Ultrasound-guided subclavian vein catheterization: Beyond just the jugular vein*

The article by Fragou et al (1), in this month’s Critical Care Medicine, provides compelling evidence that the routine use of ultrasound guidance increases the safety of central venous access by the subclavian route. In this cohort of critical care patients, cannulation was achieved in 100% of patients in the ultrasound group as compared with 87.5% in the landmark arm. Access time and the number of attempts were reduced in the ultrasound group as were arterial puncture, hematoma, hemotorax, pneumothorax, and brachial plexus injury. Catheter misplacements did not differ between groups.

This has important implications for clinicians performing such procedures, including those from critical care, anesthesia, cardiology, and other acute specialties. Landmark guided subclavian vein access has been used for many years, but its success has been marred by a small but persistent risk of arterial damage and pneumothorax (2). Such complications, even if recognized and managed correctly, are very likely to have adverse effects on an already critically ill ventilated patient. Ultrasound guidance has the potential to significantly reduce the risk of such early complications. This study follows similar findings from the same group in relation to internal jugular access (3) and I provided editorial comment in 2006 asking the question “Can you justify not using ultrasound guidance for central venous access?” (4). Similar reasoning would apply to the subclavian route following this study. It is also likely that later infective and thrombotic complications would be also reduced by a reduction in needle passes. Subclavian access (as opposed to jugular or femoral) has been recommended to reduce catheter-related infections in many local and national guidelines, e.g., the Matching Michigan initiative.

Until this study, there has only been evidence from prospective randomized studies to support the use of ultrasound guidance by the internal jugular route. Some clinicians have used this distinction to justify not using it at other sites. I would argue that it is intuitive that if ultrasound guidance reduces complications at one vascular site, then providing adequate imaging can be achieved, similar benefits should be achievable at all other commonly used sites, e.g., femoral, subclavian, and peripheral sites.

Some elements of the study deserve further comment. The entry criteria, in terms of choice of patient, and any exclusion criteria, for this or other routes of access were not clearly identified. Only planned nonurgent cases were recruited, which may limit the applicability in more urgent cases. The use of preprocedure ultrasound screening of the subclavian vein in the landmark arm is likely to have introduced bias. Operators then excluded patients with evidence of vein thrombosis and may have modified their landmark technique if the vein was seen to be very deep/superficial or empty. Ultrasound guidance was used to rescue failed landmark procedures and in those requiring procedures in the head-up tilt position. However, the study findings were significant even with any such bias, and if this had been avoided, it is likely that the advantages of ultrasound guidance would have been further increased.

Three broad categories of technique exist in relation to accessing the axillary or subclavian veins with the first two of most relevance to critical care: 1) landmark based techniques (5, 6); 2) ultrasound guidance (1, 7); and 3) radiograph screening of peripherally injected contrast flowing centrally (http://emedicine.medscape.com/article/1348912-media, Accessed July 3, 2011) (8).

Many clinicians have not yet used ultrasound guidance for the infraclavicular or supraclavicular routes of access to the axillary and subclavian vein in the belief that the presence of the clavicle blocks the image. This is true in adults, in whom the relevant section of the vein is under the clavicle, but the vein can be visualized more laterally as the axillary vein (7) (Fig. 1) and above the clavicle over the

Figure 1. Cros-sectional ultrasound image through the right side infraclavicular axillary vessels, lateral to the clavicle (as seen from the right side of the patient). Note axillary vein (V), cephalic vein (C), axillary artery (A), thoracoacromial arterial trunk (TAT) anterior to the vein, and chest wall/pleura (P). The depth of the image field is 4 cm, as depicted by the white dots on the right of the image.

*See also p. 1607.

Key Words: axillary vein; subclavian vein; central venous catheterization; ultrasonography

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area of the first rib and the apex of the pleura (9). In very young children with limited ossification, the vein can be imaged through the clavicle (10).

It can be debated whether the images shown in this publication relate to puncture of the proximal axillary or subclavian vein. I would suggest it is the former, and as such, it should be termed axillary vein puncture. Such anatomic distinctions are somewhat pedantic and relatively unimportant clinically. However, it is important clinically to appreciate that ultrasound-guided needle approaches to the vein are rather different from that practiced for landmark techniques. With ultrasound, the vein is approached at a fairly steep angle with the puncture site lateral to the clavicle. Most landmark techniques use a much flatter angle of approach with the vein punctured more medially behind the clavicle. The vein can be approached with the needle in or out of plane with the ultrasound beam, and the vessel in the transverse or longitudinal view.

The real-time ultrasound method was rated as technically difficult by the participating physicians. I regularly use a slightly more lateral approach to the axillary vein and would agree with them about procedural difficulties. The vein is deeper and smaller compared with the internal jugular vein. The associated anatomy is more complex with the presence of branches from the axillary artery (thoracocromial trunk) crossing the vein and branches of the vein (e.g., cephalic) joining it. In addition, there is the brachial plexus and pleura to avoid. It is essential that operators have the requisite skills in needle visualization and control to avoid collateral needle damage. Sharp needles to avoid vein transfixion and higher resolution ultrasound devices to show collateral structures and the introducer needle will improve success.

