what both the initial study and this study show is that the score does not outperform APACHE scores. While the score is admittedly simpler than APACHE scores, one can question adding yet another score to the intensive care unit toolbox when APACHE scores, widely and routinely used around the world, are not outperformed. The simplicity of the score may be attractive, but the complexity of APACHE II is not an obstacle since it is often routinely calculated in intensive care units and increasingly automated through electronic medical data systems (12). Furthermore, most items in the simple score (age, bilirubin, and hematocrit) seem more related to general scores such as APACHE than to ALI/ARDS, whereas another simple score, such as the lung injury score, is also predictive of high mortality (5) where all items (Pao2/Fio2, chest radiograph alveolar consolidation, positive end-expiratory pressure, and compliance) are closely related to ALI/ARDS and its therapeutic end points.

Interestingly, Ware et al (8), using data from the same ARDS Network study used for internal validation of the score by Cooke et al (3), established that clinical predictors, among which the APACHE III predicted mortality in ALI/ARDS with an area under the receiver operating...
characteristic curve (area under the curve) of 0.82 increasing to 0.85 when associated with a combination of eight biomarkers. Addition of relevant biomarkers to clinically relevant predictors in scores adds to the patient stratification possibilities in a complex disease such as ARDS (13).

Although further studies in cohorts even closer to real-life patients than the cohort of Damluji et al (2) may again confirm the performance of the score, it seems that routinely used APACHE scores have already performed well enough to stratify patients into mortality groups for ALI/ARDS studies, that other simple scores discriminate patients at high risk for mortality requiring specific management (5), and that composite tailored clinical/biomarker scores may yield the most reliable stratification and prediction of mortality in ALI/ARDS pending confirmation follow-up studies in... “real life.”

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Surviving fulminant myocarditis: Is the head the heart of the matter?*

Over the last decade, an increasing number of patients are surviving common critical illnesses such as sepsis and acute lung injury as a result of advances in critical care medicine (1, 2). Despite increased interest in the field of patient-centered outcomes after critical illnesses, there remains much to learn. For example, relatively little is known about the short- and long-term outcomes of patients with fulminant myocarditis, an acute cardiomyopathy with onset frequently after viral illnesses that can lead to cardiogenic shock and death (3). Although 6–10% of cases of acute, dilated cardiomyopathy and 20% of sudden deaths among young adults may be the result of myocarditis, the incidence and prevalence of the fulminant type of myocarditis are unknown (3). Prior investigations attempting to characterize the inhospital outcomes of patients with fulminant myocarditis have been limited by very small sample sizes and little characterization of the long-term functional outcomes of patients requiring mechanical circulatory assistance with either a ventricular assist device or extracorporeal membrane oxygenation for survival (4–6).

In the current issue of Critical Care Medicine, Mirabel et al (7) present an investigation of the short- and long-term outcomes of 41 patients admitted to their intensive care unit (ICU) with fulminant myocarditis who required either a ventricular assist device or extracorporeal membrane oxygenation. Twenty-eight (68%) patients survived beyond the ICU and four required heart transplantation. In their multivariable regression models, increased illness severity at admission as measured by the Simplified Acute Physiology Score II and a troponin-Ic ≥12 μg/DL were associated with increased odds of in-ICU mortality.

Importantly, Mirabel et al studied the functional, quality-of-life, and psychiatric outcomes out to a median of 525 days...
post-ICU of the surviving cohort. Remarkably, >50% of patients had a normal left ventricular ejection fraction at follow-up, and although 46% of survivors reported dyspnea on exertion, none had New York Heart Association class III/IV symptoms. Their cohort of fulminant myocarditis survivors reported diminished health-related quality of life (HRQOL), particularly in physical and social functioning. Furthermore, 38% and 27% of survivors reported clinically significant anxiety and/or depressive symptoms as measured by the Hospital Anxiety and Depression Scale, and 27% reported clinically significant posttraumatic stress disorder symptoms as measured by the Impact of Events Scale. The findings by Mirabel et al further reinforce the growing body of literature highlighting that critical illness survivors have diminished HRQOL compared with the general population (8, 9), and survivors, particularly those exposed to in-ICU invasive procedures, may be at increased risk of major depression and anxiety disorders such as posttraumatic stress disorder (10–12).

It is important to note that this study does have substantial limitations. Although Mirabel et al report on the largest cohort assembled to date of patients surviving fulminant myocarditis requiring a ventricular assist device or extracorporeal membrane oxygenation, the sample size of the present study remains too small to make substantial generalizations about the clinical course and outcomes of these patients. In addition, HRQOL and psychiatric morbidity outcomes were measured cross-sectionally, thus making it impossible to draw any causal conclusions between critical illness/ICU-related exposures and survivor self-reported HRQOL and psychopathology. For instance, one cannot exclude the possibility that the patients with clinically significant depressive and/or posttraumatic stress disorder symptoms after fulminant myocarditis did not have premorbid histories of major depression and/or anxiety disorders and that this psychiatric history, and not the critical illness/ICU-related exposures, confers risk for postmyocarditis psychiatric morbidity. Very few studies have explicitly examined precritical illness psychiatric disorders to answer the fundamental question of whether critical illness/ICU-related exposures increase the risk of post-ICU psychiatric morbidity independently of psychiatric history, and more work in this area is needed. Furthermore, Mirabel et al did not examine an increasingly important outcome, cognitive functioning, in their cohort. Prior studies have identified that older critical illness survivors, including patients requiring ventricular assist devices, may be at increased risk of incident cognitive dysfunction (13–15). With a mean age of 38 yrs, the cohort in the study by Mirabel et al of fulminant myocarditis survivors would have been an interesting group in which to examine postcritical illness cognitive outcomes because they should have fewer additional risk factors for pre-existing cognitive impairment given their age and low Charlson comorbidity scores.

Despite this study’s limitations, the investigation by Mirabel et al of in-ICU and longer-term outcomes of patients surviving fulminant myocarditis is an important addition to the growing body of literature focusing on patient-centered outcomes after critical illnesses. The present study reports on the HRQOL and psychiatric outcomes of the largest cohort assembled of patients surviving fulminant myocarditis that required a ventricular assist device or extracorporeal membrane oxygenation during their ICU course. The authors identify that despite relatively spared cardiac functioning, patients surviving fulminant myocarditis have diminished HRQOL, particularly physical functioning, and have high point prevalences of clinically significant depressive, general anxiety, and posttraumatic stress disorder symptoms. Although larger prospective cohort studies are needed to help elucidate the longer-term outcomes of patients requiring mechanical circulatory assistance to survive critical illnesses, the investigation by Mirabel et al adds to the emerging evidence suggesting that although the primary organs affected acutely by a critical illness may be the lungs or the heart, the brain may be the organ ultimately suffering the brunt of the long-term effects. Furthermore, the implication that patients who survive critical illnesses such as fulminant myocarditis may have substantial impairments in HRQOL and physical functioning as well as psychiatric morbidity suggests that critical illness survivors could benefit from close follow-up early on in the post-ICU course, particularly follow-up that uses a multidisciplinary approach that takes into account the breadth of challenges facing these patients to improve their quality of survivorship.

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Do-not-resuscitate orders in evolution: Matching medical interventions with patient goals*

Although do-not-resuscitate (DNR) orders have been in use for more than three decades, considerable uncertainty still surrounds their meaning and interpretation (1, 2). One issue has been concern for “DNR creep”: the tendency to assume that if patients do not want to be resuscitated, then it is permissible to withold other potentially beneficial treatments from them as well.

Anecdotally, patients often experience a lack of attentiveness from clinicians once they agree to a DNR order, with bedside rounds going from a meticulous discussion of the patient’s medical care to a cursory review before moving on to the next bedspace. These impressions have been documented in the literature as well: nurses are less likely to perform a variety of interventions for patients with DNR status (3), physicians are less likely to treat acute heart failure in DNR patients with standard diagnostic and therapeutic modalities (4), and patients with DNR orders are more likely to be denied intensive care unit admission than similar patients without such orders (5). These considerations may create a dilemma for patients: if they perceive that by agreeing to a DNR order they will be denied interventions they desire, then they may have a perverse incentive to accept something they do not want (i.e., cardiopulmonary resuscitation) to get treatments that they do.

In this issue of Critical Care Medicine, Saager and colleagues (6) provide some reassuring data to the contrary. They analyzed data from more than a half million patients drawn from >220 hospitals across the United States and found that patients with DNR orders did not have an increased risk of either minor or major morbidity at any time within the 30-day postoperative period. At least with regard to postoperative care, their findings suggest that patients are receiving the same quality of care as are similar patients without such orders.

This is reassuring news for patients with DNR orders, since it should give them confidence that they can undergo palliative surgical procedures without fear that they will receive substandard postoperative care. Beyond this important finding, however, the data also raise interesting and unanswered questions about the meaning of DNR orders themselves.

For example, the simple term “DNR order” refers to a broad variety of approaches to limiting the use of life-sustaining treatments. The methodology of the study did not allow the investigators to differentiate between these approaches, but the differences are profound and likely have an important impact upon the quality of patient care.

At one end of the spectrum, attending physicians may signify a DNR order by simply writing the three letters “D-N-R” above their signature. Studies have shown that such orders are open to a broad range of interpretation, with some assuming that they apply only to procedures directly related to resuscitation, while others assume they prohibit any interventions except those aimed solely at comfort (7).

In an effort to correct these deficiencies, many institutions have turned to the use of DNR checklists. Studies have shown that this approach dramatically reduces the ambiguity present in DNR orders, since the forms explicitly indicate which procedures are to be performed (7), but the checklist approach generates a new set of problems by turning the DNR order into a “restaurant menu,” allowing patients to choose whatever procedures they like. Not uncommonly, this approach leads to illogical combinations of interventions that lack any medical rationale (e.g., permitting the administration of resuscitation medications but without the chest compressions necessary to circulate the medications). The use of such orders can create the illusion that patient autonomy has been respected by agreeing to provide the patient with inferior care.

Over the past several years, we have entered a new era, one in which the term “DNR” is likely to become obsolete. This new approach is based on the idea that patients should have authority over determining the goals of their care, whereas clinicians are the experts on determining which procedures, if any, are likely to achieve those goals (8). Nobody desires resuscitation as an end in itself; resuscitation is only a means to achieving certain health goals, and the role of the physician is to help the patient decide which procedures make sense given the patient’s clinical condition and goals of care.

