Discrepancies in administrative databases: Implications for practice and research*

When the Centers for Medicare and Medicaid Services (CMS) issued a “notice of limitations,” which stated that the Medicare Provider Analysis and Review (MedPAR) data had an approximate 20% error rate in two billing codes (“post/intermediate”), Dr. Halpern and colleagues (1) responded by performing a 6-yr retrospective analysis comparing Medicare hospital and critical care medicine days and costs in all nonfederal hospitals sited in the United States. In this issue of Critical Care Medicine, they report their findings, which demonstrate the divergence of critical care days and costs in Medicare beneficiaries in two distinct databases: MedPAR supplemented by Health Care Information System (HCIS) compared with Healthcare Cost Report Information System (HCRIS) (2). The authors found that two codes in particular, the intensive care and cardiac critical care “post/intermediate” codes in MedPAR/HCIS, were responsible for the majority of the variance in critical care days between the two databases.

This work has three major contributions that need to be recognized. First, health services researchers and critical care clinicians are reminded that database inputs derived from clinical care have numerous threats to validity that need to be ameliorated so that conclusions drawn from administrative databases “downstream” actually represent the practices that are being modeled (Fig. 1). Second, and more specifically, Dr. Halpern and colleagues have contributed to an improved understanding of how two commonly used federal databases have become divergent, which has implications for how researchers and clinicians using these data sets for decision making address their results. Finally, within the realm of critical care medicine, the authors have improved our understanding of how the work performed and billed for daily in intensive care units (ICUs) across the United States has important public health and health policy implications when analyzed in aggregate.

Large administrative databases provide extensive data on hospital encounters, patient characteristics, organizational structures, and resource utilization associated with each discharge. Their analysis in critical care medicine has informed the discussion of topics ranging from physician practice patterns to resource utilization. The use of large databases has several advantages for both clinical practice and research. First, many of them provide broad characterizations of epidemiologic and system-level problems, often at the national level, thereby allowing inferences regarding large groups of patients (e.g., Medicare beneficiaries). Second, these databases provide important reference points for subsequent and specialized clinical or research studies of specific patient groups such as ICU patients. Third, the large number of discharges is especially important in attempting to analyze comparatively rare diseases or events with sufficient statistical power than can be accomplished with single-institution studies (e.g., aortic aneurysms). Finally, many of these databases provide linkages to one another on the basis of hospital identifiers that allow more complex and detailed descriptions of the institutions and medical care context than would be capable with a single database alone.

Despite these strengths, administrative databases also have important limitations that must be recognized before their use in research or comparative benchmarking. Administrative databases are derived from data generated during the inpatient hospitalization and are subject to numerous threats to data integrity (Fig. 1). Administrative data also do not provide detailed clinical or physiologic information. Differences in acuity and clinical status, which are particularly important for many ICU analyses, simply do not exist except in the most rudimentary forms through nonphysiologic severity of illness scores. Database analysis is not designed to provide an understanding of cause-and-effect relationships. Rather, the analyses only detect statistical associations between the outcomes of interest and variables under study. An understanding of these strengths and limitations is particularly important since the resulting characterizations of ICU care and cost may be inaccurately portrayed at the national level if these limitations are not considered or if there are validity concerns between the elements of different databases.

As it relates to the specific databases used in these analyses, two potential reasons for the discrepant findings in what is supposed to be the same study population include different data extraction programs or coding differences. When the compilation of the two databases is examined, the data extraction differences become clear. HCRIS is a compilation of the federally mandated and annually submitted hospital cost reports filed with CMS. MedPAR and HCIS originate from the National Claims History and contain billing records for all Medicare beneficiaries using hospital inpatient services (1). Thus, the MedPAR and HCIS data sets are a compilation of reimbursed Medicare claims. Of importance, both of these data sets exclude data from federal hospitals, hospitals in U.S. territories, and facilities with <6 months of cost reporting detail (3).

Coding differences occur because of variable systems and manual coding processes for chart abstraction. Several studies document the inconsistency of medical coders’ abstraction of discharge and procedure codes from patient records after discharge (4). The three most common coding differences relate to a) physician...
billing codes based on accepted procedure codes (current procedural terminology); b) disease-related groups (diagnosis-related groups); and International Classification of Diseases codes (5–7). Furthermore, the ambiguity is compounded by the mapping that needs to occur between the three different areas and the multiple methods of accounting for cost. These include different but equally allowable allocation bases, cost centers, and allocation algorithms (8).

As far as implications for critical care medicine are concerned, accurate reporting depends on the completeness and accuracy of the data housed in the medical record (Fig. 1). The databases are inconsistent when the same measure, critical care medicine codes, is compared across different administrative databases because of ambiguity in coding (4). A simple look at one code “post/intermediate” days in one database was sufficient to apparently bridge the discrepancy between the databases. Although this may not be the true reason the databases are discrepant, it highlights the need to have consistency among database inputs.

Coding for critical care medicine days is confusing. When coding ambiguities for step-down or intermediate care are combined in different databases, it is easy to understand how inconsistencies in the number of coded days arise. For example, MedPAR collapses information in individual claims so that ICU care cannot be differentiated from step-down care since both are coded as “critical care.” Although not discussed by the authors, the same problem exists in HCRIS where step-down care may be coded inconsistently since there is no mechanism to identify non-CCM step-down, subintensive, or telemetry beds. It would be easy to add levels of “critical care medicine” such that the databases all had the same subdivisions that are well defined. For instance, HCRIS and MedPAR could use the 15 ICU/CCU classifications like HCIS. Also, redefining step-down care specifically such that it was still clearly a critical care day would be an obvious fix for the problem of coding ambiguity. Furthermore, directives on how to code an “intermediate” day could be less nebulous.

Administrative databases have been used in many clinical and research studies because they are inexpensive, are readily available, and encompass virtually all acute care hospitals in the United States (9, 10). However, it is only through accurate data acquisition and analysis that they retain their value for informing clinical, scientific, or financial decision making. Every critical care provider has a role in ensuring that our documentation in the medical record accurately reflects the care we deliver at the bedside. We need to also hold our individual institutions to the standards of appropriately coding and accurately reporting these data to data repositories. Finally, the Society of Critical Care Medicine through its advocacy and policy efforts has a role in ensuring that appropriate limitations in these data are addressed before broad generalizations and extrapolations are made regarding critical care practice in the United States.

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Still searching for the magic food*

S

ince Dudrick et al. (1) demonstrated that beagle puppies could be kept alive with intravenous feedings, medical personnel that believe nutrition plays a major role in overcoming critical illness have been searching for the best formula for the critically ill or injured. Initially, the goal was to simply provide adequate calories, fatty acids, and nitrogen to meet the needs of the patient. However, multiple investigators have attempted to show that supplementation with specific nutrients can have what is essentially a pharmacologic effect, resulting in alterations in protein synthesis or immune function. Some have even shown an impact on length of stay (2–6).

In this issue of Critical Care Medicine, Dr. Wichmann and colleagues (7) present the results of a trial in which patients receiving total parenteral nutrition were randomized to receive their fatty acids in the form of either 100% long-chain triglycerides (Intralipid) or a combination of 50% medium-chain triglycerides, 40% long-chain triglycerides, and 10% fish oil (Lipoplus). The study is well designed and well executed. In addition to looking at clinical outcomes, the authors assessed leukotriene synthetic capacity and the fatty acid content of plasma phospholipids. The authors were able to demonstrate that the patients who received Lipoplus had a statistically significantly shorter length of stay than the control group. Intensive care unit length of stay was not statistically significantly different between the groups. The mortality rate was slightly higher in the Lipoplus group (4.7% vs. 1.6%), but it did not reach statistical significance (p = .14) as defined by p < .05.

The impact of nutritional supplementation on mortality has plagued many publications that demonstrate an improvement in a clinical or laboratory parameter with no significant difference in mortality. This was best demonstrated when a meta-analysis of immune-enhancing enteral formula use was performed (8). Although no significant difference was seen in mortality in individual reports, when the data were pooled the immune-enhancing formulas were seen to have increased mortality. Although Lipoplus is an intravenous nutritional supplement, the results of the current trial place it squarely in this body of literature.

The real question for critical care practitioners is “Should I use a nutritional supplement that has been shown to reduce hospital length of stay but may increase mortality?” At this point, that question is best answered by reading the manuscript and other associated literature to see where this, or any immune-enhancing supplement, would fit into the care of patients at a given institution. At our institution, we have seen a handful of patients die of complications of nutrition support during the past decade. It is hard to justify a mortality from a feeding tube or central venous catheter complication when the product to be delivered has not been shown to save lives. Thus, our approach has become one of “Because the literature does not show many lives are being saved with any given intravenous or enteral formula, the key to good nutritional support is to administer it safely.”

In the future, nutritional support research needs to be performed in a way that answers mortality questions. The need for improved nutrition support scientific research is recognized by leaders in the field (9, 10). Multicenter trials that accumulate enough patients to reach statistical significance if a real difference exists are needed. Unfortunately, this is not likely to occur in the current research milieu as the corporations that make nutrition support products are not nearly as well funded as the pharmaceutical companies. The quest for the ultimate nutritional support formulation will likely continue for the foreseeable future.

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REFERENCES


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Dear levosimendan, the right ventricle will thank you!*  

Pulmonary hypertension is typically associated with right ventricular dysfunction and represents a common and significant health threat that not only reduces the quality of life but also is associated with a poor outcome (1). Animal models that help us to better understand the pathophysiology contributing to cardiopulmonary collapse secondary to pulmonary hypertension are essential to evaluate and judge the safety and efficacy of novel therapeutic strategies.

In the current issue of Critical Care Medicine, Dr. Missant and colleagues (2) elegantly report the results of a carefully conducted laboratory experiment in which they subjected pigs to temporary pulmonary artery constriction and repetitive episodes of ischemia to induce right ventricular dysfunction. Using load- and heart rate-independent indexes, the authors succeeded in quantifying right ventricular contractility. In this context, they determined the slope of the preload-recruitable stroke work and the slope of the end-systolic pressure volume relationship, as well as ventricular afterload, calculated as the ratio of end-systolic pressure over stroke volume (effective arterial elastance). In addition, this clinically relevant model allowed for the determination of ventricular-vascular coupling by assessing the ratio of the slope of the end-systolic pressure volume relationship over arterial elastance.

The major goal of the present study was to elucidate if levosimendan may be suitable to mitigate the severity of right ventricular dysfunction resulting from acute pulmonary hypertension in association with ischemia/reperfusion injury.

Levosimendan is a new calcium sensitizer exerting a positive inotropic effect by binding to, and stabilizing, calcium (Ca²⁺)-bound cardiac troponin C (3). In addition, levosimendan contributes to generalized vasodilation within the systemic and pulmonary circulation (3). Opening of adenosine triphosphate-sensitive potassium channels of vascular smooth muscle cells and the inner mitochondrial membranes (4) as well as (to a lesser degree) stimulation of phosphodiesterase III (5) plays a pivotal role in this regard. In fact, these complex mechanisms of action open new perspectives in the treatment of a wide range of cardiovascular and pulmonary morbidities, including myocardial stunning (6), sepsis-associated myocardial depression (7), acute respiratory distress syndrome (8), and acute heart failure (9).

The study by Dr. Missant and colleagues (2) also provides evidence that in a condition where the right ventricle is acutely threatened, levosimendan lowers pulmonary vascular resistance, improves right ventricular contractility, and, most important, optimizes right ventriculovascular coupling.

These findings are in full agreement with a recent study by Kerbala and colleagues (10). In a canine model of pressure-overload right ventricular failure, levosimendan increased right ventricular contractility at a lower energy expenditure than dobutamine. In addition, levosimendan decreased right ventricular afterload and was superior in restoring right ventricular-pulmonary arterial coupling.

Results similar to what has been observed in animal studies have recently been reported in patients with acute heart failure (9). In this context, results from randomized clinical trials indicate that levosimendan improves hemodynamics better than dobutamine without obvious deleterious side effects (11). However, two recent large prospective trials of levosimendan in patients with progressive heart failure (REVIVE and SURVIVE) revealed conflicting results. Despite a trend toward early benefit in terms of hemodynamic stabilization and relieving symptoms following levosimendan infusion, these studies showed no benefit in long-term outcome (12).