It is relevant to question whether we need similar large scale prospective randomized studies of ultrasound guidance (active arm) vs. landmark (placebo arm in a pharmacologic analogy) for the femoral and all other routes. I believe there is now enough evidence for the benefits of ultrasound for it now to be considered unethical to continue to submit patients to the risks of landmark techniques for research practice if ultrasound guidance is available at that hospital. I believe that future studies should move to establishing optimum ultrasound techniques for accessing the target vessel, visualizing introducer needles, and avoiding collateral structures.

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REFERENCES


So we use less pulmonary artery catheters—But why??

There is no doubt that use of the pulmonary artery catheter (PAC) is decreasing. The multicenter Canadian study by Koo et al (1) in this issue illustrates this point very well. In this observational study, which included 15,000 patients hospitalized in five intensive care units, the proportion of patients monitored with a PAC decreased from 16% in 2002 to 6% in 2006. It is quite likely that this proportion has decreased even further since then. The indications for PAC insertion given in the study by Koo and colleagues are not very surprising (shock, respiratory failure, etc) and did not change over time. Of note is the relatively large proportion of patients who were monitored after elective surgery and the somewhat greater use of the PAC by anesthesiologists than by other specialists.

A decrease in PAC use has been observed throughout North America and Europe. I would not go so far as saying that this has occurred across the globe, because there are many places where the PAC was never widely adopted for organizational and/or financial reasons. The real question is not whether PAC use has decreased, but rather why this is the case.

I believe there are bad reasons, less bad but still debatable reasons, and good reasons (Table 1). Starting with the bad reasons, the most common reason cited for decreased PAC use (also in the article by Koo et al) is that results of prospective, randomized, controlled trials have not shown any clinical benefit associated with this technique. However, the way in which these studies were designed influenced the chances of reaching a definitive

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Table 1. Reasons why use of the pulmonary artery catheter has decreased

<table>
<thead>
<tr>
<th>Category</th>
<th>Reason</th>
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<tbody>
<tr>
<td>Bad reasons</td>
<td>Randomized controlled trials have failed to demonstrate a clinical benefit</td>
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<td></td>
<td>A good clinician does not need this additional information</td>
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<td></td>
<td>It is fashionable to follow the trend</td>
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<tr>
<td>Less bad reasons</td>
<td>Other less invasive techniques have become available</td>
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<td>ScvO₂ monitoring reduces the need for pulmonary artery catheter-derived SvO₂</td>
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<td>Reduced use below a minimum number increases risks associated with its use</td>
</tr>
<tr>
<td>Good reasons</td>
<td>The pulmonary artery catheter was overused in patients who clearly would not benefit</td>
</tr>
<tr>
<td></td>
<td>More widespread use of echocardiography has decreased the need</td>
</tr>
</tbody>
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answer to the question of whether or not PAC use may be beneficial: patients who were considered likely to benefit, as determined by the attending clinician, had a PAC inserted (because it would have been considered unethical not to do so), and were therefore not included, so that only patients who were anyway less/not likely to benefit were actually randomized in these trials; the lack of apparent positive effects on outcomes is therefore not very surprising. This is effectively the reason why randomized, controlled trials have hardly demonstrated that a monitoring technique can improve survival (2). However, is such lack of evidence a reason to stop using the PAC? No randomized, controlled trial has shown that chest x-rays can improve outcomes and a number of studies have shown that reducing the number of chest x-rays does not jeopardize outcome (3), yet would you be ready to abandon the chest radiograph?

Similar statements can be made for the electrocardiogram, echocardiogram, other imaging techniques, and so on. The fact that the PAC is an invasive technique is not relevant here.

Another bad reason for a decrease in PAC use is that physicians are merely following a fashion trend, or, even worse, they believe they are so good at their job that they actually do not need a PAC any more. This is a bit like a cardiologist claiming that with his or her excellent clinical skills, rapidly obtained troponin levels, and echocardiogram, an electrocardiogram is no longer needed or necessary. So many different monitoring techniques are now available: esophageal Doppler, transpulmonary thermodilution techniques, arterial pulse contour, and bioimpedance, to name just a few. Less invasive is of course better when it provides adequate information in a given patient. Decreased use of the PAC has, for example, paralleled the development of echocardiography and the PAC is no longer needed to diagnose conditions like heart failure, hypovolemia, pulmonary hypertension, tamponade, or valvular disease. As echocardiography training is improved, this technique will increasingly be used at the bedside. Development of smaller disposable probes even allows continuous monitoring using transesophageal echocardiography. However, many of the less invasive techniques do not provide very accurate measurements and, perhaps more importantly, they do not give the full picture; just measuring cardiac output may not be sufficient. Other parameters are needed to correctly interpret the values in individual patients (4). The PAC provides simultaneous combined information on pulmonary artery pressures, cardiac filling pressures, cardiac output, and SvO₂ values. Furthermore, ScvO₂, which can be measured without a PAC, is not a reliable substitute for the PAC-derived SvO₂ (5).