If done well, this approach dramatically alters the context of DNR discussions, with the physician’s role one of informing the patient about the procedures that should be used. Ideally, the conversation with the patient should end with the physician saying something like, “Based on all we’ve talked about … in the event of severe cardiopulmonary decline we should do procedures x, y, and z.” In other words, with this approach the patient’s “code status” becomes the outcome of the conversation, not the subject of the conversation.

This approach is leading to a variety of alternatives to the DNR order that are more functional for patients and clinicians alike. These approaches share the premise that goals do not exist in a vac-

*See also p. 1036.

Key Words: advance directives; advanced cardiac life support; cardiopulmonary resuscitation; decision making; health policy; surgical outcomes; do-not-resuscitate

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1213

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uum; most of the time the patient’s goals can be translated into coherent packages of care. For example, Vanpee and colleagues (9) have proposed a “levels of care” approach to replace DNR orders, defining four discrete care packages that range from “comfort measures only” to the full use of life-sustaining interventions. Another very popular approach is the Physician Orders for Life-Sustaining Treatment form, which maps the goals of the patient to specific packages of care around resuscitation, medical interventions, the use of antibiotics, and the administration of artificial fluids and nutrition (10).

While the data from Saager and colleagues cannot parse out the different types of DNR orders and how they impact patient outcomes, their overall conclusion is reassuringly consistent with the direction in which DNR orders, and advanced care planning more generally, is moving. They show us that physicians are able to differentiate between patients’ preferences around resuscitation and their preferences for other types of medical care, tailoring their approach to the needs and desires of individual patients, and this is very good news indeed.

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“Sepsis—It ain’t so much what you don’t know that gets you into trouble, it’s what you know for sure that just ain’t so.”—with apologies to Mark Twain*

Volumes have been written about sepsis, especially in the pages of this journal, and rightly so. Sepsis continues to be the problem child of medicine: unwanted, persistent, ubiquitous, mysterious, and maddeningly difficult to manage. Although the mortality rate has decreased somewhat in recent decades, the number of sepsis-related deaths continues to spiral higher, accounting for over 9% of all deaths in the United States (1). Sepsis is involved in some 2% of all hospitalizations, accounts for 20% of all admissions to intensive care units, and is the leading cause of deaths in noncardiac intensive care units. The concepts of sepsis and a sepsis syndrome have been with us since the days of Hippocrates (2) and have beggared for clarification ever since. Of course, when astute clinicians have had flashes of insight that could not only move science forward but save innumerable lives as well, the medical community has historically been less than receptive. Witness the response to Semmelweiss’ observations regarding puerperal sepsis and handwashing. Oblivious to the fact that Semmelweiss reduced the mortality rate on his maternity ward from >18% to <3%, he was fired from his position and ridiculed mercilessly by his contemporaries. In America, the obstetrician Charles Meigs famously proclaimed that “Doctors are gentlemen, and gentlemen’s hands are clean.” Meigs was the acknowledged leader of obstetrics in America and was also a lifelong opponent of obstetrical anesthesia, believing it to be morally dubious. Semmelweiss died impoverished in an insane asylum a few years later (3).

More than a century ago, Osler (4) was the first to recognize that there was more to sepsis than just infection, noting that “except on few occasions, the patient appears to die of the body’s response to infection rather than from the infection.” The 1991 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference belatedly sought to define the terminology of sepsis and provide guidance for treatment (5). In 2002 the European Society of Intensive Care Medicine and the Society of Critical Care Medicine initiated the Surviving Sepsis Campaign, an ongoing effort to develop and propagate evidence-based guidelines for the management of sepsis. This effort was updated in 2008, with the involvement and endorsement of 18 professional societies and organizations (6).

In spite of these efforts, the level of “sepsis literacy” remains low not only among the lay public (7) but, surprisingly,
among physicians and intensivists as well (8). Nevertheless, the Surviving Sepsis Campaign has proven to be dramatically successful in academic and community hospitals alike when guideline bundles are followed (9).

In this issue of Critical Care Medicine, Vincent and colleagues (10) present evidence that challenges an untested assumption of conventional wisdom: persistent rather than worsening organ failure as measured by the Sequential Organ Failure Assessment (SOFA) score is the most common presentation of septic patients before death in the intensive care unit. This study mined data accumulated in the fairly robust INDEPTH database, which pooled information from five industry-sponsored clinical trials of over 4,000 patients with severe sepsis. The goal of these trials was to assess the impact of treatment with activated protein C and a secretory phospholipase A2 inhibitor. The authors openly admit to several major limitations in this study, including the following: the initial studies comprising the database were not designed to explore the cause of death in severe sepsis, there is inadequate information relating to end-of-life practices, and there were no independent determinations of the cause of death. Most patients died of multiple-organ failure, with fairly stable SOFA scores in the days before death. While some individual organ SOFA scores did indicate increasing organ failure, there were no notable or characteristic patterns that could be used to predict an adverse outcome. This is in marked contrast to the recent study by Jones and colleagues (11), which showed that rising SOFA scores were of prognostic value in predicting inhospital mortality in patients with severe sepsis.

As a maturing specialty, critical care medicine has always seemed to pride itself on its foundations of science and physiology. Understanding and demystifying the pathophysiology of critical illness was and is the bedrock of critical care medicine. It seems like only yesterday that Acute Physiology and Chronic Health Evaluation appeared on the scene, using physiology to quantify risk, followed in rapid succession by the Mortality Probability Model, the Simplified Acute Physiology Score, SOFA, and a host of other tools. Indeed, it would seem that creating new prognostic scoring systems has become a virtual cottage industry, sometimes without any concern for external validity (12). Adopting the business adage that you cannot manage that which you cannot measure, these scores allowed intensivists to track not only the severity of illness but also the response to treatment and, with standardized mortality ratios, the overall performance of units over time. As we have struggled to understand disease and save lives, we seem to have given relatively little thought to how our patients die. Vincent and colleagues (10) explore this area, and the results generate more questions than answers.

Research at its best is elegant, clean, provocative, and enlightening, but for the most part, it is messy, chaotic, and contradictory. The truth may be out there, but it is rarely easy to find. We engage in research because we question the status quo, knowing that tomorrow must be better than the present. Vincent and colleagues (10) assume that most clinicians believe that death from sepsis is preceded by progressive deterioration of multiple-organ function, as measured by changing SOFA scores. In fact, we have no idea what most clinicians believe. We have no idea whether SOFA scores are routinely collected, how they are interpreted, if at all, and whether rising SOFA scores are used to determine therapy or influence end-of-life decision making. To what extent are sepsis bundles used in the treatment of severe sepsis? Do we need to create a mandated database to assess the variation in management of severe sepsis and publish the data in a format akin to the Dartmouth Atlas? Recent studies suggest that there may be a genetic predisposition to survival or death in sepsis (13). It is likely that the future will usher in a new era of biomarkers and genomic therapy for the personalized management of sepsis. In the meantime, we need a far better understanding of what we are doing and what works. Until we know where we are, we will never know how far we have come or how far we have to go. It would appear that we have barely scratched the surface and have miles to go before we sleep.

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Mitochondrial dysfunction during sepsis: Still more questions than answers*

Despite decades of research, there are few effective treatments that can be offered to septic shock patients other than antibiotics and supportive care (1). Uncertainties relating to the pathogenesis of sepsis, and more specifically the cause of multiorgan dysfunction syndrome, the putative cause of death during sepsis (2, 3), remain obstacles to progress on this front. Although most investigators agree that overwhelming activation of the innate immune response is an essential prerequisite for organ damage, strategies designed to modulate inflammation during sepsis have been disappointing (3). A growing body of evidence links cytopathic events, particularly mitochondrial, to the development of organ dysfunction (4, 5) and death (4, 6) during sepsis. The first step toward understanding this phenomenon is to better characterize the mechanisms of mitochondrial dysfunction in tissues and cells that are essential for survival.

Owing to breaches in the normal immune barriers (e.g., central venous access) and impaired immune responses, referred to as “immune paralysis,” septic patients are at particularly high risk of developing a second and frequently lethal “hospital-acquired” infection (7). The cause of immune paralysis remains unclear; however, significant alterations in peripheral blood mononuclear cell bioenergetics have been recently reported in the context of human sepsis. In a very interesting study by Belikova et al (8), it was shown that plasma derived from septic patients was sufficient to induce dramatic changes in mitochondrial function, including suppression of adenosine diphosphate-dependent (state 3) respiration and uncoupling of respiration, resulting in significantly reduced adenosine-5'-triphosphate (ATP) production in peripheral blood mononuclear cells (PBMCs). In a related study by Calvano et al (9), a genome-wide gene expression analysis of PBMCs conducted in humans treated with low-dose endotoxin showed marked suppression of multiple genes relating to mitochondrial oxidative phosphorylation, suggesting that altered PBMC bioenergetics is explained, at least in part, by a fundamental “reprogramming” of the cells in response to bacterial antigens. The Calvano study provides an alternative to the prevailing paradigm linking suppression of bioenergetic pathways to mitochondrial damage (e.g., oxidative stress) (10). Indeed, it is likely that mitochondrial pathology during severe sepsis represents the combined effects of cytopathic and genetic mechanisms, culminating in compromised bioenergetic capacity and impaired cell function.

In this issue of Critical Care Medicine, Japiassu et al (11) provide novel insights into the pathogenesis of mitochondrial dysfunction in immune cells during severe sepsis. Intact PBMCs derived from patients within 48 hrs of intensive care unit admission for severe sepsis were isolated and permeabilized for subsequent mitochondrial analyses, and the results were compared to a noninfected postoperative intensive care unit control group. Using succinate as the substrate for mitochondrial electron transport, they observed reduced state 3 respiration in septic shock patients. They did not detect significant “uncoupling” of respiration during sepsis, as reflected by their ability to inhibit oxygen consumption with the addition of oligomycin, a potent inhibitor of F1F0 ATP synthase essential for the formation of ATP at the expense of the electrochemical gradient. Altered state 3 respiration was apparently unrelated to impaired maximal electron transport, as this was equal in both cohorts in the presence of a respiratory uncoupling agent (carbonylcyanide-4-trifluoromethoxyphenylhydrazine), but was associated with a statistically significant 50% reduction in F1F0 ATP synthase activity, as reflected by the elegant oligomycin titration experiments. Finally, and in keeping with previous studies linking impaired mitochondrial function in muscle tissue to sepsis mortality, impaired mitochondrial respiration in PBMCs was associated with increased sepsis mortality. The authors reasonably conclude that altered mitochondrial respiration could contribute to so-called “immune paralysis” during sepsis (3).