Due to the significant vasodilatory properties of levosimendan, the dosage and way of administration (loading bolus followed by continuous infusion vs. continuous infusion alone) as well as the intravascular volume status of the patient should be taken into account to ensure a safe application.

To date, there is no published evidence that any other drug is capable of optimizing right ventricular-vascular coupling more effectively than levosimendan. In this context, it is especially important that, compared with other inotropic agents, this positive effect is not linked to increased myocardial oxygen demand or impaired myocardial relaxation (13, 14). Since restoration of right ventricular-pulmonary arterial coupling represents one of the key targets in the treatment of right ventricular dysfunction (15), this study strongly suggests that levosimendan may be an attractive therapeutic option in this common clinical setting.

Another important finding by the present authors (2) is the observation that in the state of reversible vasoconstriction, levosimendan exerts a significant pulmonary vasodilatory effect. This finding is consistent with previous experimental and human studies in which levosimendan resulted in pulmonary vasodilation when administered in the presence of increased pulmonary vascular resistance (8, 16, 17).

Since the right ventricle plays a crucial role within the hemodynamic system (18) and because right ventricular depression exerts dramatic effects on both pulmonary and systemic hemodynamics, prevention and treatment of right ventricular dysfunction are of paramount clinical importance. To treat this complex cardiovascular condition, we have now a triple-action compound that exerts positive inotropic, vasodilatory, and anti-ischemic effects at the same time.

The current literature on this topic, although limited in extent, supports the concept that levosimendan is a useful agent to treat right ventricular dysfunction resulting from acute pulmonary hypertension complicated by myocardial stunning. Since levosimendan likewise increases coronary blood flow (2), improves myocardial contractility (5), and ameliorates sepsis-associated cardiopulmonary dysfunction (7, 15), opening of adenosine triphosphate-sensitive potassium channels of vascular smooth muscle cells and the inner mitochondrial membranes (4) as well as (to a lesser degree) stimulation of phosphodiesterase III (5) plays a pivotal role in this regard. In fact, these complex mechanisms of action open new perspectives in the treatment of a wide range of cardiovascular and pulmonary morbidities, including myocardial stunning (6), sepsis-associated myocardial depression (7), acute respiratory distress syndrome (8), and acute heart failure (9).

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Ushering in the era of nuclear terrorism*

On November 1, 2006, former Russian KGB agent Victor Litvinenko was poisoned with Polonium 210 in London, England. He died 22 days later at University College Hospital (1, 2). His death has attracted considerable attention due to the James Bond-like methods used by his assassins and because a radioactive weapon was involved. For the medical community, Litvinenko's murder represents an ominous landmark: the beginning of an era of nuclear terrorism.

Polonium 210 is a high-energy alpha particle emitter found in trace amounts in uranium ore. It can also be synthesized by bombarding the metallic element bismuth with neutrons in a nuclear reactor (3). Although alpha particles cannot penetrate the skin, if inhaled or ingested they are lethal. Particularly concerning is the fact that alpha particle emitters like Polonium 210 are not recognized by commonly used radiation detection devices. Therefore, they can be easily transferred across borders and pose a significant threat in the hands of terrorists (1). Only a few years ago, one might have concluded that the level of scientific sophistication and financial resources necessary to generate a small, difficult-to-detect nuclear terrorism device would be restricted to only a few countries. Recent events in Asia and the Middle East suggest that in the near future this may not be the case. Would a country with nuclear capabilities that overtly supports terrorism facilitate attacks in the United States using nuclear materials? Would the country that carried out the assassination of Litvinenko provide similar technology to nations that support terrorism? It would probably be prudent for the United States medical community to assume that the answer to these questions is “yes.”

REFERENCES


*See also p. 716.
In this issue of *Critical Care Medicine*, Dr. Constantine Manthous and Dr. William Jackson Jr present a pathophysiology-based approach to the critical care of victims of a nuclear device detonation. They detail the degree of preparedness required for local officials, emergency personnel, and hospitals. They discuss the management of patients as they are received in the emergency room as well as in the intensive care unit (ICU). Most importantly, they provide a unique review of organ-specific effects of radiation with an emphasis on therapies that might be beneficial (4).

It is difficult to predict what form a nuclear terrorist attack might take. Possibilities include detonation of a small nuclear device, use of a dirty bomb, contamination of food or water, and destruction of a nuclear power plant using aircraft (in much the same way that Al Qaeda destroyed the World Trade Center in New York in 2001). Three types of injuries would be likely in patients presenting to the ICU after an event involving nuclear material: blast injuries, thermal injuries, and/or radiation injuries.

Many ICU personnel are familiar with the management of blast and thermal injuries. However, few are experienced with radiation injuries. Two types of radiation injury would be expected after a nuclear blast, prompt and residual. The severity of prompt radiation injury decreases with increasing distance from the detonation. Residual radiation injury is caused by exposure to radioactive contamination. Prompt radiation injuries have accounted for the majority of acute radiation casualties in past events (5).

Estimation of radiation dose and consideration of organ-specific effects of radiation are important elements of the clinical assessment of individuals exposed to detonation of a nuclear device. Drs. Manthous and Jackson discuss these important issues in considerable detail (4). The National Council on Radiation Protection and Measurements is currently completing a report entitled *Preparing, Protecting and Equipping Emergency Responders for Nuclear and Radiologic Terrorism* (5). This report is likely to provide additional information for ICU personnel caring for the victims of nuclear terrorism.

Palliative care for nuclear terrorism victims who survive the initial attack but receive lethal radiation or thermal exposure is an important issue that Drs. Manthous and Jackson mention only briefly in their article. I believe that this issue deserves further attention, particularly after a physician and two nurses at Memorial Medical Center in New Orleans were arrested and charged with second-degree murder for allegedly carrying out mercy killings of four patients in the days immediately following Hurricane Katrina (6).

Details of the events at Memorial Medical Center have not been fully disclosed. However, it is clear that in the aftermath of Hurricane Katrina, patients at Memorial Medical Center were suffering greatly, the staff was overwhelmed, and federal, state, and local officials provided virtually no assistance. Memorial Medical Center was isolated, without power, and under 10 feet of water for 4 days in 110°F heat. The focus on an investigation by Louisiana attorney general Charles Foti is whether Dr. Anna Pou and nurses Cheri Landry and Lori Buda administered lethal doses of morphine and midazolam to patients who might have survived the catastrophe (7, 8).

The actions of Dr. Pou and nurses Landry and Buda are relevant to a discussion of the medical response to the detonation of a nuclear device because it is conceivable that a large number of victims of a nuclear explosion might survive the initial event but suffer significant radiation exposure. It is also conceivable that the healthcare system in the affected area might be overwhelmed and that conditions might be similar to those at Memorial Medical Center following Hurricane Katrina.

How should clinicians treat patients who are suffering when the healthcare system is overwhelmed and the available workers believe they must focus their attention on victims most likely to survive? Should the medical standards during disasters (such as Hurricane Katrina) be any different from the standards that guide our daily care of patients in well-stocked, well-staffed ICUs? If not, what should the standards be? And, who should establish them?

Palliative care is now commonly integrated into critical care medicine (9, 10). During and after a disaster the resources to provide quality palliative care may be limited. However, it is during this time that palliative care may be most important. As working groups begin to establish guidelines for palliative and end-of-life care in the ICU (11), they should be encouraged to comment on disaster response with an emphasis on helping clinicians confront crises such as those faced by healthcare personnel in September 2005.

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REFERENCES
6. Charatan F: New Orleans doctor is charged with giving lethal injections during floods. *BJM* 2006; 333:218
Protocols, practice, and patients—The case of alcohol withdrawal*

In the current issue of *Critical Care Medicine*, Dr. Gold and colleagues (1) describe 95 medical intensive care unit (ICU) patients admitted solely for the treatment of alcohol withdrawal syndrome (AWS). Patient outcomes are described before and after implementing pharmacologic sedation guidelines driven by patient symptoms. These guidelines encouraged rapid titration of escalating doses of diazepam, in combination with phenobarbital or propofol. The number of patients in whom intubation and mechanical ventilation were required halved after implementation of the protocol, despite doubling the initial doses of benzodiazepines used. There was a trend toward decreasing ICU length of stay as well as the rate of nosocomial pneumonia. Striking by any standards—but what are the lessons?

The clinical relevance of the current findings is broad. One in ten North Americans purportedly consumes excess alcohol and is therefore at risk for alcohol withdrawal. In addition, alcoholism contributes to as many as 21% of admissions to ICU (2). Validated questionnaires (e.g., CAGE questionnaires or Clinical Institute Withdrawal Assessment for Alcohol Scales) are not routinely administered in the critical care setting. The current authors describe a standard validation scale, the Sedation Analgesia Scale (3), in their assessments, making their approach applicable to ICUs where such a standard sedation scale is used. Finally, the importance and impact of delirium in the critical care setting are being increasingly recognized; alcoholism doubles the incidence (4) of delirium without necessarily developing into alcohol withdrawal syndrome. There may therefore be a relevance of this titrated management approach to other critically ill alcoholic patients.

Titrating sedative drugs to patient need benefits the critically ill (5, 6). Recent publications emphasize the disadvantages of excessive sedation (4). However, in patients with alcohol withdrawal, administering additional sedation early translated into a better outcome. This may appear counterintuitive as patients had already received 200 mg of diazepam within 4 hrs. The study thus emphasizes that titration should be adjusted individually both up and down, depending on patient needs and clinical context.

Despite the lack of blinded randomization of patients to one management arm or another and uncertainty as to what drove individual practitioners to intubate, Dr. Gold and colleagues (1) managed to evaluate a very large number of patients in whom alcohol withdrawal was the reason for ICU admission. Delirium associated with alcohol withdrawal is the only category of delirium for which management strategies have been thoughtfully evaluated in hospitalized populations. This article represents the first AWS management study in a medical ICU population without “confounders.” Alcohol withdrawal probably requires a different management strategy than “garden variety” delirium, and the work by Dr. Gold and colleagues is compelling for adopting their “titrated” two- to three-sedative agent approach and for laying the ground for future studies.

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REFERENCES

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Morbidly obese patients with acute respiratory failure: Don’t reach for the endotracheal tube yet!*
Debriefing is an effective method for providing feedback and ensuring adherence to best clinical practice by residents in the intensive care unit*

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lucidating a comprehensive understanding of the basic science of injury forms the foundation of critical care medicine. On this foundation, best clinical practices are determined by the never-ending comparison of different treatment strategies. However, the only means of successfully treating future patients rests with our ability to train our residents the importance of self-evaluation in application of these best practices. In this month’s issue of Critical Care Medicine, Dr. Alison Clay and her colleagues (1) at Duke University Medical Center present their results on the use of debriefing checklists that incorporate literature-based best practices as an educational strategy to improve resident performance and ultimately patient care in the intensive care unit.

The term debrief can be traced to World War II, when it was used to interrogate soldiers on return from a mission in order to assess the conduct and the results of the mission (2). Management of a critically ill patient is similar to conduct of a military mission. Each requires application of intelligence (up-to-date scientific knowledge) to a constantly changing situation. Debriefing after a critical event in the intensive care unit allows residents to assess their response to the event and relate it to the patient’s outcome.

Debriefing differs from reviewing rotation objectives. Rotation objectives are frequently a laundry list of topics to be covered during a rotation and are typically not used in providing feedback regarding resident performance. Debriefing, on the other hand, is a feedback method that involves specific behaviors and actions applied to actual clinical situations. Furthermore, rotation objectives typically differ depending on the resident’s year of training, whereas debriefing checklists can be readily applied to residents of all levels, as they specify particular behaviors that all physicians should exhibit. Debriefing will not replace rotation objectives, as residents also need to be knowledgeable about clinical situations that haven’t actually encountered but may encounter in the future.