A worrisome reason for the decreasing PAC use is that doctors and nurses may actually be finding it more difficult to use this technique because there are fewer PACs being sited so we are becoming less familiar with the insertion technique and with reading and interpreting the data. The number of complications, which is currently relatively small, may increase as use decreases such that the risks may begin to exceed the benefits.

Finally, there are some good reasons why use has decreased. The major example in this category is that PACs were in fact used rather overenthusiastically in the past. Sometimes a PAC was inserted almost as a reflex, just because the patient was “critically ill,” although the data obtained could not have been used to help guide therapy or, even worse, for financial reward (6) or to limit any possible risk of medicolegal comeback.

So, what of the future? In the past, a PAC used to be recommended in specific settings, like persisting shock or acute respiratory distress syndrome. I think this approach is now obsolete. Rather than making decisions based just on diagnosis, we should ask ourselves whether the data obtained from the PAC could actually be used to alter therapy (in general with fluids and/or inotropic agents) in that patient; if the answer is no, then do not insert a PAC! The simple syllogism is that if a PAC can provide information that will result in changes in therapy and if these changes in therapy can improve outcomes, then a PAC must result in better outcomes. Importantly, correct use of the PAC is essential if it is to provide useful information and benefit our patients (7); this means correct collection of data (many errors arise here), correct interpretation of the data (requires good knowledge of pathophysiological alterations in the critically ill), and correct application of data such that appropriate treatment is given or change in treatment is made.

In summary, the data provided in the study by Koo et al (1) illustrate that PAC use is decreasing. Will this decrease continue to a point where the PAC is no longer used? We should certainly be selective in our use of the PAC and, if PAC use decreases to a level at which the hazards of this technique begin to outweigh the benefits, or technology advances sufficiently to provide us with a reliable adequate alternative, a time may come when the PAC does indeed become a historical relic—but we are not there yet!

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**Subdural hematoma: You can leave your hat on?**

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How chronic subdural hematoma was classified before that time [1927] I have not attempted to discover, but of this I am quite certain, that in recent years the incidence of chronic subdural hematoma has increased, as may be inferred from the mere fact that I am about to present to you a series of six cases that were treated in the Neurosurgical Clinic of the University Hospital [Philadelphia] in two years, 1932 and 1933” (1).

Eighty yrs later, things have changed substantially. In this issue of *Critical Care Medicine*, a study by Frontera and colleagues (2) describes the prevalence, discharge disposition, length of hospital stay, and cost of subdural hematoma (SDH) in 720,297 patients admitted to US hospitals from 1998 to 2007. The font is the Nationwide Inpatient Sample, an administrative database that tracks hospital discharges from 1044 hospitals in 40 American states.

Data showed an impressive 39% per capita increase of hospitalization for SDH, from 30.2 per 100,000 in 1998 to 41.9 per 100,000 in 2007, and a 36% relative increase in total hospitalization days, from 552,903 to 750,542 days. The associated increase of costs was as much impressive, from $1.0 to $1.6 billion, the major determinant being neurosurgical intervention.

The typical patient was a white male, aged ≥70 yrs, with relevant comorbidities but rare acquired coagulopathy having an emergent hospital admission for SDH. Patients pertained to all income quartiles; however, those with low income almost quadrupled from 6.9% in 1998 to 26% in 2007. Median length of hospital stay decreased from 6 to 5 days. Mortality decreased by 3%, and the number with good discharge disposition, a proxy of good recovery, increased by 11% (from 35% to 46%). However, the number of unsatisfactory discharge disposition increased too, from 17% to 20%.

The total number of neurosurgical interventions for SDH decreased by 24% (from 41% in 1998 to 31% in 2007): craniotomy decreased by 42% and burr hole drainage by 16%. Patients operated on had a decreased mortality but unchanged (craniotomy) or only slightly increased (burr hole) the percentage of good discharge disposition.

Putting these data together and interpreting them scholarly, the final message would be that prevention strategies for SDH might have been inadequate, but the efficacy (lower mortality) and efficiency (reduced length of hospital stay) of the hospital system increased over the observation period. If surgery ever contributed to these results, it did so minimally. Instead, neurosurgical interventions were the major determinant of increased cost. Should we conclude that patients with SDH are not to be operated on?

The Nationwide Inpatient Sample did not permit separation of two distinct clinical entities, the acute (aSDH) and chronic SDH. Rates of morbidity and mortality after aSDH are among the highest of all traumatic mass lesions. Not rarely is aSDH associated with intracerebral lesions and intracranial hypertension, and brain shift can be greater than the aSDH thickness. Therefore, aSDH is almost invariably surgically evacuated unless the patient is hopeless; in addition, surgery is not limited to the burr hole, because most clots are solid. In fact, aSDH is a common indication to craniotomy or even decompressive craniectomy.