A number of methodologic factors could have influenced the results of this study and could also explain why their results differ from previous reports. The selection of succinate as the electron donor bypasses complex I, a well-established target of functionally relevant posttranslational modifications (e.g., nitration, nitrosylation) during sepsis (12). Serendipitously, ignoring the effects of complex I may have helped to unveil the novel role of F1F0 ATP synthase “content,” as shown in Figure 4 of the current study by Japiassu et al (11), is problematic in that adenosine diphosphate-dependent oxygen consumption does not account for the presence of damaged F1F0 molecules (e.g., extramitochondrial liberation of the F1 subunit of ATP synthase), such as occurs in the setting of acute endotoxemia (13). Free F1 complex is potentially harmful in that it efficiently hydrolyzes ATP and could thereby contribute to intracellular ATP depletion. Other variables to consider are the effects of circulating factors during sepsis, which are shown to uncouple mitochondrial respiration in PBMCs (8) and platelets (14). These direct effects of plasma emphasize the importance of the in vivo microenvironment as a determinant of cell function in the context of sepsis, and this variable is removed during the analysis of isolated cells or mitochondrial...
preparations. Finally, given the diverse disease mechanisms and phenotypes coexisting under the moniker of “critical illness,” the selection of any critically ill control group introduces some degree of bias. The authors’ selection of a cohort of uninfected postoperative patients is reasonable; however, the severity of illness score of the postoperative group was significantly lower than that of the septic shock group, leaving the possibility that these findings are not specific to an infectious insult but rather to the physiology of critically ill patients in general.

Despite these limitations, this study emphasizes the potential importance of the $F_{1}F_{0}$ ATP synthase complex during sepsis. This complex is interesting in that it can variably produce or consume ATP, depending on the conditions. The production of ATP is favored by the availability of substrate (adenosine diphosphate) and by a greater electrochemical gradient. On the other hand, the hydrolysis of ATP is regulated by mitochondrial ATP synthase inhibitor protein IF1, which is shown to be depleted in animal models of sepsis (15). Thus, the conditions of sepsis represent a “perfect storm” for impaired $F_{1}F_{0}$ ATP synthase-dependent ATP production, wherein $F_{1}F_{0}$ ATP synthase function is suppressed (11), mitochondrial respiration is uncoupled, thereby reducing the electrochemical gradient (8), and IF1 is depleted, favoring ATP hydrolysis (15). Given the strong association of altered PBMC $F_{1}F_{0}$ ATP synthase activity with clinically important outcomes (organ failures, mortality), and the relative accessibility of blood samples in the clinical setting (e.g., compared to muscle biopsies [6]), PBMC $F_{1}F_{0}$ ATP synthase activity may prove to be a valuable prognostic tool in the setting of sepsis.

Despite steady progress toward defining the mechanisms of mitochondrial dysfunction during sepsis, a number of questions remain unanswered. Most importantly, is mitochondrial dysfunction the proximal cause of organ failure, or is it merely a mechanism to avert further cell damage relating to excessive mitochondrial oxidant production (16) or to suppress potentially self-destructive immune responses? Given the vital roles played by mitochondria in the regulation of vital cell functions, including energy metabolism, apoptosis pathways, and cell signaling and proliferation (17), it is very likely that mitochondria are mechanistically involved in both the failure and recovery of cells/organs in the context of sepsis.

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Has extracorporeal membrane oxygenation finally arrived for resuscitation and stabilization of critically ill patients?*

Extracorporeal membrane oxygenation (ECMO) has arrived as a standard treatment in emergency and critical care medicine. From its earliest uses as an experimental therapy in the 1970s and early 1980s on patients in desperate situations at a few key centers in the United States, ECMO has matured to become a standard therapy used in pediatric and adult emergency departments, intensive care units, and cardiothoracic operating theaters. Over 48,000 children and adults have received this therapy as documented by the Extracorporeal Life Support Organisation (Ann Arbor, MI). It is widely used for cardiogenic shock, cardiopulmonary resuscitation, postoperative cardiopulmonary support after heart surgery or transplantation, and respiratory failure and as an adjunctive therapy to facilitate organ transplantation; two patients were excluded because of bilateral absent somatosensory evoked potentials was noted (15).

The successful use of ECMO for resuscitation of moribund adults, with 15 of 39 long-term survivors, was first reported by Mattox (4) in 1976 and subsequently a mobile rapid deployment ECMO system in adults with cardiogenic shock, with 6 of 29 long-term survivors, by Raithel (5) in 1989. In fact, the development of a modern ultrarapid system in 1998 in Boston (6) and in 2004 in Washington (7) for early initiation of ECMO following cardiac surgery improved survival outcome from 28% to 89% in Boston and from 33% to 59% in Washington. It is increasingly accepted that the outcome of patients receiving ECMO is improved if therapy can be begun before the development of multiorgan failure or irreversible cardiopulmonary injury (8). Interestingly, Scaife et al (9) in 2007 stated that a preemptive strategy with ECMO use increases patient survival.

The debate over extracorporeal cardiopulmonary resuscitation in adults continues. In an editorial in 2008, Varon and Acosta (10) wrote they feel that, although this therapy makes physiologic sense and patient outcomes continue to improve with the use of ECMO, logistic issues and the absence of randomized control trials prevent their recommendation of it being universally available. In a center that has extensive ECMO experience, clinicians argue that ECMO has “proven” itself a safe, reliable therapy that will support life and ultimately will allow patient recovery. Their view is that “ECMO should not be withheld and that it makes a difference to the individual patient and thereafter the next..." (11). In a meta-analysis in adults in 2009, Cardarelli et al (12) found “a better survival when ECPR is used in younger patients, and implemented during or shortly after CPR,” while in Taiwan 122 adults with cardiopulmonary resuscitation with and without ECMO showed little long-term benefit, with 13 of 59 patients surviving to discharge without ECMO and 18 of 63 surviving to discharge with ECMO (13).

In patients receiving emergent ECMO, goals of therapy vary around the world. In some countries survival is the main goal, while in other countries intact survival with a good quality of life (whatever that means) is the primary goal. Thus, early prediction of long-term functional outcome may become a very important issue. The use of ECMO, hypothermia, and medications may preclude the usual clinical examination, so early outcome prediction (days 3–6) requires the use of tests such as somatosensory evoked potential or electroencephalogram (14) and neuroimaging (magnetic resonance imaging or computed tomography if the patient is still on ECMO). Fortunately, the utility of somatosensory evoked potentials is preserved with moderate hypothermia, and in one small study, a positive predictive value of 100% for bilaterally absent somatosensory evoked potentials was noted (15).

In hospitals that have cardiothoracic surgery or access to vascular surgeons and an existing ECMO program, ECMO has a clear role in resuscitation and stabilization of critically ill patients, which
will be defined by local logistics, social, cultural, and religious beliefs, and health professionals’ attitudes. Programs without ECMO will have a different strategy, but it would appear prudent to discuss all patients with a core temperature of <28°C with the regional ECMO center! Warwick Butt, MD, FRACP, FCICM

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Page the critical care epidemiologist, STAT!*
pitalized a second time, an incidence of recurrent ALI of 2.02 cases per 100,000 person years. The median time to a second case was <9 months, with a case fatality rate of 47%. Because the number of patients with a recurrent ALI was small, case-control methods were used to evaluate characteristics associated with recurrence. In this analysis, gastroesophageal reflux was significant.

Several caveats should be acknowledged from both the population-based and case-controlled methodologies. The authors discuss some of these: small sample size, lack of a standard definition of aspiration, and bias in assessing exposure variables. Others are inevitable with case-control methods (the larger the number of variables matched, the more limited the analysis of variables of interest) and population-based studies (patients dying of ALI before reaching the hospital would not be counted, as would be the case for residents developing ALI while traveling outside the county).

While its limitations are significant, the study makes two important epidemiologic conclusions. The first is that recurrent ALI is real and its incidence can be calculated. While the conclusion may seem obvious, our ability to quantify this will grow in importance as the population ages and the incidence of ALI increases and as mortality decreases and the number of patients at risk for recurrent ALI also increases. The second is that gastroesophageal reflux may play a significant role in the risk for recurrent ALI. In children with developmental disability, gastroesophageal reflux has also been linked to ALI (6). Gastroesophageal reflux plays an important role in other lung diseases, including asthma (7), chronic obstructive pulmonary disease (8), idiopathic pulmonary fibrosis (9), and chronic lung transplant rejection (10). This research is a modest but valuable first step in parsing the full extent of this newly quantified entity of recurrent ALI.

Identifying and quantifying at-risk populations with population-based methods such as this study and expanding our understanding of these populations with genetic data are essential as we face the growing challenges of critical care of a population that grows older and sicker in the 21st century. Despite the enormous resources expended in the care of critically ill patients (11), our epidemiologic capabilities have lagged behind other fields of medicine. For example, in 1973, the National Cancer Institute (Bethesda, MD) began collecting data for its Surveillance, Epidemiology, and End Results Program. This population-based registry covers 26% of the United State’s population and provides detailed data on cancer incidence and mortality, identifies temporal changes in incidence, disease extent, staging, and survival, and facilitates quality assurance (12). Imagine the effects of this knowledge to facilitate a nationwide research agenda, improve regional ICU organization, and insure consistent and effective delivery of critical care.

Is anyone calling out for a critical care epidemiologist in the midst of a code? Maybe not, but he or she plays a vital role in the ICU nonetheless (13). As we confront these challenges, we must start thinking not only of our own patients in the unit but of all our potential and actual patients nationwide.

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Opening the lungs: Do it slowly, please*

The rationale for recruitment maneuvers (RMs) in acute lung injury (ALI) and acute respiratory distress syndrome is to open collapsed alveoli, thereby increasing end-expiratory lung volume. The latter may improve gas exchange and attenuate ventilator-induced lung injury by preventing repetitive opening and closing of unstable lung units. An editorial in Intensive Care Medicine, published in 2005 (1), stated that, if at all, RMs should be done smoothly and gently to prevent harmful overdistention while recruiting collapsed alveoli. The authors referred to the experimental work by Odensted et al (2) showing that a slow RM less depresses cardiac output and less increases dead space ventilation than a rapid RM. The two RMs are hard to compare, however, because of higher airway pressures applied with the rapid RMs.