This work by Dr. Clay and colleagues (1) is pertinent and timely. Residency training in all specialties is currently undergoing a radical metamorphosis. Although keeping up with the advances in medical science has always been a challenge for our trainees, recent limitations on duty hours may result in less clinical exposure and hence a decline in experiential learning (3, 4). As a consequence, critical care faculty will need to become as innovative in education as they currently are in the treatment of sepsis and acute respiratory distress syndrome. To complicate this situation further, the Accreditation Council for Graduate Medical Education has recently initiated the Outcome Project (5), which requires all residency training programs to document competency in six core areas consisting of patient care, medical knowledge, practice-based learning, interpersonal and communication skills, professionalism, and systems-based practice. In essence, these competencies codify what we have always taught our trainees, but how this training occurs and what results have
Disparities in sepsis: What do we understand?*

Sepsis afflicts more than 700,000 patients annually in the United States (1) and is a major reason for admission to the intensive care unit. It is the tenth leading cause of death overall in the United States (2) and is the leading cause of noncoronary intensive care unit deaths (3). Despite impressive efforts by the Surviving Sepsis Campaign (4) and implementation of early goal-directed therapy (5) protocols to improve treatment strategies, mortality from sepsis still remains 20–30% (6, 7). Aside from lethality, the economic costs of caring for septic patients can exceed $50,000 per patient and account for almost $17 billion in annual healthcare costs in the United States (8).

Recently, significant inequalities in access to health care and disparities in the quality of care provided have been identified (9). Socioeconomic, racial, educational, cultural, and geographical factors have all contributed to disproportional mortality in both acute and chronic health conditions (9–12). Wong et al. (10) reported racial disparities in mortality and found that infection was second only to cardiovascular disease in contributing to life-years lost in minority populations. Racial differences in hypertension, human immunodeficiency virus (HIV), and diabetes were major contributing variables to mortality. These findings prompted the National Institutes of Health to make “eliminating health disparities” a main objective of its Healthy People 2010 initiative (13). Improving ac-

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cess to medical professionals, emphasizing preventive health, and reducing financial barriers are all important steps in eliminating disparities in health care.

Multiple studies have identified disparities in race and sex among patients with sepsis. Men are 30% more likely to develop sepsis compared with women, and black Americans have twice the incidence compared with whites and higher mortality rates (1, 14, 15). Age and chronic co-morbid conditions such as diabetes, cancer, and renal failure influence the risk for sepsis (10, 15–17) and may contribute to racial disparities with sepsis because of their disproportionate distribution among races. Most recently, however, we have reported that black patients with sepsis have a greater frequency of Gram-positive infections compared with whites and other races, even after controlling for variables that influence the inciting organism, such as the source of infection (15). These results suggest that there may be biological factors that alter the risk for sepsis, as it has been previously shown that genetics may alter the outcome with sepsis (18). For example, it is known that race-specific polymorphisms exist in the Toll-like receptor (TLR2) that is fundamental to the response to Gram-positive infections. If genetic variation may sufficiently alter the host immunologic response to modulate sepsis susceptibility, it would be the first evidence of a genetic predisposition to the development of a sepsis response to infection.

Genes, however, can only be part of the picture, and we are just beginning to understand the intricacies of racial disparities among septic patients. In this issue of *Critical Care Medicine*, Dr. Dombrowski and colleagues (19) examined causative factors behind the racial disparities. Using the 2002 New Jersey State Inpatient Database, they found that compared with white patients, black patients with sepsis were younger and more likely to have chronic co-morbid conditions such as diabetes, chronic renal failure, obesity, or HIV. The effect of some common chronic co-morbid conditions on sepsis has been investigated previously (15, 20), yet the racial disparity in septic patients with HIV is most striking. HIV was present in 12% of blacks and only 0.7% of whites, making HIV a potential contributor to racial disparities in sepsis and in race-specific differences in inciting organisms (15).

The higher incidence of sepsis in blacks also leads to greater population-based mortality. In this study, the mortality of sepsis in black men (219 per 100,000) is almost twice that of white men. Although this figure is consistent with previous data, what is new from this study is that there was no difference in case fatality rates. Despite having a population-based mortality twice that of whites, blacks with sepsis have no greater rate of dying from sepsis once hospitalized. This point is worth emphasizing as it suggests that there may be no systematic differences in treatment between races.

More than 44 million Americans lack health insurance (13). In the current study, hospitalized blacks were more than three times as likely to be uninsured than whites, and this disparity increased to nearly four times for black sepsis patients. Lack of insurance limits access to preventive health services and thus contributes not just to greater prehospitalization co-morbid conditions, but often delays decisions to seek treatment. In an acutely septic patient, delays of just a few hours in treatment can often be the difference in organ dysfunction and survival. There should be caution in generalizing the findings in this study because the difference in insurance status may be partially explained by the fact that 74% of whites qualified for Medicare solely on the basis of age, compared with only 47% of blacks. In addition, Medicaid is independently governed and financed at the state level, and therefore, the percentage of uninsured patients could be vastly different if the study was performed in another state. The underlying principle, however, is that lack of insurance may be a contributing factor in the racial disparities known to exist in sepsis.

There are important limitations to the study. The study was performed using an administrative database that is limited by the accuracy of coding and may be subject to differences in regional and institutional practice. In addition, this database lacks patient-specific information such as physiologic scores, hemodynamic parameters, and readmission rates, which could be instrumental in assessing uniformity of the sample and minimizing confounding variables. Although this method has been well validated (1), one cannot conclusively attribute mortality to sepsis when another acute illness may be present. Furthermore, the data are limited to the population of New Jersey and therefore cannot be generalized to the U.S. population without further information on racial, cultural, educational, and socioeconomic backgrounds, which vary geographically.

Diversity of the American population is among our nation’s greatest assets; however, it also presents one of its greatest challenges in terms of insuring against and treating illness. Sepsis is one of the leading causes of death in the United States, and despite the improvement in mortality in the past 20 yrs (1), there still remains a great divide in mortality among races. As the incidence of sepsis is projected to continue to rise (8), this study and others (8, 15, 17) have identified important differences in co-morbid medical conditions (e.g., HIV and diabetes) that may contribute to the disparities in sepsis. The real challenge, however, is identifying and treating the nonmedical barriers that contribute to this divide, such as access to healthcare and social, cultural, and economic conditions.

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REFERENCES

8. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the...
Moving beyond numbers... The next step forward in improving patient care*

As critical care clinicians we want to provide the best for our patients: the best monitoring, the best diagnostic tests, the best therapeutic interventions... the best care. How do we determine what the best is, get it to the bedside in a timely fashion, and keep it there, includes a number of steps. Backed by the strong movement toward evidence-based medicine, randomized controlled trials and systematic reviews have been embraced by the critical care community as the highest levels of evidence to support or refute the efficacy of new or currently used therapeutic interventions. At the same time it is recognized that we do not have this level of evidence for all therapies, and current “best” evidence may be comprised of cohort studies, case-control studies, or case series. Lack of higher levels of evidence does not infer lack of efficacy but, rather, the level of confidence we can have that a treatment is truly effective.

Between researchers and end users has been identified and clinical practice guidelines have been adopted by many as one means of bridging this gap. Although a rigorous approach to developing clinical practice guidelines has been advocated and increasingly used, development of these guidelines alone does not ensure their appropriate use. Guideline implementation has been extensively studied outside the intensive care unit, and adoption of guidelines by the targeted end users depends on the methodology used to implement them. Using a multifaceted approach, including promotion by local experts, a system of reminders or feedback and accessible summaries of the guidelines may be most useful (2, 3). Measuring adherence to the guidelines and impact on patient outcome allows evaluation of the guideline. All these steps, from summarizing the literature on efficacy to measuring guideline adherence or concordance, involve quantitative analyses. Despite a carefully planned and methodical approach to each step in translating knowledge from the primary studies to a concise package for the end user, adoption of the targeted therapy may still be found to be less than optimal.

Questions that arise at this point are: What else can be done? Why do we not see the results we expect? Are clinicians using the guideline? Do they understand it? Why do they do what they do? This last question can no longer be answered by quantitative analytic techniques alone and yet is extremely important to explore if we want to improve patient care further.

Qualitative research is necessary to explore questions of why we do what we do or do not do what is expected (4–8). It has a strong tradition within the nursing literature but little has been published in critical care journals targeting physicians. I love numbers. I am very comfortable reading, interpreting, and critically appraising quantitative research. Like many, I try to remember important numbers to quote them later, often with little success. I enjoy trying to keep up with the medical literature and have perhaps what some may consider a “concerning” excitement when new “landmark” studies are published. I even enjoy cutting and pasting tables and figures from these articles into computer slide presentations following the familiar rhythm of starting with Table 1’s baseline characteristics and Figure 1’s flow of patient recruitment to the quantitative tables on patient outcome and their accompanying statistics. Number, numbers, numbers.

Qualitative research is a different story. Here researchers with expertise in this area move beyond numbers and do so using a methodology that is foreign to most of us. They raise hypotheses and conduct interviews and focus groups or simply observe what people do while making notes or recording it all. They then spend extensive time rigorously analyzing these recordings and notes looking for patterns, theories, and themes. They use their findings to further guide...
Open lung ventilation: Waiting for outcome studies?*

One of the most important advances in mechanical ventilation in recent years has been the recognition that a protective ventilatory strategy with low tidal volume decreases morbidity and mortality when applied properly in patients with acute respiratory distress syndrome (ARDS) (1). The application of low tidal volume ventilation prevents injury from alveolar overdistension but does not avoid potential injury caused by the repetitive alveolar opening and closing. Positive end-expiratory pressure (PEEP) prevents end-expiratory alveolar collapse and improves ventilation/perfusion matching as well as gas exchange in ARDS patients (2).

Recruitment maneuvers (RMs), known also as “open lung ventilation,” were first encouraged by a randomized controlled trial performed by Amato et al (3). The open lung strategy allows a sustained increase in airway pressure to open collapsed alveoli followed by sufficient PEEP application to maintain the lungs open. The percentage of potentially recruitable lung varies among patients and directly correlates with the maintained percentage of open lung after application of PEEP (4).

REFERENCES

Most studies of RMs have used physiologic end points, including the study by Dr. Toth and colleagues (5) appearing in this issue of Critical Care Medicine. The effects on oxygenation during open lung ventilation have been variable between studies and may be related to the heterogeneity of patients studied or the method used for recruitment (6). Sustained improvement in oxygenation with open lung ventilation was better achieved in paralyzed patients (7) and if larger tidal volume (8) or relatively lower but adequate PEEP levels (9) were applied during RMs. In animal models of acute lung injury, RMs did not worsen right or left ventricular function (10). The loss of hypoxic pulmonary vasoconstriction due to alveolar recruitment may counteract the negative hemodynamic effect of high airway pressure use. Adverse hemodynamic effects of RMs appear to be more common in patients with reduced chest wall compliance or limited oxygenation response from recruitment (11).

Improved gas exchange seen during RMs is likely related to opening of the atelectatic alveoli from lung recruitment. The impact of RMs on extravascular lung water (EVLW) is less clear, and the relationship between application of PEEP, EVLW, and oxygenation remains complex and controversial. Experimental studies on this subject have yielded variable results. Application of PEEP has caused decreased (12), increased (13), or unchanged (14) EVLW measurements. The presence of intravascular occlusions and hence perfusion defects in patients with ARDS may account for the variability when measuring EVLW.

Dr. Toth and colleagues (5) investigated the relationship between the application of PEEP during recruitment maneuvers and oxygenation, EVLW, and hemodynamic changes. Their open lung ventilation algorithm incorporated application of continuous positive airway pressure of 40 cm H2O for 40 secs followed by a decremental PEEP protocol to determine the PEEP level that maintains oxygenation after lung recruitment in 18 sedated paralyzed ARDS patients ventilated with a pressure control mode.

The findings of this study once again illustrate the beneficial effect of RMs on gas exchange and oxygenation as well as the relative safety of this strategy (14). Oxigenation improved significantly after lung inflation compared with baseline and remained significantly elevated at 30 mins but not at 1 hr postintervention. Conversely, sustained increase in oxygenation (4–6 hrs postinflation) was described by similar work applying decremental PEEP protocols after lung opening (15, 16). A lower PEEP achieved during titration, patient heterogeneity, and different methods of recruitment probably accounted for variability of results between these studies. Overall RMs were well tolerated in the study by Dr. Toth and colleagues (5). Significant respiratory acidosis developed, but acid-base balance returned to baseline 30 mins after lung recruitment, whereas only two patients required increased inotropic support to maintain cardiac output.

The authors did not find any significant change in measured EVLW volume despite improvement in oxygenation, suggesting atelectasis reversal as the primary mechanism by which RMs improve gas exchange in ARDS patients. Limited information was given by the authors regarding the method used to measure EVLW in the studied patients. Nevertheless, the study results are not enough to clarify the unsettled relationship between the optimal PEEP and EVLW for the reasons mentioned before.