Chronic SDH is often liquid. Trauma is always the cause, but symptoms may not start until weeks or even months after a trivial head injury, which can be forgotten. Surgical evacuation is the only possible treatment in case of chronic SDHs that are thick enough to cause neurologic signs or symptoms or are associated with midline shift (3). Burr hole craniostomy with drains is the most popular and effective surgical technique (4). Twist-drill craniostomy and craniotomy are alternative surgical procedures; however, recurrence is much higher with twist-drill craniostomy, whereas craniotomy is associated with a much higher morbidity.

If surgery is the main option for both aSDH and chronic SDH, why did only 30% to 40% of patients with emergent hospitalization for SDH in the Frontera study have neurosurgical evacuation?

One possible explanation is that patients were hopeless. The number of patients with severe comorbidity increased significantly in 2007 compared with 1998, suggesting that some of these patients could not be offered surgery because of a fragile systemic condition. Neurologic severity using validated scores such as the Glasgow Coma Scale score was not available to define the proportion of patients with deep coma. However, mortality declined over time, indicating that hopeless patients were not a significant proportion of the study population.

Patients might have had nonsurgical SDHs either because of one or both of the following: the neurologic condition was not seriously altered or the SDH was small with no brain midline shift. If this explanation holds true, spontaneous resorption of small SDHs might be the natural evolution of both acute and chronic SDH in a higher percentage than previously thought (5). This would

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*See also p. 1619.

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also explain the reduced length of hospitalization observed during the study period and the increased costs associated with surgery, a proxy of clinical severity; only the most severe patients, a minority, required surgery and had prolonged hospitalization.

The authors rightly conclude from their data that there is no clear evidence that current management practices are leading to improved outcomes. Future epidemiologic studies should consider adding a minimum set of data to gain insightful knowledge: SDH categorization as acute or chronic, the patient’s neurologic severity at hospital admission, and neuroradiologic details such as the hematoma volume and the brain midline shift. With these data available, it would be possible to define the real proportion of SDHs that resolve spontaneously as well as the factors influencing spontaneous SDH resolution. Such an attainment would be key to select those patients for whom surgery is not indicated and hospitalization merely adds to costs.

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Data“-omics” and intensive care unit patient care*

In this issue of Critical Care Medicine, Ahmed and colleagues (1) reported the benefit of a novel user interface based on electronic information needs of intensive care unit care providers, with the specific goal to reduce the task load and errors of cognition. Their experiments proved that specific user interfaces developed based on an understanding of provider information requirements reduced task load and cognition errors of the caregivers in the intensive care unit.

It should be a common sense that reduced information load is always associated with improved cognition and minimized possibility of making errors. The key issue of the future potential clinical importance of this study is how to accurately or properly derive the novel user interface electronic environment from the standard electronic environment. If the former is well derived and established, the improved cognition will benefit clinical care. It can thus be logically deduced that properly developing individual subsets of novel user interface electronic environment data information targeted at different fields of medicine would reduce the total data overload, improve the cognition efficiency, and reduce the source of medical errors. In other words, it makes computer science maximally serve humans.

In recent decades, the wide application of the computer has brought revolutionary changes in all fields of science and all aspects of human life. The amount of information handled by a computer memory exceeds what we can instantly handle in our brain. With the advancement of modern computer engineers, astronomical amounts of data can be stored into a computer. However, the essence is that the human brain generates computers, and the data stored in computers can only be properly used through the direction of the human brain. No matter how abundant the data being stored in whatever capacity of computers, only a fraction of the data at any time are required for a particular purpose. Only the human brain can pick up the right data and properly use the data for the specific task. This fact stresses the importance of developing special electronic user faces targeted for special applications, which lead to the maximal efficiency of using the data, reducing the cognition errors, and really benefiting our patients. This issue is particularly true in the field of emergency medicine and critical care, where split-second delays or a tiny cognition error may cost the life of a patient.

In the past decade, there has been an explosive development of “-omics” sciences, just to name a few, genomics (e.g., [2]), proteomics (e.g., [3]), metabolomics (e.g., [4]) pharmacogenomics (e.g., [5]), transcriptomics (e.g., [6]), nutrigenomics (e.g., [7]), etc. Nowadays, the advanced modern biomedical techniques have been able to generate as many biological data as possible, and the advanced modern computers can store as many data as we can generate. However, the most difficult task which we are facing now is not generating more data, nor storing more data, but analyzing the data and deriving what really are useful to the diagnosis, monitoring, and treatment of a particular human infirmity. This presents a real challenge to all experts in bioinformatics specialties and clinical care. I believe that to make all “-omics” science become specific powerful tools directly applicable to clinical treatments, they may have to un-
Nicotine replacement therapy in critically ill patients and the long-range risks of comfortable inaction* 

“There are risks and costs to action, but they are far less than the long range risks of comfortable inaction”—John F. Kennedy

Inpatient hospitalization (and its smoke-free environment) is the ideal time to introduce smoking cessation because an estimated 70% of smokers indicate a desire to do so, yet it is an often overlooked opportunity to impact one of the leading causes of preventable morbidity and mortality (1). Traditionally considered to be the role of the primary care provider, intervention such as nicotine replacement therapy (NRT) can easily originate in the controlled setting of the hospital; however, among patients with acute illness or injury, NRT is seldom given any consideration in actual or potentially life-threatening situations.