In the current issue of Critical Care Medicine, however, the concept of slow RM is further elaborated. Silva et al (3) report on the impact of pressure profile and duration of RM on morphofunctional and biochemical variables in experimental lung injury. The latter was induced by cecal ligation and puncture and after 48 hrs, rats were subjected to a RM with continuous positive airway pressure targeted to 30 cm H2O. RMs were performed with a direct or slow stepwise increase to the same airway pressure for a duration of 15 or 30 secs. The main result was that RMs with slower airway pressure increase improved lung function while at the same time gene expression of interleukin-6, type 3 procollagen, and caspase 3 in lung tissue was decreased, suggesting less overdistention-induced proinflammatory, profibrotic, and pro-apoptotic responses.

The results thus indicate that the time-dependent airway pressure increase is critical in improving gas exchange and minimizing ventilator-induced lung injury. Recently, the same group of investigators compared in a model of paraquat-induced ALI a RM of 40 cm H2O continuous positive airway pressure for 40 secs with three different strategies of 10–180 sighs/hr to 20–40 cm H2O (4). Again, the time and pressure appeared critical. Alveolar hyperinflation, lung and renal epithelial cell apoptosis, and type 3 procollagen mRNA expression improved with lowering the sigh frequency from 180/hr to 10/hr. In contrast, if the pressure was lowered to 20 cm H2O, lung mechanics and histology deteriorated. Both studies suggest that both too little and too forceful RMs are associated with ventilator-induced lung injury and activation of inflammatory responses, potentially contributing to distant organ injury (4, 5). Despite some limitations, addressed by the authors (3), the observations may have clinical implications.

In patients with ALI/acute respiratory distress syndrome, a RM may result in a transient increase in oxygenation with few serious adverse events, but an outcome benefit has not yet been demonstrated. For example, a large randomized clinical trial in patients with ALI/acute respiratory distress syndrome, a multifaceted protocolized ventilation strategy designed to recruit and open the lung resulted in a nonsignificant difference in barotrauma and all-cause hospital mortality compared with an established low tidal volume protocolized ventilation strategy (6). Subsequently, systematic reviews concluded that, currently, the routine use of RMs in adults patients with ALI should not be recommended and RMs should only be considered for use in selected patients and circumstances such as life-threatening hypoxemia (7, 8). However, the change in PaO2/FiO2 ratio on RM, being determined by mixed venous Po2 and venous admixture, ie, ventilation to perfusion mismatching (9), is insufficiently correlated to actual alveolar recruitment assessed by computed tomography scanning, whereas the increase in compliance and decrease in dead-space ventilation together have the highest predictive values (10). Dynamic compliance and tidal excretion of CO2 may thus better guide recruitment (and limit overdistention, respectively) than oxygenation responses to RMs, because recruitment may inversely correlate to overdistention for a given lung volume. Ideally, the effect of RM on the lung tissue should be monitored directly to distinguish among closed, open, and overdistended alveoli, thereby allowing patient tailoring for maximum recruitment at minimum overdistention to prevent ventilator-induced lung injury and remote organ injury. One bedside technique is, of course, electrical impedance tomography, but increases in impedance are less when lung volumes are high (2, 11). Nevertheless, electrical impedance tomography and its combination with lung mechanics or nitrogen washout/washin-based end-expiratory lung volume measurements to calibrate electrical impedance tomography images have been used to predict potentially recruitable lung and monitor RMs in patients (12). Different RMs are currently used, including intermittent sighs, incremental positive end-expiratory pressure, high pressure-controlled ventilation, sustained inflation maneuvers, and the best RM is unknown (7, 8, 13). We support that RM should be patient-tailored rather than standard-applied, because airway pressure-dependent responses may vary among patients, conditions, etiologies, morphologies, and stages (10, 12). This may also apply to potentially harmful circulatory events (8). Furthermore, timing and frequency of the RM, ie, early in the disease course or as rescue therapy, is still an open question as well as the optimum duration of its effect and the optimum positive end-expiratory pressure level to keep the lung open after the RM (14). Otherwise, these confounding factors will hamper the design and execution of a sufficiently large prospective trial with patient-oriented outcomes.

Taken together, the study by Silva et al (3) and the stepwise increase in airway pressure used add to the current concept of patient-tailored (vs. standard) RMs in attempts to limit ventilator-induced lung injury and improve outcome of human medicine.
Stemming electrical outage in myocardial infarction*

It used to be thought that myocardial infarction prompts only fibrotic scarring, with attendant electrical dysfunction, during healing. It is increasingly apparent that stem cells, endogenous or exogenous, can provide new contractile cells for lost ones. In this issue, Zheng and colleagues report from Guangzhou, China, that stem cells were injected into an infarct. That is so unless the newly induced cardiac arrest (2, 3). In both sets of experiments, the improved electrical stability after cell therapy may result from enhanced coronary perfusion afforded by better contractility. Another mechanism might involve the construction of small blood vessels by the pluripotent cells.

Indeed, new contractile cells seeded into infarcted myocardium need perfusion to remain viable. Perhaps existing blood vessels can be repaired by artificially added cells. Otherwise, new vessels must grow from the periphery of the infarct. That is so unless the newly induced vessels can carry oxygenated blood directly from the chamber of the left ventricle instead of from the coronary tree. This intriguing possibility is consistent with the fact that some lower vertebrates (such as frogs) naturally lack coronary blood vessels and rely on diffusion of nutrients from the blood chambers into spongy muscle. However, if frog-like myocardial perfusion is involved in the function of infarct-injected stem cells, then large animal experiments may prove less successful than those involving small animals.

Cardiac disease is now a prime target for stem cell-based therapeutics. In a randomized clinical test (the PRECISE trial underway in Europe), autologous adipose-derived stem and other “regenerative” cells are injected into hearts of patients with nonrevascularizable ischemic myocardium. Preliminary results presented at the annual meeting of the American Heart Association indicate a trend toward reduced mortality and sustained improvements in maximum oxygen consumption and ability to perform physical activity.

Pluripotent cell-based therapies are hoped to functionally repopulate the hearts of patients with cardiac dysfunction after myocardial infarction. In a landmark and controversial experiment reported in 2007, functional cardiomyocytes derived from human embryonic stem cells were injected into an infarct site in a rat model (4).

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*See also p. 1082.
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The report by Zheng et al (1) supports the concept of stem cell therapy as an attractive means of mending human heartbreak, but the article does not involve an attractive method for harvesting the therapeutic cells. For proof-of-concept experimental purpose, the cells conveniently came from excised hearts of newborn rats. The killed donors are said to be allogeneic, but they were at least kissin’ cousins of the recipients. That is, immunosuppression was not required for apparently successful grafting. Although some types of pluripotent stem cells, even xenobiotic ones, may prove to be immunologically privileged (5), the problem of graft rejection makes autologous cells of most clinical interest for cardiac repair.

In the experiments by Zheng et al (1), a fixed dose of five million cardiac stem cells was injected into the free wall of the infarcted ventricle, and the animals were studied at one time point (6 weeks later). Longer studies addressing electrical stability, contractility, and any aberrant stem cell proliferation (including malignancy) will be of interest.

Fortunately, scientific advances are addressing ethical dilemmas in stem cell therapy. Stem cells can be isolated from various tissues, including subcutaneous fat. Furthermore, induced pluripotent stem cells can be obtained from adult somatic cells (6, 7).

Dr. Shinya Yamanaka initially used multiple viruses to insert four reprogramming genes into the genomic DNA of cells so induced to exhibit pluripotency. However, the viruses, and one of the four genes (Myc), carry risk of carcinogenesis. Induction no longer requires Myc nor viruses (8–11). Indeed, the miracle of induced cellular pluripotency can now be performed without treating cells with DNA (12).

A very recent method to reprogram somatic cells into stem cells involves messenger RNA (13). The messenger RNA allows cells to synthesize reprogramming factors, whereupon the messenger RNA is degraded and does not persist in the so-called RiPS cells.

The adult heart naturally contains some pluripotent cells (14). Another goal of research is to pharmacologically spur those cells into repairing injured myocardium. Perhaps transdifferentiation, a technique that might permit reprogramming scar tissue components directly into functional myocardial and endothelial cells, will be vital to the future of cardiac regenerative medicine.

In an interesting twist on the experiments by Zheng et al, other investigators are injecting deliberately defective stem cells into hearts. In that way, molecular mechanisms of arrhythmia can be explored (15).

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The brain boggles the mind*

The innate immune response is activated on recognition of infection or injury. A tight regulation of this inflammatory response is vital to ensure that it does not spin out of control and become harmful to the host. Recently, a neural circuit involving the central nervous system, the vagus nerve, and immune cells has been identified that controls the inflammatory response in a reflex-like manner (1). The central nervous system and the immune system are tightly linked through humoral, endocrine, and hard-wired connections. The afferent vagus nerve provides the central nervous system with real-time information on the status of immunologic activation in the body but also responds by activating its efferent activity, which suppresses the activity of immune cells through an interaction of vagus nerve-derived acetylcholine and immune cells. This immune reflex functions to suppress inflammation to prevent inflammatory responses to become generalized. Knowledge of this newly discovered connection between the nervous system and the immune system has provided important new insights in the regulation of the immune response in a variety of preclinical models such as sepsis, pancreatitis, and lung injury (2–5). In these studies, vagotomy or blockade of peripheral acetylcholine receptors resulted in an increased inflammatory response, whereas stimulation of the efferent vagus nerve or activation of peripheral acetylcholine receptors resulted in decreased inflammation. Other studies subsequently identified the spleen as the target organ for the interaction between the vagus nerve and the immune system (6) and identified the molecular mechanisms involved in acetylcholine-mediated immune suppression (7).