Their investigation also focused on the hemodynamic effect of open lung ventilation. Interestingly, Dr. Toth and colleagues (5) assessed cardiac preload by measuring intrathoracic blood volume. The latter was shown to be of higher clinical value in assessing cardiac preload compared with central venous pressure or pulmonary artery occlusion pressure measurements in coronary artery bypass graft patients with ARDS receiving positive pressure ventilation (17). As expected, the application of high airway pressures caused an increase in central venous pressure and significantly reduced intrathoracic blood volume, stroke volume, and cardiac index during the opening procedure, whereas the mean arterial pressure remained unchanged. These detrimental hemodynamic changes gradually resolved and eventually returned to close to their respective baseline values 30–60 mins after recruitment. It would be useful to know whether the observed decrease in cardiac output during inflation would have translated into end organ perfusion reduction, despite an unchanged mean arterial pressure. Of note, the effect of three consecutive RMs on gastric mucosal perfusion was recently investigated by Claesson et al. (18) in ten patients with acute lung injury. Similarly to the study by Dr. Toth and colleagues (5), cardiac index was significantly reduced but mean arterial pressure decreased only after application of the third recruitment maneuver. More importantly, there was a trend toward gradual decreases in gastric mucosal perfusion.

Apart from all the physiologic studies suggesting a potential benefit of recruitment maneuver in terms of gas exchange, no data are yet available that demonstrate the ability of such strategy to improve patient outcome. Thus several questions are raised: What is the most effective method of recruitment to maintain oxygenation? What is the real effect of RMs on end organ perfusion? Finally, do RMs have any significant impact on survival in severely hypoxemic ARDS patients?

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Mortality and tracheotomy*

Tracheotomy has become a common procedure in the intensive care unit (ICU) for patients requiring long-term mechanical ventilatory support. Current American College of Chest Physicians-sponsored Consensus statement favors tracheotomy for airway management if need for mechanical ventilation is anticipated to be >21 days. Furthermore, the 1989 Consensus Conference view recommended use of tracheotomy in patients requiring long-term ventilatory support (1). Benefits of tracheotomy have been the focus on intense study in recent years (2–14).

In this issue of Critical Care Medicine, Dr. Combes and colleagues (15) present a retrospective review on tracheotomy, evaluating the effect of tracheotomy on ICU and hospital mortality in patients requiring >3 days of mechanical ventilation. The authors reviewed the charts of all patients admitted to their ICU over a 3-yr period. Over this 3-yr period, 506 patients required mechanical ventilation for >3 days, and 66 of these patients underwent tracheotomy after a mean of 12 days of translaryngeal intubation. The data revealed that patients who underwent tracheotomy had lower ICU and in-hospital mortality rates. However, they had longer ICU length of stay and more total days of mechanical ventilation. The total workload for managing patients with tracheotomy was higher; however, the per-

day workload was lower for tracheotomized patients.

Previous studies have evaluated the benefits of tracheotomy vs. translaryngeal intubation in critically ill patients. Krolle et al. (2) conducted a prospective cohort study to evaluate clinical predictors and outcomes for patients requiring tracheotomy. The hospital mortality of patients with tracheotomy was 13.7% vs. 26.4% for patients not undergoing tracheotomy. Freeman et al. (3) conducted a large retrospective review of 43,916 patients who underwent tracheotomy for a variety of clinical reasons. In this study, median days of mechanical ventilation before patients underwent tracheotomy was 9 days. Data analysis showed tracheotomy was associated with improved ICU and hospital survival of 78.1% vs. 71.8%.

Frutos-Vivar et al. (4) conducted a prospective observational cohort study evaluating the outcome of mechanically ventilated patients requiring tracheotomy. In this study, a mortality benefit was noted in the ICU (odds ratio, 2.22; 95% confidence interval, 1.72–2.86), but overall hospital mortality was unchanged. In summary, these three studies consisted of a diverse population of patients, utilized a nonrandomized study protocol, and the studies were not designed to reveal specific differences in mortality between tracheotomy and conventional translaryngeal intubation. Thus, the associated improved survival may have reflected selection bias of patients for tracheotomy to those expected to survive hospitalization as compared with those who would otherwise be expected to die or who were extubated. Interestingly, in the article by Dr. Combes and colleagues (15), no significant differences were noted between the two patient populations' clinical characteristics at time of ICU admission or ICU day 3. An interesting but not reported variable would have been the clinical characteristics of the patient population on the day of tracheotomy.

Most studies designed to specifically address mortality benefits of tracheotomy compared with translaryngeal airway management have focused on timing of tracheotomy. In this regard, well-conducted studies have shown improved mortality with early tracheotomy. Rumbak et al. (5) evaluated the benefits of early tracheotomy (within the first 2 days) vs. late tracheotomy (days 14–16) in critically ill medical patients. This study noted a statistically significant reduction in mortality with early tracheotomy (31.7% vs. 61.7%, respectively). Chintamani et al. (6) evaluated the benefits of early tracheotomy in patients with closed head injury. In this study, early tracheotomy was performed after an average of 2.18 days. Mortality in the early tracheotomy group was 36% compared with 58% in the late tracheotomy group. Boynton et al. (7) evaluated the mortality effect of tracheotomy timing in surgery and trauma ICU patients. Median timing of early tracheotomy was 4 days as compared with 14 days for the late tracheotomy group. This study showed decreased mortality in the early tracheotomy group. Although these three studies showed mortality benefit with early tracheotomy, several other well-designed studies addressing mortality benefits of tracheotomy have not shown any statistically significant benefit (8–12).

*See also p. 802.

Key Words: tracheotomy; respiration; artificial; mortality; intensive care units; outcome assessment

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various study outcomes regarding mortality and tracheotomy may reflect the heterogeneity between the patient populations in regard to illness severity and co-morbid diseases. Some of these studies had notable differences between the two study populations. Arabi et al. (12) studied the benefits of early tracheotomy (up to 7 days) in trauma patients. Although no mortality benefit was noted in this study, the Glasgow Coma Score was lower in the patients selected for early tracheotomy. Saffle et al. (11) evaluated the benefit of early vs. delayed tracheotomy in intubated and acutely burned patients. No mortality benefit was noted in the early tracheotomy group; however, patients in the early tracheotomy group had more severe burns and lower PaO2/FiO2 ratios.

Another confounding variable in comparing various studies evaluating mortality and the timing of tracheotomy is the diversity of the definition of early tracheotomy. The definition of early tracheotomy varies with each study (i.e., 2 to 7 days), and some studies define early tracheotomy as up to 7 days. This is a critical point, as studies evaluating benefits of tracheotomy in regard to pneumonia have clearly shown benefits only with early tracheotomy, with less benefit noted the longer tracheotomy is delayed (5, 8, 13).

The article by Dr. Combes and colleagues (15) reveals tracheotomy was associated with greater length of mechanical ventilatory support as compared with those patients who did not undergo tracheotomy. This finding is likely related to the fact that those patients not selected to undergo tracheotomy were either extubated or died. Several previous studies have evaluated the benefits of early tracheotomy with regard to days of mechanical ventilation. Rumbak et al. (5) noted a significant decrease in the days of mechanical ventilation with early tracheotomy (7.6 vs. 17.4 days). Rodríguez et al. (8) noted similar findings of decreased days of mechanical ventilation with early tracheotomy (12 vs. 32 days). Boudker et al. (9) also noted significantly shorter days on mechanical ventilation with early tracheotomy (14.5 vs. 17.5 days). Arabi et al. (12) reported early tracheotomy was associated with fewer days of mechanical ventilation (10.9 vs. 18.7 days), despite statistically significant lower Glasgow Coma Score in the early tracheotomy study population. Lesnik et al. (14) and D’Amelio et al. (16) reported fewer days of mechanical ventilation with early tracheotomy: 6 vs. 20.6 days and 4.6 vs. 11.7 days, respectively. The important feature of these five studies is the study contrasted early vs. delayed tracheotomy as related to days of mechanical ventilation. The study designed by Dr. Combes and colleagues (15) compared tracheotomy with continued translaryngeal intubation. The data thus likely reflect selection of patients for tracheotomy as those deemed by clinicians most likely to survive and thus incurred more overall days of mechanical ventilation.

The authors quantified workload using the Omega score to estimate resource utilization. That the total increased workload as measured by Omega score was higher for tracheostomized patients likely relates to the total increased length of hospitalization, as the authors note lower per-day Omega scores for tracheostomized patients. In this regard, tracheotomy has several known benefits in regard to patient care. Benefits include a well-tolerated, stable airway, requiring minimal if any sedation, the potential for oral feedings, enhanced communication, early ambulation, and easier pulmonary toilet and oral hygiene.

In summary, tracheotomy continues to be a common procedure performed in the ICU. The benefits of tracheotomy in regard to mortality, incidence of pneumonia, length of hospital and ICU stay, and patient comfort continue to remain an area of active study. This article further supports the finding that tracheotomy offers mortality benefit as compared with continued translaryngeal airway management. In regard to timing of tracheotomy, data suggest that the earlier the patient undergoes tracheotomy, the more likely the patient will benefit from the procedure. Additional studies addressing long-term patient outcomes, patient characteristics defining likely need for prolonged mechanical ventilation, and resource utilization of these patients are needed.

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You never know—One of your patients with cancer might surprise you*

As intensivists, we are often called on to prioritize patients for intensive care unit (ICU) management. In our individual triage processes, we consider a variety of variables when allocating ICU beds: patient characteristics, published evidence, personal experience, and hospital guidelines, to name a few. The process must be ethical, equitable, unbiased, and transparent (1). In this issue of Critical Care Medicine, Dr. Lecuyer and colleagues (2) have challenged us to change our opinions of patients with cancer. Instead of seeing them as people suffering with a disease that will eventually kill them, we are being asked to see them as people living with a chronic illness that may have minimal impact on their day-to-day lives, who are as deserving of aggressive medical care as anyone with liver failure, congestive heart failure, or emphysema.

As described by the authors, the early literature on cancer patients admitted to the ICU was not reassuring (3). The triage guidelines that were developed at that time were formulated in such a way as to preserve the use of limited ICU resources and direct them toward the patients who might derive the most benefit—in short, those with a hope of survival. However, more recent studies have shown improved outcomes for various groups of critically ill cancer patients (4–10). In fact, outcome of critically ill patients with solid tumors is comparable to the outcome of general ICU patients with severe sepsis (11, 12). Despite this, there continues to be a pervasive feeling that patients with cancer are somehow less deserving of ICU care.

Making things more complicated is the idea that it might be difficult to properly identify those cancer patients who are the best candidates for ICU care. Perhaps this is due to a natural inclination to link the outcome of the acute event with the characteristics of the cancer, despite the evidence to the contrary (4). In fact, in an earlier study from the same institution, our inability to accurately predict the outcome of sick cancer patients was highlighted. In that analysis, the 30-day survival of patients who were considered “too sick” for ICU admission was 26%. More concerning was the surprisingly low 30-day survival (78.7%) of the patients considered “too well” for ICU admission (10).

Dr. Lecuyer and colleagues (2) evaluated 188 critically ill cancer patients who required mechanical ventilation. Excluded were other critically ill patients, HIV-infected patients, and recipients of allogeneic stem cell transplants, as they even now have very poor outcome after mechanical ventilation (13, 14). The authors’ goal was to assess the impact of a broader admission strategy to the ICU by admitting patients who were not at the start of their cancer treatment course or in complete remission as well as to identify any prognostic factors that would help identify patients for whom prolonged ICU care and mechanical ventilation would not be appropriate. Worth noting is that the majority of the patients had acute leukemia or non-Hodgkin’s lymphoma, which is not typical of most institutions.

This study had a fairly high mortality rate (47%) within the first four ICU days, despite the lack of any limitation of care. However, this may represent the severity of the underlying critical illness. More interesting is the 20% hospital survival rate, which begins to approach the survival rate of general ICU patients with severe sepsis. Although this does not help evaluate the single patient as a potential ICU candidate, it is certainly high enough that we must consider aggressive ICU care in this group of patients (15).

As regards their search for clinical variables that could help identify patients for whom prolonged ICU care would not be reasonable, the authors were less successful. It should come as no surprise to most that a patient with five organ systems in failure on day 5 is a patient with a high mortality risk. Multivariate analysis could not identify individual factors associated with hospital survival, although it was noted that no patient requiring intubation after day 3 survived. Perhaps this could help stratify these patients within our own minds as ones at particularly high risk of death.