In this issue of Critical Care Medicine, in a study by Cartin-Ceba et al (2), the role of NRT in the management of critically ill patients and the safety of such treatment is explored. The authors described the impact of NRT on the outcomes of active smokers admitted to a medical intensive care unit over a 2-year period from 2007–2009. During the study period, 2741 consecutive admissions to a tertiary academic hospital, intensivist-staffed intensive care unit were screened for eligibility and 2199 patients were excluded as they were not active tobacco users. Of the remaining patients determined to be active tobacco users, there were 116 patients who were considered to be “low-acuity” admissions and were thus eliminated from the study. Forty-six patients were either on smokeless tobacco or currently on NRT. Twenty-three patients were readmissions to the intensive care unit and 27 patients declined to participate in the study, resulting in 330 active smoking patients to participate in the study. NRT was introduced by transdermal patches at a 21-mg dose for 174 smokers admitted to the intensive care unit. The remaining 156 smokers admitted to the intensive care unit did not receive any form of NRT. Using a prospective, observational cohort model, the authors tested the hypothesis that in-hospital mortality would be increased among smokers receiving NRT. A secondary aim of the study was to evaluate the association of NRT use with hospital length of stay, intensive care unit mortality, intensive care unit and 28-day mechanical ventilator-free days, estimation of organ dysfunction using Sequential Organ Failure Assessment methodology at 48 hrs and 72 hrs, and control of pain, delirium, and agitation. Patients with active smoking in the 30 days before hospitalization were included in the study, whereas patients <18 yrs of age, current use of NRT, and low-acuity patients admitted to the intensive care unit were excluded from the study. There were no statistically significant differences noted in all-cause mortality or in a majority of the secondary outcomes among the two groups, although patients receiving NRT had an increased intensive care unit length of stay with positive Confusion Assessment Method for the Intensive Care Unit scores and more patients required the use of physical restraints. Patients receiving NRT also required higher cumulative doses of opioids and benzodiazepines, although they also required lower cumulative median doses of dexmedetomidine and haloperidol.

There are several limitations to this study, including the retrospective study design, the lack of a true randomized and controlled trial, lack of standardized data collection regarding length and duration of tobacco use, exposure to secondhand tobacco, and the inability to control for variables such as opioid analgesic effects.
concomitant substance use or abuse (benzodiazepines, methamphetamine, opioids, alcohol, etc.), and physician discretion in prescribing NRT. As stated in the article, the authors failed to collect information on alcohol consumption and psychoactive drug use before hospitalization making evaluation of the possible association between NRT and mental status changes impractical. Lacking the ability to fully evaluate adverse drug reactions and cytochrome P-450 interactions also limits the generalizability of this study. Most importantly, the study protocol required self-reported tobacco use on admission. Because many patients tend not to be forthcoming about tobacco use (and family members may be unaware of tobacco use), accurate assignment to the appropriate group may be flawed. Notwithstanding the limitations of this study, there are practical points that warrant strong consideration related to tobacco use and smoking cessation.

There are limited data regarding the appropriateness of use and safety of NRT in acutely ill patients. In a retrospective study of patients admitted to a neurosurgical intensive care unit, a study by Panos et al (3) found no difference in secondary outcomes such as overall mortality, rates of subarachnoid hemorrhage rebleeding, angiographic vasospasm, intracerebral hemorrhage rebleeding, and ischemic stroke. A study by Seder et al (4) evaluated 3-month mortality as a primary end point and delayed cerebral ischemia resulting from vasospasm, angiographic, and transcranial Doppler evidence of vasospasm and delirium as secondary end points among active cigarette smokers admitted to a neurointensive care unit with acute subarachnoid hemorrhage. They reported no differences in the frequency of delayed cerebral ischemia or vasospasm, although seizure activity ($p = .024$) and delirium ($p = .006$) were more common in patients who received NRT. A study by Mayer et al (5) examined the causal relationship of delirium among brain-injured patients admitted to a neurologic intensive care unit and found that each had a history of heavy tobacco use and demonstrated clinical improvement with transdermal NRT within hours.

In the landmark article entitled, “Cigarette Smoking: The Natural History of a Dependence Disorder,” published in the British Journal of Medical Psychology, Russell was the first to describe the addictive properties of nicotine: “if it were not for the nicotine in tobacco smoke, people would be little more inclined to smoke than they are to blow bubbles” (6). Four decades later, the role of cigarette smoking in chronic disease morbidity and mortality is firmly established. Current data from the Centers for Disease Control and Prevention estimate that 46 million people (20.6% of all individuals aged >18 yrs) smoke cigarettes (7) and cigarettes are responsible for one of every five deaths in the United States each year. Cigarette use accounts for over $193 billion annually in healthcare costs and lost work productivity in a country that at the same time is struggling to overhaul a damaged healthcare system (8). The global impact of tobaccoism is also significant: an estimated 5.4 million people die each year as a result of tobacco-related illnesses, a number that could rise to over eight million deaths annually by the year 2030 (8).