In this issue of Critical Care Medicine, Minutoli et al (8) describe an important new discovery that further maps the vagal immune reflex. The authors describe a set of experiments that identify the melanocortin 4 receptor in the brain as the upstream initiator of the vagal immune reflex and show that stimulation of this receptor in the brain results in activation of the vagal immune reflex. Furthermore, in a widely used model of pancreatitis, activation of these receptors activated efferent vagus nerve activity and decreased pancreatitis severity. The importance of this study is not the fact that modulation of the vagal immune reflex is able to ameliorate pancreatitis severity because this has been shown before (2). Furthermore, the same group has published several similar articles that show that the effects of melanocortin 4 receptor agonists are not specific to pancreatitis but are present in other inflammatory diseases as well (9–11). The major contribution of this study is, however, the potential identification of the melanocortin 4 receptor in the brain as the upstream target of the vagal immune reflex. In subsequent studies, the authors should strive to further convince us that indeed this receptor is essential by performing studies in α7 nicotinic acetylcholine receptor (the downstream target of the vagal immune reflex) knockout mice as well as by measuring the effects of melanocortin 4 receptor activation on the activity of the sympathetic nervous system as well as cortisol release. Also, I would be very interested to understand how activation of the afferent vagus nerve, by an inflammatory stimulus in the periphery, leads to activation of melanocortin receptors, which then might activate efferent vagus nerve activity. The exact identification and mapping of the processes taking place in the brain will be a long and daunting task but Minutoli et al have given us an important first clue on what is going on in the brain during activation of the vagal immune reflex. The many secrets the brain still possesses for us will boggle our minds but as these pathways become better defined, we will be getting closer to using them for clinical benefit.

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*See also p. 1089.
With the recognition that inflammation and coagulation are inextricably linked and contribute to the pathobiology of the sepsis syndrome, several anticoagulants have been investigated in patients with sepsis, severe sepsis, and septic shock (1). Only human recombinant activated protein C (drotrecogin alfa), however, has been shown to decrease mortality in a single randomized trial (2). In this issue of Critical Care Medicine, Li and colleagues (3) present the results of experiments examining the ability of unfractionated heparin to decrease markers of coagulation and systemic inflammation in an Escherichia coli-challenged mouse model of sepsis. Similar to previous animal studies, very high dose heparin (2500 IU/kg) increased mortality in mice following intratracheal inoculation with \textit{E. coli}, while lower doses of heparin (100 and 500 IU/kg) did not significantly affect mortality. In addition, heparin administration at doses expected to prolong the activated partial thromboplastin time to 1.5–2.5 times that of the baseline did not reduce laboratory markers of coagulation activation or systemic inflammation compared to placebo.

Expanding on a previously conducted meta-analysis examining the impact of heparin in live animal models of sepsis (4), Li et al (3) performed a meta-analysis and metaregression to explore the effect of heparin in animals. In lipopolysaccharide-induced models of sepsis (n = 22 comparisons; odds ratio 0.15, 95% confidence interval 0.09–0.25, \( p < .0001 \)) and surgical polymicrobial challenge models (n = 15 comparisons; odds ratio 0.23, 95% confidence interval 0.13–0.41, \( p < .0001 \)), heparin administration was highly associated with decreased mortality. However, in monobacterial challenge models, the odds ratio for death associated with heparin administration compared to placebo was not statistically different (n = 7 comparisons; odds ratio 1.65, 95% confidence interval 0.66–4.14, \( p = .29 \)). Although the authors concluded heparin to be nonbeneficial in monobacterial challenge models, the data, as presented, may not support this conclusion. This may be particularly true given the paucity of data investigating accepted therapeutic heparin dosing to achieve an activated partial thromboplastin time that is 1.5–2.5 times that of the baseline. Instead, the data suggest that very high dose heparin (n = 5 comparisons) increases mortality in monobacterial infection and that there is insufficient evidence (n = 2 comparisons) to conclude, or exclude, a benefit of therapeutic heparin, when dosed to prolong the activated partial thromboplastin time to standard therapeuetic ranges—ranges that were originally established in animal models of thrombosis >30 yrs ago (5).

Heparin exerts its anticoagulant effect by primarily enhancing antithrombin-mediated inactivation of factors Xa and thrombin (IIa), and because thrombin generation is intimately linked with inflammation, heparin thus acts as an inflammatory agent. Heparin has also been shown to have anti-inflammatory properties that are independent of its role as an anticoagulant (4). Although Li and colleagues (3) did not find a reduction in either activation of coagulation or inflammation, their study advances a growing body of evidence suggesting that heparin administration may improve outcomes in sepsis. For example, in specific animal models of sepsis, heparin improves survival in two meta-analyses (3, 4). In humans, a retrospective propensity-matched cohort study of patients with septic shock found that therapeutic heparin administration was associated with improved survival (6). Pooled analyses from prospectively collected, but nonrandomized, data from the placebo arms of three phase III trials in sepsis suggest a survival advantage associated with prophylactic dose heparin that was independent of the study drug under investigation (7). Since the use of heparin in these studies was a postrandomized characteristic, one must be cautious not to overinterpret this observation or draw conclusions.

At this time it is unknown if heparin is an important adjunctive therapy in the management of sepsis. However, given the high mortality rate associated with sepsis and the published evidence supporting a potential role for heparin, clinical trials of heparin in patients diagnosed with sepsis should be considered. In support of this notion, a recently presented national survey found that 90% (n = 281) of Canadian critical care physicians believed future trials of either unfractionated or low molecular weight heparin were warranted in patients with severe sepsis or septic shock (8). Despite what appears to be widespread support for such a trial, important challenges exist with regard to the design, conduct, and funding of such a trial.

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Targeted temperature management: The jury returns with a verdict*

The therapeutic hypothermia (TH) was first described in 1938 for the treatment of a patient with disseminated cancer (1). This was based on observations in the laboratory that mild hypothermia appeared to decrease the rate of growth of malignant tissue. The patient was administered a barbiturate and covered with ice packs to achieve a target temperature of 91°F (32°C). This temperature was maintained for several days, apparently without adverse effect. Subsequently, TH was used in the late 1930s in patients with severe traumatic brain injury (2). During the 1950s, there were many anecdotal reports and small case series of the use of TH in a range of patients with critical illness (3). Indications for TH at that time outside the operating room included severe head injury, stroke, intracranial hemorrhage, post inhospital cardiac arrest, and sepsis. Notably, the use of TH occurred in general wards without mechanical ventilation or invasive monitoring. In the operating room, TH was also becoming widely used at that time for neurologic protection during cardiac procedures.

However, between 1960 and 1990, there were few reports of the use of TH outside the operating room. This apparent lack of interest or experience in the possible role of TH coincided with the development of critical care units. It is surmised that critical care physicians may have considered that the normalization of vital signs (including temperature) in critically ill patients was the preferred approach for the improvement of outcomes. Also, there was some emerging data on the association of (accidental) hypothermia with coagulopathy (4) and an increased rate of sepsis (5).

Current interest in TH was renewed in the early 1990s, initially as a treatment of anoxic neurologic injury and then subsequently in other forms of neurologic injury. In patients with cardiac arrest, it had been known for many years that hypothermia during a cardiac arrest was neuroprotective (eg, during cold water near-drowning); however, hypothermia that was induced after resuscitation from cardiac arrest did not appear to be helpful (5). One of the first laboratory studies that tested the efficacy of postarrest hypothermia was by Sterz et al in 1991 (6). In that study, anesthetized dogs were subjected to 10 mins of no-flow cardiac arrest followed by 5 mins of cardiopulmonary resuscitation, then allocation to normothermia or brief mild hypothermia (34°C for 4 hrs). There was a significant improvement in neurologic outcome at 72 hrs in the animals that were cooled after return of spontaneous circulation. On the basis of this and other similar laboratory studies, preliminary clinical trials of TH induced after return of spontaneous circulation were conducted and these appeared to show feasibility and safety (7, 8). Subsequently, prospective, randomized trials were conducted that showed efficacy (9, 10). These trials have led to a recommendation by the American Heart Association that TH be instituted as soon as possible after resuscitation in patients with an initial arrest rhythm of ventricular fibrillation (VF) or pulseless ventricular tachycardia (11). Concurrent with these clinical trials in out-of-hospital cardiac arrest, there has been considerable research into the application of TH in a range of other conditions such as neonatal hypoxic–ischemic encephalopathy, traumatic brain injury, spinal cord injury, and ischemic stroke.

In this issue of Critical Care Medicine, Nunnally et al (12) describe the outcomes of a conference that was convened to evaluate the current evidence for TH in a wide range of conditions. This conference used a “jury” consisting of interested but not expert critical care physicians representing five societies of critical care medicine. The jurors listened to the evidence presented by key expert researchers and, on the basis of the evidence presented and their own additional literature review, formulated recommendations on the use of TH in a range of conditions.

There are several notable outcomes of this consensus meeting. First, the jury recommended that “therapeutic hypothermia” should be replaced by the term “targeted temperature management” (TTM). The argument for this change is persuasive. Such a change in name would increase the recognition of the key role that temperature management has in the care of patients in the critical care unit rather than the current focus on TH alone. For example, some patients with neurologic injury and fever may benefit from TTM with the target set at normothermia (13). Also, selected patients without neurologic injury may benefit from a target temperature set at hyperthermic levels. In the latter, fever treatment using antipyretics and/or cooling blankets is commonly undertaken despite the lack of proven benefit and evidence of possible harm (14). Thus, the use of the term “targeted temperature management”
would apply to many more patients in the intensive care unit compared with TH.

Most of the recommendations of the conference are consistent with those from other expert groups. The jury proposed a weak recommendation for TTM (33–35.5°C) in neonates with suspected severe hypoxic–ischemic encephalopathy. This is similar to the more recent recommendation of the American Heart Association guideline that graded the evidence for TTM in neonates at risk of hypoxic neurologic injury as a class IIa recommendation with a high level of evidence (15).

One important outcome of the consensus meeting was the finding by the jury that there is interest but little compelling evidence for TTM in conditions other than postventricular fibrillation cardiac arrest and neonatal hypoxic–ischemic encephalopathy. There was a large number of clinical conditions with laboratory evidence of benefit from cooling postinsult or injury for which there was insufficient evidence for the jury to make any recommendation.

Fortunately, there is likely to be considerable progress in this area over the next few years with clinical trials either planned or currently recruiting that will address the possible role of TTM in a range of common critical care conditions. As at December 2010, one clinical trial registration web site listed 140 clinical trials under the search term “hypothermia” (see www.ClinicalTrials.gov) and of these, 63 trials are currently recruiting patients.

Although TTM after VF cardiac arrest to 32–34°C was strongly recommended by the conference jury, there is still much about this treatment that requires further investigation. In particular, the jury noted the lack of data for treatment with TTM in patients with non-VF arrest or inhospital arrest. Also, the jury noted the lack of data on the optimal timing and technique of TTM. These issues are being addressed by phase III randomized, controlled trials that are currently recruiting.