Overall, the way in which this study can be most useful to the practicing intensivist is by reminding us that we care for individual people, not cohorts of critically ill patients. You never know—one of your patients might pleasantly surprise you.

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*See also p. 808.

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Eliminating pressure ulcers: Do specialty beds or specialty nurses matter more?*

Pressure ulcers have plagued critically ill patients since the beginning of immobility. Multiple studies focusing on this disease entity have identified factors contributing to the development of these ulcers (1–5). Historically, these factors have included prolonged hospital stay, the presence of sepsis, age, malnutrition, and emergent admission (6).

These risks appear fairly predictable. Intuitively, the longer the time a patient is nonambulatory and acutely ill, the higher is this patient’s risk for pressure ulcer. Sepsis and emergency admission create longer hospital stays without patient mobility, whereas poor nutrition promotes muscle wasting and soft tissue loss. The nonambulatory state allows the impact of bony prominences on external surfaces to become pronounced and facilitate skin breakdown.

Knowing the risks for decubitus ulcers has not necessarily decreased their incidence. In many cases, the immobility in these patients is frequently difficult to correct. Consequently, clinicians have pondered numerous ways to minimize the detrimental impact of the contact surface. Various types of beds and mattresses have been invented to prevent decubitus formation (7). Certain fluidization techniques have been described and championed as decubitus-free (8). However, none of these methods has achieved enough success and popularity to become the standard in intensive care. A recent retrospective analysis concluded that several interventions, including the use of certain support surfaces, patient repositioning, nutritional optimization, and sacral skin moisturizing, were appropriate strategies to prevent pressure ulcers (9).

Other authors have focused on treatment after the development of pressure ulcers (10). Certain interventions such as therapeutic ultrasound and electromagnetic therapy have been employed but not found to be uniformly beneficial (11, 12). Recently, many clinicians have employed vacuum-suction therapy to treat decubitus ulcers (13).

In this issue of *Critical Care Medicine*, Dr. de Laat and colleagues (14) demonstrate a decrease in ulcer formation in critically ill patients extending to 1 yr by focusing on a hospital-wide system rather than on a specific intensive care unit mattress. Perhaps the most novel aspect of this system was its hospital-wide nature, which appeared to provide a longer term benefit to the prevention efforts. The two aspects of their program that appear crucial to prevention efforts include the use of the specialty mattress and the training of “contact nurses” who educated and consulted the managing nursing teams about best practices of decubitus prevention. Although transfer to an air mattress was included in their prophylaxis guidelines and was certainly vital to their ambitious initiative, the more crucial part may have been the contact nurses, whose role, depending on their involvement, may have been functioning as de facto “decubitus police.”

Although the results of this study are impressive, it suffers from the absence of any cost data. Certainly many clinicians and administrators in our cost-containment era would ponder the merits of the specialty beds and the training of nurses vs. the cost incurred by a single decubitus ulcer. This type of analysis would undoubtedly strengthen this article. I invite the authors to perform a subsequent study where such questions could be answered.

Other readers might question the origin of de Laat and colleagues’ positive effects. Could their decreased ulcer rates over the study period be a validation of the mattress they used? Or were their results simply a manifestation that Hawthornian principles were alive and well in their institution? The investigators essentially created a team of trained personnel whose major purpose appeared to be decubitus ulcer prophylaxis. Maybe their system is telling us that people, not beds, are creating the extended difference. Further studies would need to be performed to answer these questions. These studies might include the use of multiple mattresses for high-risk patients in a randomized fashion or the adoption of more intricate guidelines that would replace the contact nurse component.

But such analysis would diminish the accomplishments of these investigators. Why ignore the good results these clinicians achieved with the bimodal approach? Maybe they have been successful in decubitus prevention whereas so many others have not because they used a mul-

*See also p. 815.

Key Words: immobility; prolonged hospital stay; emergency admission

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mple-prong strategy instead of a single intervention (i.e., a particular bed).
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Septic plasma-induced oxidative stress in endothelial cells:
A sensitive bioassay predicting outcome in septic shock?*

During the past decades, we have witnessed a surge of interest in biological markers to identify patients with sepsis who are at a higher risk of developing multiple organ failure and to predict outcome. Markers of inflammation, such as C-reactive protein and white blood cell count, have proved to be far from ideal in predicting the severity and outcome of sepsis (1). Many reports have focused on proinflammatory cytokines that are believed to be central to the pathophysiology of sepsis syndrome (2, 3). The prognostic usefulness of plasma proinflammatory cytokine concentrations is, however, limited by large interindividual variations in patients with sepsis (4) and differences in the expression of antiinflammatory cytokines (5, 6). The continuing search for clinically reliable markers led to the identification of, among others, procollagen (7, 8), activity of the transcription factor nuclear factor-κB in peripheral blood monocytes (9), and the antiinflammatory macrophage marker soluble CD163 (10) as early independent predictors of mortality. However, a single biological predictor of sepsis severity and outcome will likely remain elusive because of the complexity and heterogeneity of the underlying molecular mechanisms.

In this issue of Critical Care Medicine, Dr. Huet and colleagues (11) describe a simple cell assay to predict mortality: monitoring the production of reactive oxygen species (ROS) by human umbilical vein endothelial cells (HUVEC) in response to a mixture of mediators. The authors report that the ability of plasma from septic shock patients to evoke ROS production by naïve HUVEC positively correlates with the severity and mortality of septic shock. The vascular endothelium is a source of and target for ROS and reactive nitrogen species (1, 12). ROS induce microvascular endothelial dysfunction and/or damage, one of the critical events during the early phase of sepsis (1, 12). If the endothelium cannot repair itself, more sites of damage will develop, ultimately contributing to the development of multiple organ failure. Sepsis is associated with profound changes in plasma oxidative status as evidenced by the presence of chemically stable ROS-catalyzed products, as well as by decreases in antioxidant defense mechanisms (13, 14). However, oxidant and antioxidant activities in the plasma are difficult to evaluate at the bedside, yet the imbalance of oxidant and antioxidant mechanisms contributes to the development of multiple-organ failure. To overcome such difficulties, Dr. Huet and colleagues (11) tested the impact of whole plasma on ROS production by HUVEC loaded with the fluorescent dye 2,7-dichlorofluorescein (DCFH) diacetate.

The assay rests on the untested assumption that prolonged storage and/or freezing/thawing would not affect the capacity of plasma to induce DCFH oxidation.

Plasma from 21 septic shock patients (17 males and four females; 19 tested positive for bacteria) and ten healthy male volunteers was collected daily for 5 days and assayed. All patients received appropriate antibiotics, norepinephrine, and corticosteroids. The overall mortality rate was 47%, and death occurred 11 ± 9 days after intensive care unit (ICU) admission. Dr. Huet and colleagues (11) found that plasma obtained on day 1 (the day of admission to the ICU) from septic shock patients evoked rapid (peak response within 10 mins) increases in ROS production by naïve HUVEC. ROS pro-

*See also p. 821.

Key Words: reactive oxygen species; endothelial cells; plasma from septic patients; septic shock; sepsis outcome

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duction evoked by plasma collected on day 1, day 3, and day 5 was consistently and markedly higher in nonsurvivors than in survivors and correlated with simplified acute physiology score II and systemic organ failure assessment (SOFA) scores at day 1. A positive statistically significant correlation was detected between changes in SOFA scores and changes in the ability of patient plasma to evoke ROS formation in HUVEC during the 5-day study period. Consistent with previous clinical observations, septic shock patients have had markedly elevated plasma and red blood cell thiobarbituric acid-malondialdehyde levels and significantly reduced glutathione peroxidase and catalase activities. Plasma vitamin A levels were lower in septic shock patients than in healthy volunteers, whereas no differences were detected in vitamin E levels and Cu/Zn-superoxide dismutase activity in these two groups. Interestingly, no correlation was found between Cu/Zn-superoxide dismutase, glutathione peroxidase, or catalase activity, vitamin concentrations, red blood cell glutathione disulfide/reduced glutathione ratio and SOFA scores, SAPS II, and mortality of the septic patients. These latter observations underscore the limitations inherent to measuring only one biomarker related to oxidative stress.

Dr. Huet and colleagues (11) show that their in vitro HUVEC assay is sufficiently sensitive to detect differences in ROS production by plasma from survivors and nonsurvivors, even though this assay does not allow the identification of the plasma components responsible for the observed effects. Thus, it remains to be investigated whether plasma from survivors and nonsurvivors exhibits quantitative or qualitative differences. The authors do not provide information on the impact of septic plasma on endothelial cell viability. A decrease in the number of viable cells would diminish the sensitivity of the assay. Bacterial constituents, cytokines, and advanced oxidation products present in the plasma of septic patients are capable of activating endothelial cells. Lack of mediator specificity of the assay may, paradoxically, contribute to its potential usefulness. Indeed, the assay endpoint (DCFH oxidation) is likely a result of the dynamic interplay between proinflammatory cytokines (e.g., priming or synergistic actions), the opposing actions of proinflammatory and antiinflammatory cytokines and prooxidant and anti-oxidant activities.

What oxidant species does the DCFH assay detect? Within the cell, DCFH is readily oxidized by H2O2 and hydroxyl radicals and to a lesser degree by superoxide (15). Because NO also reacts with DCFH (16), it remains to be determined what portion of DCFH oxidation was due to ROS formation. Soluble mediators present in the plasma of septic patients may activate endothelial NO synthase in naïve HUVEC. Considering the dual role of NO in the regulation of cardiovascular function (17), increases in NO production by endothelial NO synthase in response to septic plasma would not necessarily indicate deterioration of endothelial function. The short incubation time of HUVEC with patient plasma in the assay would argue against contribution of inducible NO synthase to increases in NO formation.

The study has obvious limitations, which the authors acknowledge. First, additional studies with a larger number of subjects, including patients with a more diverse etiology of sepsis, as well as septic patients without shock, will be needed to reinforce the clinical usefulness of this assay. Second, studies with microvascular (or other types of) endothelial cells are also warranted, for HUVEC may not be the most sensitive cell type to septic plasma. Third, HUVEC responses to septic plasma might have been confounded by the presence of medicaments, glucocorticoids in particular, received by the patients. Finally, future studies should also focus on identifying plasma constituents and the mechanisms underlying DCFH oxidation evoked by plasma from septic shock patients.

These concerns notwithstanding, the study by Dr. Huet and colleagues (11) is a promising initial step toward the development of a global biological test that might be more sensitive than individual analysis of plasma constituents in predicting the severity sepsis and outcome of septic patients.

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Dr. Higgins and colleagues (1) report in this issue of *Critical Care Medicine* the latest iteration of the Mortality Prediction Model, MPM$_0$-III. This tool predicts hospital mortality for patients admitted to intensive care units (ICUs) based on readily accessible data available within the first hour of ICU admission. MPM$_0$-III was developed from the Project IMPACT database, supplanting MPM$_0$-II (2), which is now more than a decade old.

In developing MPM$_0$-III, the investigators have exploited the breadth of the Project IMPACT database, spanning 135 ICUs from nearly 100 hospitals and including >120,000 patients. As with earlier MPM models (2, 3), there is much to commend MPM$_0$-III. It remains much easier to use than other scoring systems, requiring only age and crude, essentially binary, assessments of mental status, physiology, and disease state. Although its discrimination is slightly inferior to that of more complex models, MPM$_0$-III performs well enough to be used in the situations where a predictive model is called for, such as for stratification of ICU populations.

MPM$_0$-III may also prove to be a preferred tool for comparing mortality rates across ICUs. Simplicity of use makes MPM$_0$-III practical for units with only limited resources for data collection. In addition, the score is largely unaffected by ICU care itself. Many therapies currently deployed in the early ICU period for very ill patients, such as hypothermia and low tidal volume ventilation, may artificially inflate risk in models more dependent on postadmission physiology.

As is often the case, the development of a scoring system brings to the fore interesting issues beyond the prediction of risk. With MPM$_0$-III, these include a marked increase in mortality risk when some ICU therapies are proscribed at admission, absence of lead time effects, negative risk associated with gastrointestinal hemorrhage, dramatic improvement in standardized mortality ratios when earlier versions of MPM are applied, and identification of a “zero factor” group with minimal risk of death.