Nicotine is a drug with potent psychoactive properties; its stimulant properties result in euphoria and enhanced mental awareness, whereas the depressant effects of nicotine produce a sense of relaxation and decreased tension (9). Nicotine acetylcholine receptors in the brain result in the release of dopamine and stimulation of the mesolimbic system (the reward pathway). Nicotine increases endorphin levels and corticosteroid levels while altering the bioavailability of serotonin and dopamine (10). CYP-2A6 is primarily responsible for the oxidation of nicotine and its subsequent physiological effects are influenced by substances such as grapefruit juice, pilocarpine and other muscarinic receptor agonists, phenobarbital, rifampicin, and dexamethasone. In patients with elective and nonelective cessation of smoking, symptoms of withdrawal begin within hours with maximum intensity in the first week (10).

The physiological effects of nicotine include adrenocorticotropic hormone and serum cortisol levels, increased blood viscosity and decreased fibrinolytic activity, and results in acute elevations in white blood cell counts and the inflammatory markers interleukin-6, tumor necrosis factor-α, and C-reactive protein (11). Nicotine has been shown to demonstrate activation of the hypothalamic–pituitary–adrenal system and inhibition of nitric oxide production. It is this latter process that is thought to be responsible for peripheral and systemic vascular disease. Increases in cortisol have an adverse effect on lipid profiles, bone density, central adiposity and its associated disorders, and reproduction (11). In adults, the pulmonary effects of tobacco and chronic obstructive pulmonary disease are well established; in patients undergoing surgical procedures, current cigarette use increases pulmonary-related complications by 300% even in the absence of chronic pulmonary disease. Smoking cessation before surgery does not reduce pulmonary complications; it is this population of patients that had the most complications after pulmonary surgery (12). The incidence of graft failure among smokers is threefold higher compared with nonsmokers and there is a strong association with ever smoking with abdominal aortic aneurysmal development; one that in fact is 250% stronger compared with coronary artery disease (13). Smoking cessation carries a significant reduction in cardiovascular mortality risk and exceeds that of other prophylactic therapies such as statins, aspirin, and β-adrenergic antagonists.

Much of the literature on smoking cessation and NRT is based in the outpatient setting with limited available data on its implementation during acute hospitalization. The use of NRT is patients with unstable angina or recent myocardial infarction has not been studied. Although there are limited data on the topic, NRT is considered safe for use in patients with cardiovascular disease (14). Patients currently prescribed doxetilate (a class III antiarrhythmic agent) should avoid NRT as a result of increased incidence of arrhythmia and QT prolongation (14). Future studies poised to evaluate the treatment effects of NRT should also incorporate a double-blind, placebo-controlled design to eliminate systematic error and evaluate the physiological impact on patients with acute, critical illness (15).

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REFERENCES

1. Fiore MC; for the Tobacco Use and Dependence Clinical Practice and Guideline Panel, Staff, and Consortium Representatives: A clinical
Critical genetic variations in critical illness*

T he initial sequencing of the human genome, completed ∼10 yrs ago, demonstrated that there are millions of genetic variations in the human genome. This finding triggered many studies aimed at determining the role of genetic variation in human disease, including in critical illness. Many early studies in this field showed conflicting results, which have been attributed, in part, to poor study design and an incomplete understanding of differences in linkage disequilibrium patterns between different races and ethnicities. Weaknesses of early studies, as well as important considerations in study design, have been discussed in a number of reviews, both for genetic association studies in general (1, 2) and specifically for studies of critical illnesses (3). Genetic association studies in the intensive care unit (ICU) population are especially complex since the patient population is heterogeneous and the illnesses are often acute rather than chronic.

One pathologic process found in the ICU for which genetic and genomic approaches appear to be yielding significant findings is sepsis and septic shock. Early studies identified a number of genes in which specific genetic variations were fairly consistently associated with outcome in sepsis or septic shock (for review see [4–6]). However, it is likely that many more genetic variations are involved in outcome since multiple pathologic processes are involved in sepsis and septic shock. Consequently, additional carefully designed studies are required. One approach is to examine a number of genes involved in a pathway involved with specific pathologic processes that occur in sepsis. In this issue of Critical Care Medicine, Nakada and colleagues (7) take such an approach in a well-designed genetic association study examining whether genetic variants in candidate genes involved in the response to angiotensin II are associated with outcome in septic shock patients. (Currently, the candidate gene approach is the most reasonable approach in critically ill patients since the number of individuals needed for a well-powered genome-wide association study is prohibitive.) The candidate genes chosen include the genes for angiotensin converting enzyme, angiotensin II receptor type 1, and angiotensin II type 1 receptor-associated protein (AGTRAP), which decreases signaling through angiotensin II receptor type 1. These genes were chosen because their protein products regulate the level of, and response to, angiotensin II. In addition, there is evidence suggesting that angiotensin II is involved in the pathogenesis of sepsis and septic shock. Angiotensin II is an important regulator of vascular tone (8, 9) and is elevated in severe septic shock patients (10).