For example, in a North American trial, patients post-out-of-hospital cardiac arrest were allocated to either paramedic cooling using 2000 mL of cold saline or standard care with encouraging results for the post-VF group (16). However, in a concurrent Australian trial, no outcome benefit was found with this strategy and this trial was stopped early for futility after 234 patients had been enrolled (17). Subsequently, the North American investigators have started a larger trial of 1200 patients allocated to either paramedic cooling after resuscitation or standard care (NCT00391469).

Given that there is compelling laboratory evidence of improved outcomes if cooling is induced during resuscitation (5), the Australian investigators have started two concurrent clinical trials of cooling during cardiopulmonary resuscitation using a rapid infusion of 20 mL/kg ice–saline in both VF arrest (NCT01172678) and non-VF arrest patients (NCT01173393).

The conference jury could make no recommendation on the role of TTM after severe traumatic brain injury, either early after injury (prophylactic hypothermia) or later for control of intracranial hypertension. This finding concurs with the 2007 Brain Trauma Foundation guideline that made a similar recommendation on temperature management after severe traumatic brain injury (18). Large clinical trials testing the role of TH in severe traumatic brain injury are currently underway. The POLAR trial (prophylactic hypothermia to lessen traumatic brain injury) is currently recruiting in Australia and New Zealand and will allocate 512 patients to early (prehospital or emergency room) hypothermia and maintained for 72 hrs or normothermia (NCT00987688). The primary outcome measure for this study is the extended Glasgow Outcome Score at 6 months postinjury. This study should determine whether early cooling to 33°C improves outcomes after severe traumatic brain injury.

In Europe, the Eurotherm3235 study will address the possible role of TH (32–33°C) as an alternative to barbiturate infusion in the treatment of intracranial hypertension (ISRCTN34555414). In a prospective, randomized trial, hypothermia will be induced in half the patients with raised intracranial pressure after the usual initial standard treatment measures such as drainage of intracranial hematoma, insertion of external ventricular drainage, hypertonic solutions, and sedation. This study will recruit 1800 patients and should provide valuable evidence to clarify the role of TH as a treatment alternative to barbiturate infusion (see www.eurotherm3235trial.eu).

The jury was unable to make a recommendation for TTM in patients with acute ischemic stroke and this is a similar finding to the recent recommendation by the American Heart Association (19). In many laboratory studies, TH appears to be beneficial; however, clinical trials present significant challenges. Most patients with ischemic stroke are awake and current methods of surface cooling generally require sedation to suppress shivering. The control of temperature and suppression of shivering in a “stoke unit” outside the critical care unit is therefore problematic in many hospitals. One approach is the use of intravascular cooling with evidence that this approach may be better tolerated by patients than external cooling pads (20). This technology (together with thrombolysis) for treatment of acute ischemic stroke is the subject of a current clinical trial in North America (NCT01123161).

The role of TH after spinal cord injury is a particular area that should be a research priority. This injury is devastating and carries a very high morbidity rate, particularly in young people. There is compelling evidence from laboratory studies that TH is beneficial (21, 22), yet the only published clinical report to date is a small case series (23). It is anticipated that larger, randomized, controlled studies showing safety and feasibility of TH compared with standard care (normothermia) will be conducted in the near future. If preliminary studies show that TH can be safely and effectively implemented early after spinal cord injury, then phase III studies could be considered.

In summary, the report by Nunnally et al provides a useful update of the current evidence for TTM in a range of critical care conditions. Clearly, very much more work is needed to clarify the role of TTM, but there is considerable research currently underway. We would hope that in the years to come, a reconvened jury would be able to make strong recommendations for TTM that are applicable to a broad range of critically ill patients.

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Although the cortical microcirculation can readily be observed and quantified in experimental models of focal cerebral ischemia, human ischemic stroke has heretofore been largely inaccessible to these observations. In this issue of *Critical Care Medicine*, Pérez-Bárcena and coauthors (1) have taken the first steps to fill this gap in our knowledge by reporting, in a small but carefully conducted clinical investigation, the direct visualization of the cortical microcirculation in six patients (ages 20–45 yrs) who required craniotomy for deep lesions—nonruptured aneurysms (two cases), meningiomas (two cases), and III ventricular tumor (one case)—that were assumed to have left the overlying cortex unaffected.

The method used in this study was sidestream dark-field imaging (SDF), a technique pioneered by Dr. Ince, a coauthor of the present article (2). SDF, a successor to the method of orthogonal polarization spectral imaging, has been widely applied to study the superficial microcirculation of accessible organs (eg, skin, tongue, skeletal muscle, and serosal surfaces ofpleura, kidney, and ileum). The method has been especially useful in characterizing abnormalities of the sublingual microcirculation in the settings of myocardial infarction (3), heart failure (4), hypothermic circulatory arrest (5), cardiogenic shock (6), septic shock (7), and high altitude (8).

Using the SDF method, the authors assigned a visually based microvessel flow grade (none, intermittent, sluggish, or continuous) and assessed the proportion and density of perfused microvessels in the observed field (1). In control subjects, they observed continuous microvascular flow, whereas cortical microvessels in the central ischemic zone of the patients with stroke showed intermittent or absent flow. Although nearly all microvessels were perfused in control brains, the proportion of perfused vessels was reduced by one-third and perfused vessel density index was lower by approximately half in the central ischemic zone of the patients with stroke. Although the method used here did not permit measurement of microvascular flow velocity, a recent SDF study of the sublingual and ileal–serosal microcirculatory beds has demonstrated a tight linear correlation of capillary microcirculation in patients with stroke*.

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*See also p. 1126.

Key Words: stroke; microcirculation; hemicranietomy; sidestream dark-field imaging; thrombolysis; albumin; cerebral ischemia.

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vascular flow index and capillary flow velocity (9).

As has been extensively reviewed (10), microcirculatory derangements in ischemic stroke have many potential underlying causes, including intravascular obstruction by stagnant red cells, adherent leukocytes, aggregated platelets, fibrin masses, and/or endothelial swelling as well as active vasoconstriction and/or extrinsic microvascular compression from edema and elevated intracranial pressure. The SDF method used in the present study (using a wavelength in the hemoglobin-absorption range) imaged only the intravascular contents, not the vessel wall. Furthermore, the method was limited in its ability to distinguish cortical arterioles and venules because the rapid flow rate in the former exceeded the ability of the method (with its 25 frames per second imaging rate) from measuring flow velocity directly. Microvessel type, however, is important; for example, our own experimental studies of focal ischemia by confocal microscopy have revealed that during the early moments of postischemic recirculation, cortical venules (but not arterioles) specifically develop prominent foci of vascular stagnation associated with thrombus-like aggregates and adherent corpuscular structures consistent with neutrophils (11).

An essential question raised by studies of this type concerns the nature of reperfusion itself. The present study evaluated the cortical microcirculation at only a single surgical time point (range, 24–120 hrs poststroke) after craniectomy and dural opening (1). It is possible that the antecedent thrombolytic therapy and surgical decompression had afforded at least a modicum of microvascular reperfusion at the time of the SDF observations. One notes with particular interest that in this series, five of the six patients with stroke received thrombolytic therapy. Intriguingly, in the single patient who did not receive thrombolysis, the proportion of perfused vessels was markedly lower (17%) than in the thrombolysed group (range, 51–74%). If these observations were confirmed, they would provide a mechanistic correlate to the clinical improvement seen after thrombolytic therapy in patients with acute ischemic stroke (12) by showing that thrombolitically induced large-vessel reopening is, in fact, accompanied by improved microvascular hemodynamics.

In experimental focal cerebral ischemia, we have shown that high-dose albumin therapy (ALB) is markedly neuroprotective (13), and recent evidence suggests that this effect is mediated in part by intravascular mechanisms. Thus, when a stable thrombus is produced in a rat cortical arteriole by laser irradiation, microvascular flow velocity measured by in vivo two-photon microscopy distal to the thrombus falls to 10–13% of control levels and is unaffected by saline–placebo administration; however, after ALB administration, microvascular flow velocity increases substantially despite persistence of the thrombus (14). In this model, sublytic doses of the thrombolytic agent, reteplase, lead to a small rise in microvascular flow velocity distal to the arteriolar thrombus, but this effect is further augmented when ALB is coadministered (15). These results support an effect of thrombolytic therapy on the cerebral microcirculation and suggest that ALB therapy may be adjunctively beneficial. This conclusion is supported by a recent exploratory efficacy analysis of data obtained in the first stage of a large randomized multicenter clinical trial of ALB therapy in patients with acute ischemic stroke, the ALIAS (Albumin in Acute Stroke) Trial; namely, in a target population of patients with stroke treated with thrombolysis, those patients who also received high-dose ALB showed a 10% higher proportion of favorable 3-month neurologic and functional outcome than those thrombolyzed patients who received saline–placebo (46.7% vs. 36.6%) (16). Taken together, these observations emphasize the potential importance of the cerebral microvasculature as a therapeutic target in stroke.

One must be cautious in overgeneralizing the findings of this study, remembering that the patients studied here had a malignant, space-occupying form of ischemic stroke. It is possible that the microcirculatory events in milder forms of ischemic stroke may differ considerably from the findings reported here. Nonetheless, the authors of the present article are to be congratulated on their pioneering observations and should be encouraged to extend their investigations to a larger series.

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Experimental studies on ischemic neuroprotection: Criteria for translational significance*

Experimental studies on neuroprotection for ischemic stroke can be broadly categorized into those that address and explore pathophysiological mechanisms of the disease or those that are focused on discovery of potential neuroprotective agents and strategies or a combination thereof. Pharmacologic ischemic protection continues to be a highly desirable goal in the field of stroke. Over the past two decades, numerous experimental studies have focused their attention on neuroprotection with a variety of pharmacologic agents that have demonstrated significant neuroprotection in well-characterized animal models of ischemic stroke. However, translational research in clinical stroke trials with these neuroprotective agents has been disappointing (1). A wide variety of reasons is postulated for the failure of such translational studies; on one end, the validity and appropriate characterization of the animal models used is questioned and an inadequate clinical trial design at the other end of the spectrum. It is imperative that for such laboratory-based studies of translational significance, special attention should be focused on use of well-characterized animal models that incorporate: 1) aged animals reflecting comorbidities (e.g., hypertension, diabetes, and hypercholesterolemia) observed in human stroke as opposed to the use of young and healthy animals; 2) both sexes to allow for sex-based differences; and 3) blinded randomized studies after transient as well as permanent focal ischemia. Additionally, it is important that the route of delivery of neuroprotective agent(s) be translated readily into humans with adequate penetration of the drug through the blood–brain barrier coupled with appropriate dose–response and toxicology studies. Effects of the drug on important physiological parameters (systemic blood pressure, heart rate, arterial blood gases, serum glucose, core body temperature) and on survival as well as long-term functional (at least 30 days) and histologic outcomes must be rigorously evaluated. Furthermore, replication of results in two animal species and two laboratories is desirable. For drugs demonstrating promise in rodent animal models, it is suggested that testing be carried out in primate models to characterize functional outcomes (cognitive, sensorimotor, and behavioral) (2, 3). In fact, over a decade ago, many of these prerequisites and recommendations with subsequent refinements were put forth by a group comprising academic and industry representatives, also known as the Stroke Therapy Academic Industry Roundtable (STAIR) criteria for preclinical translational studies in ischemic stroke (2, 3). It is to be noted that validation and predictors for these criteria for clinical efficacy are lacking in the absence of a successful neuroprotection in a human clinical trial (2, 3).