Just over 5% of patients in the Project IMPACT database had limitations placed on care they were to receive by the time of ICU admission. These limitations were associated with double the odds ratio for death, similar in magnitude to a 2-decade increase in age. “Full code” status was therefore added as a variable in MPM$_0$-III. Proscription of various interventions may be a cause of increased mortality, a marker of underlying risk not captured by other MPM$_0$-III variables, or both. To the degree that code status’ contribution to the model stems from its being a marker of otherwise unmeasured risk, the accuracy of MPM$_0$-III may be culturally sensitive, decreasing when applied to groups either more or less inclined to limit care than the reference population.

The most recent iterations of the Acute Physiology and Chronic Health Evaluation (APACHE) models, APACHE III (4) and APACHE IV (5), include terms for lead time bias, enumerated as days hospitalized before ICU admission. In the Project IMPACT data set, lead time was associated with mortality, but adding it to MPM$_0$-III did not improve predictions when other variables were taken into account, a phenomenon that has been observed previously (6). Given the size of the population used, it seems implausible that a significant and consistent lead time effect was missed during the development of MPM$_0$-III. The discordance between MPM and APACHE suggests either that lead time effects are embedded in other MPM$_0$-III variables or that these effects vary between institutions.

In the 14 yrs between the development of MPM$_0$-II and MPM$_0$-III, gastrointestinal hemorrhage evolved from a marker of increased to decreased risk. This may be partly attributable to improvements in care, such as the use of proton pump inhibitors for high-risk lesions (7). However, as the authors note, this may also reflect differences in ICU use between data sets, for example, less acute patients being admitted to ICUs for endoscopic procedures and subsequent monitoring in the MPM$_0$-III population. Differing admission patterns could be a consequence of time or practice location. In fact, MPM$_0$-II was developed in academic ICUs, whereas MPM$_0$-III is derived primarily from North American community facilities, where ICU admission criteria might be substantially different.

Application of the MPM$_0$-II model to the Project IMPACT database results in significant overestimation of mortality (8); the mortality rate in the Project IMPACT data was nearly one third lower than that in the population used to develop MPM$_0$-II. Although as intensivists we find it attractive to credit advances in critical care for this sharp decline, such rapid progress seem doubtful. Rather, the need to create a zero factor for 14% of patients points to a different conclusion. A model using only MPM$_0$-II covariates was overwhelmed by low-risk patients, and the zero factor was needed for calibration.

The survival of patients without any risk factors (98%) would otherwise exceed the best survival the model could predict. These elective surgical cases are analogous to the low-risk gastrointestinal hemorrhage cases alluded to previously, reflecting differences in how ICUs are used in different types of hospitals. Whether zero factor patients benefit from ICU admission is a question that should be addressed, particularly considering their large numbers. That nonoperative patients cared for in intermediate care areas have higher mortality than zero factor patients raises questions regarding allocation of ICU resources (9).

Scoring systems for critically ill patients appear to have limited shelf lives. MPM and APACHE required recalibration because they overestimated mortality. In contrast, the previous version of the Simplified Acute Physiology Score, SAPS II (10), underestimated mortality in the population used to develop SAPS 3 (11), which was more geographically diverse. This inconsistency from three essentially similar systems suggests that the populations granted entrance to the ICU may be as important as the care delivered in determining mortality ratios.
Actin-binding plasma gelsolin: A potential future ally in the fight against sepsis*

There have been myriad plasma molecules whose role in trauma, burns, and sepsis has been studied; a number of them demonstrated associations with the course of the disease, but very few could be manipulated such that outcomes were improved (1). In this issue of Critical Care Medicine Dr. Lee and colleagues (2) show that the septic insult is associated with decreased plasma gelsolin levels and suggest that gelsolin replacement may represent a potential therapy for sepsis.

Gelsolin is an 82-Ra monomeric protein found in the plasma and many types of cells in the tissues of vertebrates. This protein appears to regulate the length of actin filaments, and its activity is modulated by Ca2+ and polyphosphoinositides (3, 4). Therefore, in plasma, gelsolin is thought to function, in conjunction with vitamin D-binding protein, in the elimination of circulating actin. Plasma contains two secreted proteins, Gc-globulin and plasma gelsolin, which coordinate to depolymerize actin filaments. Gelsolin severs actin filaments to promote their rapid depolymerization, whereas Gc-globulin binds to actin monomers to shift the actin monomer-polymer equilibrium toward depolymerization and to prevent repolymerization (3, 4).

The actin-scavenging proteins clear actin, the abundant but normally intracellular protein that is exposed to extracellular spaces or released into the circulation after tissue injury (5, 6). The spillage of large amounts of actin may overwhelm the capacity of the circulating actin-scavenging proteins, resulting in scavenger depletion and the persistence of actin within the microvasculature. The latter is thought to contribute to the pathogenesis of organ injury at remote sites from the primary insult. Decreased circulating levels of Gc-globulin and gelsolin have been noted after severe injury (6), whereas it has been reported that actin and actin-gelsolin complexes are increased in the plasma of critically ill patients (5, 7), including those with acute respiratory distress syndrome (8–10). In addition, an association between reduced plasma levels of gelsolin and Gc-globulin and poor clinical outcome in a wide spectrum of diseases has been demonstrated (11–17).

If plasma gelsolin (pGSN) prevents local and remote injury by ameliorating the toxic effects of actin released into the microcirculation, the early depletion of circulating gelsolin levels may contribute to the progression of the actin-mediated injury state. Dr Lee and colleagues (2) weigh in on this issue by looking at plasma gelsolin levels at an early time point in sepsis and at the effect that the exogenous infusion of gelsolin has on the outcome of septic animals.

Using two well-established experimental models of sepsis (cecal ligation and puncture and lipopolysaccharide models) the investigators demonstrate that pGSN levels decrease in sepsis. Furthermore, replention of pGSN with exogenous gelsolin significantly improves the survival of septic animals in both the cecal ligation and puncture and lipopolysaccharide models. To validate their results, the authors use lipopolysaccharide-resistant animals and prove that it is the septic effect of lipopolysaccharide and not the lipo-

*See also p. 849.

Key Words: sepsis; gelsolin; trauma

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polysaccharide molecule that causes the decrease in pGSN levels. Although the study confirms the initial hypothesis, it appears that the favorable prognosis is not due to the direct effect of the exogenous gelsolin on the circulating actin. Surprisingly, the study demonstrates that the actin levels remain unchanged after the gelsolin administration, leaving the mechanism unclear. The authors hypothesize that it could be attributed to gelsolin quantitative insufficiency or qualitative incompetency. Furthermore, it could be an effect of plasma gelsolin per se.

Several experimental studies have attempted to treat sepsis by blocking or enhancing certain aspects of the inflammatory response (1). Tumor necrosis factor, interleukin-1, interleukin-18, and high-mobility group-1 have been notoriously specific targets for inhibition; although results were impressive in experimental models, none of the clinical trials have been successful. The final answer regarding gelsolin’s role in sepsis is not fully revealed in the present study; however, Dr Lee and colleagues (2) certainly open our minds to the field of scavenger molecules in sepsis and add one more piece to the puzzle that many investigators try to put together to improve the survival in patients with sepsis. These kinds of studies are important because they depict markers that are worth investigating in future trials. However, before new clinical trials are launched, there must be careful consideration of why previous interventions were not effective. The concept of blocking a single elevated cytokine or enhancing a single defense mechanism may be too simple to deal with the complexity of the pathophysiology of sepsis.

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REFERENCES

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Sepsis-induced myocardial depression: Where is the missing link?

*When all think alike, no one thinks very much—Albert Einstein*

Since the ancient Greeks, we have learned that the pathophysiology of human diseases relies on blood-borne humoral factors. That has been the case of the sepsis-induced myocardial depression and its associated morbidity and mortality, which has remained untouched during the last decades. Despite the growing knowledge of the possible involved mechanisms, our understanding of this serious condition is still in its infancy.

New approaches regarding severe sepsis and septic shock are now available, reducing mortality with strict adherence to evidence-based management protocols (1). Therefore, one should expect a better understanding of the septic-associated cardiac derangements. Unfortunately, that has not been proved entirely true.

We have learned from Parker et al. (2, 3) that different patterns exist between survivors and nonsurvivors. The former exhibit reduced ejection fraction and increased left ventricular end-diastolic dimensions, probably reflecting an adaptive response. The latter are unable to dilate for compensating the reduced performance, probably due to a less compliant ventricle grossly infiltrated by polymorphonuclear cells that lie within the myocardial fibers (4). Liberation of troponin I, a highly sensitive and specific myocardial biomarker corroborates this hypothesis (5). Nowadays, accumulative evidence has emerged from experimental studies addressing subcellular mechanisms involving sodium and calcium (6, 7). In this issue of Critical Care Medicine, Dr. Jozefowicz and colleagues (8) have demonstrated in an elegant manner the protective effect of fenofibrate on the reduction of myofilament Ca sensitivity, thereby preventing cardiac dysfunction. The same authors have previously reported reduced myofilament Ca sensitivity in endotoxemic rats (9) and rabbits (10). In the present article, these protective effects were attributed to a possible induction of peroxisome proliferator-activated receptor-α activation by fenofibrate administration. That action would protect endothelial dysfunction and histologic injury in endotoxemic shock (11). The subcellular mechanisms responsible for myocardial depression during sepsis remain unclear, but accumulative evidence points to the phosphorylation of troponin I as a major contributor to the reduced myofilament Ca response of septic myocardocytes, ultimately jeopardizing contractile function. However, as highlighted by the authors, the precise mechanism of fenofibrate protection remains undefined, but new insights are always welcome and have potential therapeutic effects (12).

Earlier, others have postulated that sodium and calcium accumulation by cardiomyocytes could be prevented by amiloride administration, leading to improved myocardial contraction (6). Ionic derangements may possibly account for some of the abnormalities observed in sepsis. The impairment observed may be related to functional abnormalities as postulated by some authors, but it is very likely that morphologic changes participate at least in the nonsurvivors’ group.

Underlying mechanisms may include toxic effects of reactive oxygen species that could hinder energy production by disturbing oxidative phosphorylation, but these effects could not be demonstrated in the present article. The consequence of severe energy failure could be cell death by either necrosis or apoptosis. Instead, what we actually see in autopsy studies is an interstitial myocarditis with varying amounts of cellular necrosis (4). Accordingly, recent studies in endotoxic rodents also confirm that apoptosis in cardiac tissue is in fact a rare event, despite the caspase cascade activation (13).

A recent endotoxic rat study demonstrated reduced ryanodine receptor activity and a marked decrease in isolated papillary muscle contractility. The possible involved mechanism would be impaired intracellular Ca trafficking by blocking Ca release from sarcoplasmic reticulum (14).

Others have speculated that sepsis-associated cardiac dysfunction may reflect myocardial hibernation, secondary to down-regulation of the cellular function, in the setting of preserved oxygen tension and myocardial perfusion (15).

It is exciting to figure out how far we have gone and how distant we still are from the whole truth. Several questions remain unanswered. Why are there so many differences between survivors and nonsurvivors? Which are the most important abnormalities, the functional or the histologic ones? Where is the missing link? Can we use recognized models from cardiology to explain sepsis-induced myocardial depression? I do not think so. As pointed out by Albert Einstein: “Imagination is more important than knowledge.”

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REFERENCES

3. Parker MM, Shelhamer JH, Bacharach SL, et al: Profound but reversible myocardial de-

**PEEP in the morning, PEEP at night**

S

imilar to the well-known children’s author, Dr. Seuss, positive end-expiratory pressure (PEEP) has received a great deal of press. During mechanical ventilation, PEEP is used on one patient, two patients, red patients, and especially blue patients. Barach et al. (1) first described the use of PEEP in 1938. Ashbaugh and colleagues reported (2) in the classic adult respiratory distress syndrome (ARDS) article that patients had improved oxygenation with lower FIO2 concentrations with the use of PEEP. The benefits of PEEP for patients with ARDS and acute lung injury (ALI) include improvement in lung mechanics, gas exchange, and alveolar recruitment. Alveolar changes from the use of PEEP preserve currentdistention, prevent closure during expiration, and use collapsed areas of the lung (3). PEEP may limit the amount of injury from mechanical ventilation due to the prevention of alveolar collapse.