The paper by Nakada et al (7) is also of interest because it is a good example of the complexity of examining the role of genetic variation in critical illness and the issues that must be addressed to perform a well-designed genetic association study. The authors examine genetic variation by examining genotypes of specific single nucleotide polymorphisms (SNPs) in the chosen genes. SNPs selected for genotyping are linkage disequilibrium-tag SNPs in both coding and noncoding (potentially regulatory) regions of the gene. Since the cohorts examined were primarily Caucasians, linkage disequilibrium-tag SNPs were selected using Caucasian SNP genotyping databases. However, for angiotensin II receptor type 1 and AGTRAP, the authors were only able to successfully genotype ∼35% of the identified linkage disequilibrium-tag SNPs. Consequently, there are many genetic variations in those two genes that have not yet been explored. In addition, the linkage disequilibrium-tag SNP approach only examined SNPs with a minor allele frequency of 5%; consequently, genetic variations present at lower frequencies are not examined in this study.

The authors used two different cohorts to examine the selected genetic

*See also p. 1641.

Key Words: angiotensin II; angiotensin II type 1 receptor-associated protein; genetic variation; polymorphism; septic shock; sepsis

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demonstrated that a specific genotype (GG), at a specific polymorphic site (rs11121816) in AGTRAP, is associated with mortality in patients with septic shock both in the derivation and the replication cohort. This genotype also appears to be associated with decreased mean arterial pressure and increased heart rate. In addition, the authors have demonstrated association of the GG genotype at this site with a functional consequence, a two-fold increase in gene expression of AGTRAP. Increased expression of AGTRAP would be expected to decrease the response to angiotensin II by decreasing signaling through angiotensin II receptor type 1. The association of the GG genotype with decreased mean arterial pressure and increased heart rate is consistent with increased expression of AGTRAP, suggesting that increased levels of AGTRAP are negatively modulating angiotensin II signaling.

While the work of Nakada et al (7) clearly indicates that the GG genotype at rs11121816 is associated with increased mortality, decreased mean arterial pressure, and increased heart rate, many questions remain. One question is whether the identified variation (in intron 1) is the causative variation or is in linkage disequilibrium with the causative site. As the authors point out, that particular SNP in the Caucasian population is in linkage disequilibrium with eight other SNPs, all of which are in untranslated regions of the gene (in introns 1, 4, and the 3′ untranslated region). Presumably, one of these nine SNPs is in a region involved with regulation of expression of AGTRAP. This finding is similar to recent findings of others that suggest that many of the SNPs that impact disease are in noncoding, regulatory regions of genes and may act either through regulating transcription, splicing, or stability of the mRNA (11–13).

Another question is raised by characteristics of the cohorts examined in this study. The cohorts were primarily composed of Caucasian individuals. It will be important to determine whether the same association is observed in other races and ethnicities. This is particularly important because linkage disequilibrium patterns differ between races and ethnicities, as do outcomes in critical illnesses.

Lastly, the authors’ findings indicate that genetic variation within the angiotensin II signaling pathway may impact outcome in septic shock; however, the authors have only examined the genes for three proteins in this pathway; there are many other proteins involved with the response to angiotensin II. Presumably, genetic variation within other members of this pathway could affect outcome or modify the effect of the identified genetic variation in AGTRAP. It will be of interest to examine genetic variations in other members of this pathway and examine how genotypes at polymorphic sites in all genes within the pathway impact association with outcome in septic shock. Is it possible that, similar to enzyme pathways that have a specific rate-limiting step, there is a variant, or gene, that is a critical determinant of the impact of genetic variation in that particular pathway’s effect on outcome? How might critical variants in different pathways impact the role of genetic variation on outcome? Such questions are particularly important since both the cost of DNA sequencing and the time required for sequencing an individual’s genome have decreased dramatically (11, 14). Physicians in some disciplines have already begun to use knowledge of genetic variation in clinical practice, and in the future it is likely that many patients will have sequencing information outlining the genetic variants present in their entire genome. Consequently, the search for genetic variations that impact critical illnesses, and the understanding of which of these genetic variants are most critical in a specific clinical setting, will be essential to allow intensivists to use genetic information to personalize the care of critically ill patients.

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REFERENCES
1. Newton-Cheh C, Hirschhorn JN: Genetic association studies of complex traits: Design and analysis issues. Mutat Res 2005; 573:54–69
5. Sapru A, Quasney MW: Host genetics and pediatric sepsis. Open Inflammation 2011; In Press
Thenar tissue oxygen saturation monitoring: Noninvasive does not mean simple or accurate!* 

Critical illnesses are often characterized by inadequate tissue oxygenation and it is commonly thought that survival requires recovery of normal cellular oxygen metabolism. Critical care physicians are well aware of the limitations of central hemodynamics to monitor the resumption of the metabolic homeostasis in their patients. Although in specific conditions such as sepsis, central venous oxygen saturation and/or lactate concentrations may provide better information than central hemodynamics to guide resuscitation (1, 2), appropriate monitoring of tissues oxygenation remains the intensivists’ holy grail.