With this perspective, in this issue of Critical Care Medicine, Chen et al (4) report a hypothesis-driven experimental stroke study with cinnamophilin (8R, 8’S)-4, 4’-dihydroxy-3, 3’-dimethoxy-7-oxo-8,8’-neolignan, an agent isolated from Cinnamomum philippinensis (5) and significant neuroprotective properties that can be attributed to its pluripotent effects as an antiperoxidative cytoprotectant and free radical scavenger (6) and an anti-inflammatory agent (7). It also exhibits an antiarrhythmic action by inhibiting Ca⁺ (L-type) and Na⁺ currents in cardiac muscle (8, 9). Additionally, the agent readily crosses the blood–brain barrier and has a slow delay in the brain (7). This group of investigators has previously demonstrated that treatment with cinnamophilin provides significant neuroprotection with a prolonged therapeutic window for up to 6 hrs after the onset of focal cerebral ischemia both in vitro and in vivo (10). In the present study, the authors build on their previous work by a more detailed investigation of longer end points (7 and 21 days) for outcomes in electrophysiological (somatosensory evoked potentials), functional (neurobehavioral), and histologic outcomes by studying the differential effect on gray and white matter (with myelin basic protein immunohistochemistry) in a well-characterized rat model of transient focal ischemia. Few experimental studies in ischemic stroke have focused on differential neuroprotective effects on both gray and white matter as well as on recovery of electrophysiological function. The present study is unique in this regard. Specifically, treatment with cinnamophilin under controlled conditions: 1) improved somatosensory evoked potentials in the ischemic hemisphere as well as the contralateral nonischemic hemisphere at 7 days postinfarct as compared with vehicle-treated controls; 2) attenuated cortical and subcortical infarct volumes at day 7 (33% vs. 39% in controls) and at day 21 (48% vs. 32% in controls) and increased survival of degenerating ischemic neurons as well as significantly reduced axonal and myelin injury; 3) resulted in significant improvement in daily sensory and motor functional deficits. It is intriguing to note that the investigators started treatment with cinnamophilin at the onset of reperfusion after 90 mins of focal cerebral ischemia; the present study would have been greatly strengthened if treatment was begun at 6 hrs of reperfusion like in their previous study (10). Despite these limitations, the study by Chen et al provides further evidence for pharmacologic ischemic neuroprotection with cinnamophilin in a number of important domains. Future studies with this agent should incorporate the recommended preclinical STAIR criteria for rigorous experimental investigation that may lead to more meaningful trans-

*See also p. 1130.

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Difficulties in human response to illness or injury have been attributed to genetic variation since at least the second century, when familial bleeding disorders were first described (1). Given that genes define, in part, all human phenotypes, it is logical to conclude that variance in DNA sequence alters the host response to illness and injury, and that physiologic stress associated with life-threatening disease exposes genetic anomalies that might otherwise go unnoticed. Thus, the ability to more accurately predict outcomes and to better-understand the link between genetic variance and individual patient responses has obvious appeal to critical care clinicians and researchers alike.

The era of “genomic medicine” has fostered hundreds of studies to assess genetic variation associated with critically ill patient phenotypes. Polymorphisms defining traits of patients with or at risk for sepsis (2) and lung injury (3) are among the most well-reported, and significant numbers of publications describe genetic associations in trauma (4) and burn (5) phenotypes. Pharmacogenomic traits are of particular recent interest, because improved prediction of individual patient responses to medications holds the promise of reducing adverse drug events (6) in the medication-rich environment of critical care. These and numerous other inquiries have been conducted to define germline, gene expression, mitochondrial DNA, and epigenetic predictors in critical illness.

In this issue of Critical Care Medicine, Dr. Dahmer et al (7) report associations between surfactant protein B gene variants and the need for mechanical ventilation in a study of 395 African American children with community-acquired pneumonia. Two of seven selected tag single nucleotide polymorphisms were significantly associated with mechanical ventilation in univariable analyses, with these same two single nucleotide polymorphisms showing independent, relatively large effects in multivariable regression (odds ratios, 2.27 and 3.00). These effect sizes are notable considering the challenges described and effect sizes typically reported in gene association studies (8). The strengths and limitations of their work are generally well-described by the authors, with a few additional points of note. First, to the researcher’s credit, the article largely conforms to published standards for reporting genetic association studies (9). Second, the authors imply that statistical corrections for multiple comparisons are unnecessary given plausible mechanisms underlying the associations studied. Based on this rationale alone, the possibility of a type I error arising from repeated testing should not be dismissed. A more conservative analytical approach would have included correction for multiple comparisons in the present study. Finally, the haplotype analysis should be regarded as preliminary because of the small number of possible haplotypes sufficiently represented and the potential that random effect could account for the statistical significance observed.

Accepting that these and other limitations are outweighed by the strengths of this well-conducted study, what can we glean from the effort? The results are intriguing, in part because of the large effect sizes and plausible mechanisms proposed. As with all gene association studies, these results require independent confirmation because the reproducibility of these types of studies is relatively low (10). If results of the current study are confirmed, then clinical interventions in patients with surfactant protein B risk alleles should be tested. Choosing optimal interventions to study will be challenging because there are diverse preventive, diagnostic, and therapeutic opportunities related to community-acquired pneumonia. Surfactant protein B polymorphisms may be one of the relatively few instances when a small amount of variation in a single gene is sufficient to inform meaningful changes in care.

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*See also p. 1138.

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In closing, we consider an editorial that appeared in these pages 10 yrs ago, which likened an early candidate gene association study to the proverbial search for a needle in a haystack (11). The report by Dr. Dahmer and colleagues demonstrates both the significant progress made since then and the many challenges that remain. The authors formulated a hypothesis a priori based on well-founded previous knowledge of genetics and proteomics and tested their hypothesis in a new population via a well-executed multicentered trial. These results notwithstanding, the challenges in discovering and applying genetic information to improve care for the critically ill and injured remain substantial. Many critical care phenotypes are difficult to consistently define and are influenced by provider judgment and a host of other confounding factors. Furthermore, it is now clear that individual genetic effects are typically small (e.g., odds ratios <1.2) and are potentially masked by multiple gene–gene and gene–environment interactions. These challenges often remain underappreciated, although they have been well-described with respect to both candidate gene (12) and genome-wide (13) association studies. As DNA sequencing costs continue to decrease (optimistically, a full human sequence might soon cost approximately $1000) (14), we look forward to future reports that genotype and list additional loci in every population study to better-assess ancestry, gene–gene interactions, and other phenomena. There is a great deal more to learn before fully realizing the potential of using genetic variation to define clinically important phenotypes in critical care.

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Yes, SIRS—I think we have come full circle*

The search for the elusive therapeutic weapon to combat intractable shock continues. Optimism in the 1970s and 1980s that corticosteroids would feature prominently in the therapeutic armamentarium of shock faded in the face of evidence suggesting its administration conferred no benefit and likely harm (1, 2). However, over the last decade, there has been renewed interest after the recognition that adrenal insufficiency (AI) occurs with increased frequency in intractable shock and the presumption that corticosteroid replacement therapy will sideline AI as a major contributor to the pathophysiology and poor outcomes in intractable shock (3–6). These studies and a recent consensus statement (7) suggest that severe shock was associated with a high adrenocorticotropic hormone:cortisol ratio, which reflected a normal hypothalamic and pituitary response but an impaired ability to synthesize cortisol (3, 4). More importantly, the failure to increase endogenous cortisol after a stimulation test was associated with poor outcomes (6, 7).

The presumption that replacement therapy will benefit patients led Hebbel and colleagues (8) to undertake protoco-lized corticosteroid supplementation in children with systemic inflammatory response syndrome and vasopressor-dependent shock. Their report is the product of a retrospective chart review to determine the incidence of AI and to determine whether corticosteroid supplementation would be associated with decreased vasopressor requirements. They found that 69 of 78 (88%) of the study cohort had a form of AI (absolute adrenal insuffi-

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1232 Crit Care Med 2011 Vol. 39, No. 5
ciency, n = 44 [55%]) and relative adrenalin insufficiency (n = 39 [50%]) and that steroid supplementation was accompanied by statistically significant decreases in median dopamine dose (10 to 4 μg/kg/min) and norepinephrine (0.175 μg/kg/min to 0.05 μg/kg at 4 hrs).

Will these findings assist the practitioner in deciding if and when to treat with steroids? These findings are unlikely to change current practice, as outlined in the American College of Critical Care Medicine guidelines (9), and our “gut instinct” to try steroids if things are not going well for several reasons. Shortcomings of retrospective studies aside, a decrease in vasopressor dose is a favorable but unconvincing surrogate for better outcomes. However, this study was not designed to show a robust, clinically relevant difference in outcomes (decreased mechanical ventilation, shock resolution, decreased organ failure, or decreased mortality) to sway the critical care practitioner (8). In addition, protocol violations are very common when shock guidelines are implemented even under rigorous conditions (10) and there is a significant perception–reality gap in our therapy habits to sepsis (11). Therefore, one needs to know whether these are consecutive patients or whether patients with protocol violations were excluded. In addition, the wide range in pathology in a relative modest number of patients and a 56% (five of nine) response to steroids in those without confirmed AI renders steroid supplementation in patients with AI as only one of the plausible explanations for improvement. Others may be a tincture of time, inaccuracies in AI evaluation, impotency of endogenous steroids, or the need for pharmacologic rather than physiological doses. Also, systemic inflammatory response syndrome can be of varying severity and Pediatric Risk of Mortality III or Pediatric Logistic Organ Dysfunction scores are insensitive as indicators to stratify severity of shock and determine who is most likely to benefit.