It is generally accepted that mechanical ventilation with no PEEP is injurious and, conversely, that using excessive PEEP may also be detrimental, but finding the optimal PEEP may be somewhat elusive. The absolute number for “best” PEEP has been debated in the literature for years without a clear consensus. Multiple studies both in animals and humans have attempted to answer this question. The ARDS Clinical Trial Network reviewed 549 patients with ARDS who received mechanical ventilation comparing high PEEP vs. low PEEP and found no difference in survival, organ failure, or ventilator-free days when controlling for ARDSnet strategy of 6 mL/kg tidal volume of ideal body weight (4, 5). It appears that the best PEEP must be individualized to improve oxygenation, minimize lung injury from mechanical ventilation, and preserve cardiac function.

The ability to easily measure and determine the best PEEP for the individual patient continues to elude practitioners. Many methods have been tested, but ease of use and feasibility continue to be problems. Gattinoni et al. (6) demonstrated by computed tomography (CT) that the disease process in patients with ALI is heterogeneous. A study in 2000 examined 71 patients with ARDS and compared CT scans at 0 and 10 cm H2O PEEP (7). Patients with diffuse disease by CT showed improved alveolar recruitment without overdistension compared with patients with lobar changes, who demonstrated overdistension and only slight improvement in recruitment. In a recently published study, CT scans were used to assess the relationship between recruitable lung tissue and the effect of PEEP (8). The authors found wide variation among individual patients in the amount of recruitable lung tissue. Application of PEEP maintained aeration in this segment of lung tissue. Chest CT scans of patients with ARDS/ALI are beneficial in determining “optimal” PEEP for individuals. Unfortunately, this technology is not widely available.

Various respiratory mechanics have been studied in an attempt to find a simple, easily reproducible measure that can be applied routinely at the bedside. Investigators have determined that recruitment with PEEP may occur along the entire volume-pressure curve (9). In a canine model, all of the changes demonstrated in the static pressure volume curve were not seen in the dynamic pressure-volume curve (10). Dynamic respiratory mechanics have been shown to be more beneficial than static pressure-volume curves in a small selection of patients. These conflicting results highlight the differences in the animal and human models. Although laboratory experiments are the first essential step in bringing understanding of disease and treatment to clinicians, all research done on animals may not be applicable to human patients with ARDS/ALI (11).

In this issue of *Critical Care Medicine*, Dr. Bellardine Black and coworkers (12) present comparisons of the effects on oxygenation, static elastance, dynamic respiratory resistance and elastance, and

*See also p. 870.

Key Words: positive end-expiratory pressure; acute lung injury; acute respiratory distress syndrome; lung compliance; respiratory mechanics; computed tomography
whole-lung image by CT with PEEP ranges from 7.5 to 20 cm H2O. Lung injury was induced by repetitive whole-lung lavage with 0.15 M NaCl (40 mL/kg) in five sheep. PEEP titrations were performed in increments of 2.5 with a recruitment of lung with 30 cm H2O PEEP and peak airway pressure of 20 cm H2O for 30 secs in pressure-control mode. After 10 mins of ventilation, measurements and CT images were obtained. Oxygenation was best at PEEP of 15 cm H2O. At 15 cm H2O, PEEP decreases in elastance and resistance occurred. At 17.5 cm H2O, elastance increased consistent with over-distension and resistance decreased. In this animal model, it appears that dynamic mechanics may be used to guide recruitment without overdistension. These types of measurement can be easily done at the bedside and would greatly aid the clinician in managing patients with ARDS/ALI. Further work must be completed in humans to validate this technique and examine the translation to the bedside in the intensive care unit. Non-invasive guidance of lung management tools in critically ill patients has potential promise to optimize PEEP in the morning and PEEP at night.

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REFERENCES


10. Adams SB, Cakar N, Marini JJ: Static and dynamic pressure-volume curves reflect different aspects of respiratory system mechanics in experimental acute respiratory distress syndrome. Respir Care 2001; 46:686–693

Understanding another acute respiratory distress syndrome*

R etinoic acid syndrome represents a potentially life-threatening complication that occurs during treatment of acute promyelocytic leukemia (APL) when all-trans retinoic acid is used in addition to other chemotherapy. In a report from 1998 that included 413 patients, 15% experienced retinoic acid syndrome during the course of their induction treatment (1). Primary clinical signs of retinoic acid syndrome in this cohort of 64 patients included pulmonary distress (89%), fever (81%), pulmonary infiltrates (81%), weight gain (50%), pleural effusion (47%), renal failure (39%), and pericardial effusion (19%).

More recent reviews on this subject indicate that the combination of all-trans retinoic acid with more traditional chemotherapy can significantly improve induction of remission in patients with APL in addition to reducing the incidence of relapse (2). When combined with chemotherapy, all-trans retinoic acid contributes to complete remission in >90% of patients with APL, with an expected cure of approximately 75% with this combination (2). However, retinoic acid syndrome continues to remain a major side effect of this chemotherapeutic approach. Clinicians have discovered that dexamethasone is useful in decreasing the incidence and severity of retinoic acid syndrome, but the underlying pathophysiology for this treatment complication has remained elusive.

In this issue of Critical Care Medicine, Dr. Tsai and colleagues from Taipei, Taiwan, report the results of a number of ingenious experiments designed to provide an in vitro model of the retinoic acid syndrome (3). These investigators used a co-culture system with pulmonary 549A cells in the (lower) primary cell culture well and APL cells grown on the (upper) insert membrane. In response to chemotactic signals generated by the A549 cells, APL cells migrate through the porous insert membrane and are subsequently quantified on the underside of the membrane insert by microscopy. To investigate specific biochemical pathogenesis, exogenous chemokines were added to the primary cell culture well superphase in addition to antibodies to receptors for these cytokines added to the insert well. Additionally, either the A549 or APL cells could be stimulated or modulated by addition of various other exogenous chemical mediators.

Major conclusions from a series of well-controlled experiments include the following: a) all-trans retinoic acid represents the primary determinant governing transmigration of APL cells in this model;
b) A549 cells constitutively produce and release both interleukin (IL)-8 and growth-regulated oncogene (GRO)-α, which appear additionally crucial for transmigration of the APL cells; c) the same positive effect on APL transmigration can be achieved by exogenous administration of either of these two cytokines; d) all-trans retinoic acid enhances the secretion of IL-8 but not GRO-α; e) APL cells also constitutively produce and secrete IL-8 but not GRO-α; f) antibodies against cell receptors for IL-8 and GRO-α markedly reduced APL transmigration; g) binding of IL-8 but not GRO-α to APL cells was enhanced by all-trans retinoic acid; h) dexamethasone added to the system reduced APL transmigration apparently through its action on modulating A549 cell production of chemokines.

The acute respiratory distress model of Dr. Tsai and colleagues addresses APL cells that undergo maturational differentiation in response to all-trans retinoic acid with subsequent leukoagglutination in the lungs as a primary pathophysiological mechanism accounting for retinoic acid syndrome. Although as early as 1887, Metchnikoff (4) introduced the concept of host auto injury orchestrated by phagocytes, Hammerschmidt (5) popularized the notion of neutrophil-mediated lung injury as “frustrated phagocytosis.” Since then, multiple investigations have ascertained the key role of neutrophils in the pathogenesis of acute respiratory distress (6–12). From the model, it appears plausible that all-trans retinoic acid may also affect the behavior of some pulmonary epithelial cells (A549 cells in the model) in terms of facilitating this process through synthesis and release of chemokines such as IL-8.

Obviously this in vitro cell co-culture model is far from the clinical events of the intensive care unit, but the principles of decreasing lung compliance associated with diffuse alveolar-capillary membrane leak and an associated alveolar inflammatory storm involving activated neutrophils still apply (13–15). The authors’ co-culture system does not include the endothelial cell, which represents the first stopping point for emigrating neutrophils on their way through the interstitial space into the alveolus (16). In addition, the immobilized cell lines used by the investigators oversimplify the lungs’ complex, multicellular environment (17). A549 cells, originally derived from a human pulmonary adenocarcinoma, morphologically and biochemically most closely resemble alveolar type II cells (18). One wonders if in the in vitro situation all-trans retinoic acid might not only induce chemokine production by these cells but also possibly induce their own differentiation toward alveolar type I cells, which actually provide most of the pulmonary surface area interface with lung endothelial cells, where most neutrophils would be expected to transmigrate (19).

On the other hand, this model has clearly identified additional potential targets for therapy to address retinoic acid syndrome. Accordingly, antagonism of IL-8 before administering all-trans retinoic acid, at least in the early phases of acute promyelocytic leukemia chemotherapy, might reduce migration of differentiating granulocytes into the lungs as perpetrators for acute respiratory distress syndrome. Perhaps a differential gene array strategy before and after all-trans retinoic acid of APL cells as well as A549 pulmonary cells might identify additional candidate biochemical targets that could be further scrutinized using this cell culture model (20).

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Genetic influences on severe lung injury: How many more genes?*

Acute respiratory distress syndrome (ARDS) is a devastating and complex disease with a high mortality and morbidity in both children and adults (1–4). A diverse array of precipitating factors lead to ARDS, including direct injury to the lung such as pneumonia, aspiration, or pulmonary contusion, and indirect injury to the lung such as sepsis, transfusion, or non-pulmonary trauma. Despite these various causes, the pathogenesis of ARDS appears to progress through similar biological processes such as inflammation, cellular activation and proliferation, and coagulation. These processes result in lung epithelial cell destruction, endothelial cell disruption, and increased vascular permeability. For many years, clinicians have observed wide variability in the susceptibility to ARDS in at-risk patient populations as well as wide variability in the severity and outcome once the lung injury has progressed to ARDS. Do genetic determinants lead to individual variability in risk for progression to more severe lung injury or multiple organ failure? Our improved understanding of the epidemiology and molecular mechanisms of severe lung injury is beginning to provide clues about the observed heterogeneity.

Many diseases seen in the critical care setting are likely to be influenced by the genetic makeup of the individual patient, and studies suggest that the pathogenesis of many of these diseases lies in a set of complex interactions between genes and the environment. Recently, efforts have been undertaken to examine whether there exist genetic risk factors for acute lung injury and ARDS. There is a growing list of human genetic polymorphisms for which an association with the susceptibility to, and/or severity of, lung injury has been demonstrated (Table 1). Gene expression profiling in various models of severe lung injury has identified additional candidate genes that may play an important role in lung injury. This technique has improved our understanding of the pathogenesis of acute lung injury and ARDS and has implicated involvement of at least five fundamental biological processes (5), including inflammatory responses, immune responses, cell proliferation, chemotaxis, and blood coagulation. Thus, candidate genes for lung injury could potentially be genes involved in any of these processes. Future techniques may identify an even larger list of potential candidate genes that may harbor genetic variations that play a role in lung injury.

In this issue of Critical Care Medicine, Dr. Zhai and colleagues (6) examine the influence of three single-nucleotide polymorphisms located in the promoter region of the gene coding for NFκBIA, the cytoplasmic inhibitor to nuclear factor NF-κB (NFKBIA), on the susceptibility to ARDS in a cohort of at-risk Caucasian adults. When certain cell types are activated, NFKBIA is degraded allowing for the translocation of the transcription factor NF-κB to the nucleus and activation of a number of target genes including those coding for cytokines and chemokines (7–10). When the individual single-nucleotide polymorphisms in NFKBIA were analyzed, no difference was observed between the non-ARDS at-risk control group and the ARDS group; however, one haplotype (−881G/−826T/−297C) was found more frequently in those patients who developed ARDS (p = .03). This association was strongest in males and those with direct lung injury. However, the effects of the −881G/−826T/−297C haplotype on NFKBIA cytoplasmic levels are not known and only inferred as being involved in regulation of transcription from their location in the promoter region. It is also possible, as the authors point out, that these single-nucleotide polymorphisms may be in linkage disequilibrium with the causative polymorphic site, which could potentially lie in the coding region of the NFKBIA gene and affect the function of NFKBIA.

Although the study of Dr. Zhai and colleagues suggests that the NFKBIA haplotype may influence the development of ARDS, many other variations in multiple genes might also influence the disease process. As Table 1 points out, candidate gene association studies in humans have identified at least six genes located on six different chromosomes in which variations are associated with the susceptibility to and/or outcome from severe lung injury. At some point, these polymorphisms as well as an unknown number of other polymorphisms will need to be analyzed together in the same population to identify a grouping of variations predictive of disease susceptibility or severity and perhaps treatment response. However, the challenge is numbers; with every additional gene variation that is added to the analysis in a study population, the study group needs to be larger to obtain adequate numbers for appropriate analysis. Other factors such as ethnicity, gender, and age may also be important, and to address these variables, even larger study groups would be needed. Thus, large, multiple-institution, multinational studies involving thousands of well-defined and characterized patients with acute lung injury and ARDS as well as an at-risk population are needed.

The study of Dr. Zhai and colleagues demonstrates another potential genetic

*See also p. 893.

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Table 1. Genetic polymorphisms associated with the development of lung injury

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme</td>
<td>17</td>
<td>11, 12</td>
</tr>
<tr>
<td>Tumor necrosis factor-α</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Pre-B cell colony-enhancing factor</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Surfactant protein B</td>
<td>2</td>
<td>15–17</td>
</tr>
<tr>
<td>Myosin light chain kinase</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>NFKBIA</td>
<td>14</td>
<td>6</td>
</tr>
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NFKBIA, inhibitor to nuclear factor κB-α.
risk factor for ARDS and suggests that the NFKBIA haplotype may be useful as a predictor for the development of ARDS in at-risk adults. The molecular explanation for such an association remains to be determined as does the degree of risk conferred by this variation compared with other genetic variations also shown to be associated with lung injury. Ultimately, this information not only will further our understanding of ARDS but also may lead to the development of more directed therapies based on the individual's genetic makeup.

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Never the tube! Try the mask!*  

Noninvasive positive pressure ventilation (NPPV) has become a standard therapy for the treatment of acute respiratory failure (ARF) in select populations and is increasingly being used in the critical care and acute care setting. However, the use of NPPV in patients who have decided to forego intubation (do not intubate, DNI) is controversial. NPPV can be used in these patients to alleviate respiratory distress and provide some additional time to finalize affairs. On the contrary, the use of NPPV in these patients could be inappropriate, providing a form of life support for patients who do not desire it, potentially adding to discomfort and prolonging the dying process. Clarke et al. (1) questioned whether the use of NPPV for terminally ill patients violates the biomedical principle of “first, do no harm.”

Clinician–family communication in the intensive care unit (ICU) is an area in need of improvement. Specific concerns have been raised about whether patients and their families have an adequate discussion and clear understanding about the goals of care when NPPV is used in different circumstances. If clinicians are not certain about the goals of care for patients with ARF, this precludes clear discussion about the role of NPPV. In response to this potential problem, the Society of Critical Care Medicine formed a task force on the palliative use of NPPV to develop a framework for using NPPV in patients with ARF, especially for those patients who decline endotracheal intubation or who are receiving palliative care. In this issue of Critical Care Medicine, Dr. Curtis and colleagues (2) report the conclusions of this group in an article that depicts and discusses the various possible applications of NPPV in DNI patients (2). The idea of the authors to classify the use of NPPV for patients with ARF in one of three categories is original (2). Briefly: 1) NPPV as life support with no preset limitations on life-sustaining treatments; 2) NPPV as life support when patients and families have decided to forego endotracheal intubation; and 3) NPPV as a palliative measure when patients and families have chosen to forego all life support, receiving comfort measures only. However, concerning classification in three categories, it would have been useful

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*See also p. 932.

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to provide data on the percentage of patients with ARF treated by NPPV and pertaining to categories 2 and 3. Unfortunately, there are currently few data in the published literature that help to differentiate patients in categories 2 and 3. This is an important first area for future research. In a large, multiple-center, observational study, approximately 10% of patients (114 of 1,211 screened patients) treated with NPPV for respiratory failure had DNI orders (3). In this last study, concerning the location of therapy, there was an equal repartition between the ICU and the hospital ward. Dr. Curtis and colleagues (2) conclude that NPPV should be applied after careful discussion of the goals of care, with explicit parameters for success and failure, by “experienced personnel” and “in appropriate healthcare settings.” So, NPPV might also be considered for category 3 patients in the hospice setting. This point of the location of therapy is crucial. Indeed, it is certain that some training is necessary for physicians, residents, respiratory therapists, and nurses before optimal routine daily use of NPPV can be expected. In my experience, and in my opinion, the experience gradually acquired (through several years of utilization of NPPV techniques) is the principal factor in the development of the techniques of NPPV. Clearly, the staff training for obtaining the skills of “experienced personnel” is one of the principal challenges for the application of NPPV among patients with DNI orders, outside the conventional units for application of the technique. This is also an important area for future research.

In all cases, caregivers are encouraged to make greater efforts to discuss end-of-life desires with terminally ill patients and their families, including possible use of NPPV, before the onset of ARF. If patients and their proxies are to be fully informed, prognostic information is desirable. Previous studies have identified a number of predictors for success of NPPV. In DNI patients, two studies showed that patients with congestive heart failure or chronic obstructive pulmonary disease had a relatively good chance of surviving to discharge when treated with NPPV, whereas those with pneumonia or cancer had poorer prognosis (3, 4). In fact, the better prognosis in hypercapnic respiratory failure than in hypoxemic respiratory failure is not very specific to the patients who choose to forego endotracheal intubation. In addition to the type of ARF, strong cough and wakefulness were associated with greater hospital survival in one study (4). One can deliver the practical message that the respiratory therapist’s bedside assessments of cough and whether the patient is awake are of significant value in predicting which patients are more likely to survive. Concerning the poor prognosis of cancer patients in category 2, it could be underlined that some healthcare providers may believe that the ICU admission of patients with cancer is doomed to futility. However, over the last 10 yrs, several advances have been made in the early diagnosis and management of patients with various types of malignancies, resulting in a decrease in overall mortality. Then, even if there are only limited data about the benefit of NPPV among patients with cancer in category 2, one could believe that in non-palliative care patients, a trial of ICU support, with treatment of ARF with NPPV, should be offered. This involves ICU support for a limited period of time, after which the cancer patients’ clinical course should be reevaluated. NPPV has been proved to reduce the need for endotracheal intubation and decrease morbidity and mortality rates in patients with immuno-compromised states, most of them with hematologic malignancies (5). These results provide evidence that ICU management would benefit cancer patients referred earlier to the ICU for noninvasive diagnostic and therapeutic strategies. In my opinion, even if specific data on patients who have declined intubation are lacking, NPPV must be employed at an early stage of ARF among cancer patients in general and, more particularly, in the patients of category 2 for whom intubation will not be carried out. A good collaboration between the oncologists and the ICU practitioners is necessary to try to achieve this goal. This is also an important area for future research.

The work by Dr. Curtis and colleagues (2) can make it possible to improve management of patients with ARF. Future studies are clearly needed to evaluate the clinical outcomes of using NPPV for DNI patients and to examine the perspectives of patients, families, and clinicians on use of NPPV in these contexts. So, before being able to fully recommend “Never the tube! Use the mask!” we must thoroughly evaluate the place of NPPV in the treatment of patients who choose to forego endotracheal intubation: Never the tube! Try the mask!

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Randomized, controlled trials in the emergency setting: A matter of physician-patient relationships, responsibility, and trust*

Several years ago a clinical trial of a blood substitute called PolyHeme finished with worrisome results. These lines from Thomas M. Burton open an article in the *Wall Street Journal* titled, “Amid Alarm Bells, A Blood Substitute Keeps Pumping,” which was published February 22, 2006 (1). It describes a trial in trauma patients, such as victims of shootings or car accidents, to evaluate an artificial blood substitute called PolyHeme (Northfield Labs, Evanston, IL). The article points out that several years ago, a clinical trial of PolyHeme finished with worrisome results and that this trial was quietly shut down while the results were not publicly disclosed. Nevertheless, the Food and Drug Administration (FDA) allows Northfield Laboratories to test its blood substitute in a new trial without the consent of trauma patients, who are often unconscious. This new trial led to the above-mentioned *Wall Street Journal* article, which was interpreted by the Alliance for Human Research Protection on February 27, 2006 (2). They stated that artificial blood experiments on trauma patients violate the FDA’s waiver of informed consent rule. This rule, adopted by the FDA, is granting waiver from informed consent requirements for trauma patients under specified conditions, such as life-threatening situations (3).

These events emphasize the risk of participating in randomized, controlled trials (RCTs) and the responsibilities of all involved to guarantee the safety of enrolled patients. In this issue of *Critical Care Medicine*, Drs. Morris and Nelson present an analysis of the circumstances in which RCTs should be designated as minimal risk, allowing institutional review boards (IRB) to approve their conduct with a waiver of informed consent if obtaining informed consent is not feasible (4). This is explicitly of relevance in the case of emergency patients who are often not able to grant informed consent for participation in research. An IRB may only choose to waive the requirement for informed consent if a study poses no more than minimal risk. Studies posing more than minimal risk may only be approved with an exception from informed consent, granted by the Department of Health and Human Services. This federal procedure is much more energy and time consuming than the IRB waiver procedure. Therefore, the authors wish to determine which types of emergency research should properly be considered minimal risk and, thus, potentially eligible for a waiver of informed consent at the institutional level. The authors claim it has not yet been established whether any RCT could be considered minimal risk at all. As such, the article by Drs. Morris and Nelson covers an extremely relevant subject, because the vast majority of intensivists believe that RCTs are the most scientifically appropriate study design for investigating a new drug or a new therapy in adults and children with a life-threatening condition and that RCTs of potentially life-sustaining therapy for critically ill patients are ethical (5).

The ethical analysis of Drs. Morris and Nelson (the concept of) of minimal risk, including both physical and psychological aspects, seems to cover the whole range of potential harm associated with the participation in research in the broadest sense. However, their main reason for stretching the opportunities to allow research with a waiver of informed consent—to maximize medical progress—can hardly be judged as a morally neutral argument, as it seems to reflect the view of the researcher more than the clinician. Therefore, this ethical analysis should be interpreted within the context of the fundamental competition between the researcher’s need to collect valid data and the clinician’s need to protect the best interest of the patient (6).

In critically ill patients, the process of decision making to include patients in RCTs is a dynamic process between patient and physician. The physician has to deal with a complicated mechanism, including acute agony in the situation of severe illness or a life-threatening condition. In unconscious adults, but also in children, this comes to proxy-decision making, or decision making together with the physician preferably within the concept of “sacred trust” (7). The concept of sacred trust addresses the unique relationship between one patient and one primary care physician. Current health care has shifted from singular relationships to a complex multidisciplinary model, particularly in the intensive care setting. In this modern model, relationships shift to a team of specialty practice physicians, who often are not aware of personal values and wishes of the patient (8). Enrolling these patients in an RCT aggravates the responsibility of the physician to guard the benefit of the patient. The physician has to realize that randomization takes the choice of therapy from the patient and the physician; also, ethically, a physician should only participate in blinded studies if he/she believes that all treatments under study have potentially equal therapeutic benefits (9). The physician should be convinced of the concept of equipoise. Equipoise is often one of the first arguments used in discussions about including patients in RCTs. Equipoise should exist throughout a clinical trial and while the trial is conducted and data are collected. The conviction of clinical equipoise may be compromised by the awareness of data from uncontrolled trials that may bias toward the experimental treatment, particularly in case a patient from a control group deteriorates. At the moment of decision making, the physician also has to evaluate his own motive to include a patient in a trial, including scientific and other motives.

Drs. Morris and Nelson point out that patients and their families usually place great trust in their physicians, and many of them believe that optimal decisions are...
made if treatment choices are left in the hands of treating physicians. This is particularly so in pediatric trials, in which a third party is involved. Evaluation of the attitude of the parents shows that they prefer the physician to take as much responsibility as possible (10). Another conclusion of the same study was that there was an apparent discrepancy between parents’ evaluation of the adequacy of the information delivered and evaluation of their understanding and memorization. In mothers of children with leukemia who were participating in RCTs, it was found that the mothers were poorly informed about the purpose of the trial and about the possibility of side effects (11). These findings support the role of the physician as a trusted representative who is responsible for adequate and objective information about the risk involved, both for children and adult patients (12).

The work of Drs. Morris and Nelson is a thorough analysis of minimal risk in RCTs; they provide us with criteria to determine whether an RCT poses more than minimal risk, and they emphasize the significance of avoiding the negative psychological impact of participating in RCTs. We also believe that the article by Drs. Morris and Nelson appeals to the balance of carefulness, responsibility, and trust between physicians and patients on the one hand and medical progress on the other.

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