There is also disagreement about methods of testing for AI, and doubt remains whether we should be measuring free cortisol rather than total cortisol in the critically ill. These unresolved issues have led some to conclude that corticosteroid testing cannot be recommended to determine which patient should receive hydrocortisone (12).

With the reservations of the study outlined and little to guide us in the care of children, we need to rely on the experience in critically ill adults in shock. In adults, addition of low-dose hydrocortisone has led to decreased time to shock reversal (12, 13) and improved survival (14, 15). The finding of an increased incidence of AI as age increases by Hebbard et al may be a reflection of the adult physiology in the older child. However, it is difficult to tease out a watershed age from the data provided because the ages were not stratified (median age, 84 months; range, 25–295 months).

Based on current evidence, it is difficult to argue for or against the use of corticosteroids in children with systemic inflammatory response syndrome and vasopressor-dependent shock. It seems that testing is unlikely to help in determining who should receive steroids, and test results, even if helpful, may not be available to facilitate time-sensitive rational treatments. Therefore, should we even test? In addition, this study and others have shown that at least in children, there is a very little downside to giving low-dose replacement corticosteroids. Most children with systemic inflammatory response syndrome and vasopressor dependency will have multisystem organ dysfunction. Should we then assume that the adrenal gland is compromised and AI is likely? Armed with scant data and few contraindications, should we therefore give corticosteroids to all children in whom vasopressor dependency is present? If this approach is unsatisfactory to the purists, would another study resolve this issue? Because of the complexity of the target population, I doubt that a study to resolve these issues is practical and, even if done, likely to sway practitioners’ current practice patterns. Therefore, it may be prudent to simply assume that steroids may help some and a therapeutic trial administered with a healthy dose of skepticism is warranted in those with vasopressor-dependent shock.

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Pulmonary morbidity of catheter-related pediatric venous thromboembolism: Old problem, new worry*

Pediatric venous thromboembolism (VTE) may be a new epidemic in pediatric tertiary care. Two recent epidemiologic analyses have shown that VTE incidence appears to be on the rise (1, 2). Together, these studies estimate that VTE occurs in 4.2–5.8 per 1000 pediatric hospitalizations. This is roughly a tenfold increase compared with the first estimates from the Canadian registries of only approximately 0.53 per 1000 hospitalizations, which were published approximately 15 yrs ago (3). The reasons for the increasing frequency of this complication are not clear, but many experts believe that it may result from improved survival of children with previously fatal conditions (4, 5). In the past these children may have died before development of VTE, they may be developing VTE as a consequence of more intense medical interventions, or both. Alternatively, the increase could be secondary to increased awareness and recognition or the influence of pediatric obesity or other environmental factors on thrombotic risk (2, 5).

Pediatric VTE is known to have both acute and chronic consequences. Acutely, VTE is associated with an estimated twofold increased risk of inhospital death (2). When considering the chronic nature of VTE, there are two major concerns: recurrence and postthrombotic syndrome. The overall risk for recurrent VTE is approximately 5–10% and may be higher for those patients with one or more continuing risk factors (6–8). Postthrombotic syndrome is the clinical manifestation of chronic venous insufficiency resulting from damage caused by prior VTE. Symptoms may include varicosity, chronic edema, pain, and even venous ulcers and may range from minor cosmetic problems to major symptoms limiting daily activities. The incidence of clinically significant postthrombotic syndrome is estimated at approximately 10% (6).

Like with many pediatric conditions, VTE clinical research is hindered by the relative infrequency of the condition as well as relevant outcome measures. Although mortality, recurrence, and postthrombotic syndrome are all clinically relevant and important outcomes, they are infrequent enough that powering clinical studies using them as end points becomes prohibitive as a result of the exceedingly large sample sizes required. Additionally, both recurrent VTE and postthrombotic syndrome require prolonged periods of follow-up adding to the cost and complexity.

In this issue of Critical Care Medicine, Faustino et al (9) hypothesized that catheter-related thrombosis may cause ventilation–perfusion mismatching resulting from nonmassive pulmonary embolism, which may lead to prolonged mechanical ventilation and/or lengthen stays in the critical care unit. To study this question, they performed a secondary analysis of a pre-existing pediatric intensive care unit data set, identifying patients with catheter-related deep vein thrombosis developing after admission to the pediatric intensive care unit. Control subjects without deep vein thrombosis were identified using a computerized matching scheme. These data strongly suggest that patients without VTE had significantly more ventilator- and intensive care unit-free days. Not surprisingly for a sample of this size, mortality was statistically similar between the cases and control subjects. Whether the differences in ventilator-free days were actually related to ventilation–perfusion mismatching were not assessed in this study but this is an intriguing question.

These data offer interesting new VTE outcome measures that would not require long-term follow-up for assessment. They may lend themselves to use in clinical studies of VTE occurring in the pediatric intensive care unit but would obviously not be relevant to patients with VTE who do not require intensive care. They have the added advantage of being continuous variables rather than dichotomous outcomes that have traditionally been used.

Severity of illness, using a validated index, was similar between the cases and control subjects, so it is unlikely that the differences can be explained by disease factors other than thrombosis. Alternatively, could the knowledge of thrombosis have influenced the clinical decision to extubate? Similarly, could the intensive care unit-free days be explained by a clinical desire to more closely observe anticoagulated patients? What about non-catheter deep vein thrombosis, for instance, lower extremity deep vein thrombosis after major trauma? Are they also associated with prolonged ventilation? Additional prospective study, including sensitive measures of ventilation–perfusion matching, predefined algorithms for extubation, and adjustment for any hospital policy-driven intensive care unit days required to administer anticoagulation or other medications, is needed to validate these data and to delineate the pathophysiology causing these patients to require prolonged ventilation. If these outcomes are validated, we will not only have new outcomes to follow that are much more investigator-friendly, but clinically relevant. As the authors point out, prolonging mechanical ventilation increases the risk for developing ventilator-associated pneumonia. If the pathophysiology is indeed the result of microemboli, then we will have new questions to consider regarding the long-term pulmonary morbidity that may be associated with what is currently considered subclinical pulmonary embolism.

It is clear that pediatric VTE is a growing problem that is associated with significant acute mortality and chronic morbidity. The time is ripe to perform clinical

*See also p. 1151.

Key Words: thrombosis; morbidity; pediatric; postthrombotic syndrome; outcomes

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Providing a good death*

At the start of this century, the British Medical Journal argued that we need “a new approach to death” and went on to list principles of a good death (1). Patient-centered factors such as spiritual guidance, privacy, dignity, and the ability to retain control over factors such as location and those present when death occurs were key identified elements. Providing patient education about death, good symptom management, and open communication were key physician-centered elements. This editorial serves as a clarion call for intensive care unit physicians and nurses to provide better end-of-life experiences for patients and their families. In the United Kingdom, approximately half of deaths occur in hospitals (2). In the United States, 40% of deaths occur in hospitals and 20% during or after an intensive care unit admission (3). A substantial proportion of deaths follow withdrawal of life-sustaining measures (4). Providing empathetic and thoughtful end-of-life care is essential for intensive care unit staff and requires both provider self-reflection as well as understanding the patient’s goals and values.

Knowledge about a patient’s social, cultural, and religious background enhances provider understanding of factors that impact decisionmaking. Patients and families consistently rank communication among the most important skills for a healthcare provider (5, 6). The American College of Critical Care Medicine and the Society of Critical Care Medicine have developed guidelines for support of the family in the patient-centered intensive care unit (7). These guidelines emphasize the importance of shared decisionmaking, communication skills, and cultural sensitivity. Lo et al (8) have provided a practical guide for physicians to discuss spiritual issues at the end of life. The authors present advice on responding to a patient’s spiritual concerns, responding to patients of different faiths from one’s own as well as offering limits as to what care is appropriate for a physician to provide.

Healthcare providers must endeavor to provide medical care that is concordant with patient and family wishes, understanding that this may run counter to their own preferences. Patients and physicians may differ on cultural, racial, societal, and religious factors. An understanding of one’s own beliefs and biases is an important step forward when providing culturally sensitive care to patients of different backgrounds (9). Studies have also shown that physician biases influence communication effectiveness, care provided, and patient satisfaction (10). To mitigate unintentional effect of provider biases, physicians need to be aware of their own predispositions and strive to elicit patient values and preferences.

In this issue of Critical Care Medicine, Frost and colleagues (11) shed light on the complex nature of end-of-life decision-making. The authors present a systematic review of 102 controlled, survey, or observational studies of patient or healthcare provider characteristics that affect decisionmaking among adult patients. Patients in the included studies were either currently or potentially critically ill. Qualitative studies were excluded. The authors should be commended on their thorough and thoughtful review of studies of such disparate designs and varied outcome measures.

The authors discuss some common themes from the included studies related to patients and healthcare providers. Patient-related factors focused on age, comorbidity, functional status, gender, and ethnicity. Less frequently identified patient-related factors included religious affiliation, socioeconomic status, prior experience with critical care, and setting. There were fewer studies on healthcare provider-related factors, which included specialty training, years in practice, and geographic location. The authors provide a detailed appendix summarizing the included articles and rating their quality as suggested by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (12) group as well as other criteria. This

REFERENCES


*See also p. 1174.

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comprehensive appendix is an invaluable resource for clinicians, because it centralizes a large data set spanning 25 yrs of medical research. Readers may easily identify studies related to their particular interest and see a detailed rating on their overall quality.

The articles included in the current review are heterogeneous and the conclusions drawn by the various studies are often contradictory. This heterogeneity in data prevented a quantitative analysis of the various studies. This variability also highlights patient and healthcare provider diversity. Healthcare providers must therefore consider this varied information while individualizing their approach to educate and support patients and their families in making end-of-life decisions. Although the review is informative, no unifying conceptual framework is presented to encourage methods to enhance cultural sensitivity, communication, or engender patient-centered preferences.

The article by Frost and colleagues (11), although having some limitations, remains important for clinicians because it provides a thorough review of the current literature related to end-of-life decisionmaking. The review of the studies is informative and the appendix provides an invaluable reference of the included studies. Greater understanding of the complex nature and various factors important to end-of-life decisionmaking for both patients and providers will likely improve patient care and satisfaction.

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