Interpretation of Thenar Tissue Oxygen Saturation Is Not Straightforward 

In recent years, noninvasive assessment of tissue oxygen saturation (StO2) using near-infrared spectroscopy technology has become popular in the intensive care unit (3). It is commonly accepted that using information from light absorption by tissues, one may obtain the mean StO2 from a mixture of tissues, including skin, adipose tissues, muscles, and small vessels. In addition, by combining measurements of thenar StO2 and a transient forearm arterial occlusion, one may assess tissue oxygen uptake (from the desaturation slope) and functional microcirculation (from the resaturation slope). In practice, a number of factors may affect the reliability of near-infrared spectroscopy-derived StO2 measurements (Table 1). In addition, in this issue of Critical Care Medicine, the article by Lima and colleagues (4) demonstrated in an elegant clinical investigation that, in critically ill patients, peripheral perfusion was a major confounder in the interpretation of basal StO2 and its kinetic during arterial occlusion test. These authors observed that thenar StO2 and the resaturation slope varied more with abnormal peripheral perfusion than with central hemodynamic status or with underlying critical illness. Peripheral perfusion may be influenced by numerous factors such as ambient temperature; underlying cardiovascular, neurologic, or metabolic diseases; and drugs (e.g., vasoactive agents, anticoagulants). Therefore, according to Lima and colleagues’ work, assessment of peripheral perfusion should be part of interpretation of thenar StO2 data. Their findings may also help understand the heterogeneity in the results of studies assessing the prognostic value of thenar StO2 or its correlation with central venous oxygen saturation (5, 6). Of note, the design of Lima and colleagues’ study required that initial resuscitation and stabilization preceded inclusion to the study (4). Thus, it remains unclear to what extent abnormal peripheral perfusion may influence measurements of StO2 during the initial resuscitation of hemodynamically unstable patients.

Should StO2 Be Assessed at Other Muscular Sites? 

The near-infrared spectroscopy technology may allow assessing StO2 at various muscular sites, including the masseter, the deltoid, or the pectoralis. The thenar has been so far the most popular site because it is the only site allowing one to perform the occlusion test. However, given the demonstration of the major influence of an abnormal peripheral perfusion on the thenar StO2 data (4), territories such as the deltoid or the masseter may provide more reliable information. Indeed, peripheral perfusion may be less likely abnormal in the shoulder or the face than in the hand. Previous studies have shown a nice correlation between the masseter StO2 and central venous oxygen saturation in patients with severe sepsis or septic shock (7). Additional investigations are needed to confirm or not that assessing StO2 at the masseter, deltoid, or pectoralis levels may provide more reliable information on regional tissue oxygenation during critical illness.

Table 1. Factors influencing thenar tissue oxygen saturation measurements

<table>
<thead>
<tr>
<th>Patient’s environment</th>
<th>Endogenous factors</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>Ambient temperature</td>
<td>Age</td>
<td>Vasopressor (α1 agonist), vasopressin</td>
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<tr>
<td>Noise</td>
<td>Core temperature</td>
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<td>Pain, agitation</td>
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<td>Obesity</td>
<td>Underlying diseases affecting small vessels</td>
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<td>Edema</td>
<td>Pain, agitation</td>
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<tr>
<td>Obstructed areas</td>
<td>Hemoglobin, hematocrit levels</td>
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<tr>
<td>Underlying diseases affecting small vessels</td>
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<td>Pain, agitation</td>
<td>Hemoglobin, hematocrit levels</td>
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<td>Drugs</td>
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<tr>
<td>Anticoagulants</td>
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*See also p. 1649.

Key Words: tissue oxygenation; monitoring; muscles; critically ill

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Fish oil is not the fix for acute lung injury*

From 1999 through 2006, three similar investigations reported that a particular enteral nutrition formula decreased pulmonary and systemic inflammation and improved clinical outcomes in patients with acute lung injury (1-3). The formula used in each study (Oxepa; Abbott Labs, Abbott Park, IL) is a high-fat/low-carbohydrate product enriched with omega-3 fatty acids (including eicosapentaenoic acid [EPA] and docosahexanoic acid [DHA]), γ-linolenic acid (borage oil), and antioxidant vitamins. In each of the three studies, patients were randomized to receive the enriched formula or an isonitrogenous, isocaloric formula, also high fat/low carbohydrate (Pulmocare; Abbott Labs). Although each study has been criticized for methodologic issues, the aggregate results are quite consistent.

The study by Gadek et al (1) randomized 146 patients, 98 of whom were deemed evaluable (e.g., tolerated target feeding for 4 days). The evaluable patients who received the enriched formula experienced less pulmonary neutrophil recruitment, improved gas exchange, fewer days of ventilator support, and fewer new organ failures. An intent-to-treat analysis showed that the significant differences in clinical outcomes (time on ventilator; new organ failures) remained in favor of those patients receiving the enriched formula. Although the study was not powered for a mortality outcome, there was a trend in favor of the enriched formula in both the evaluable and the intent-to-treat groups (intent-to-treat analysis: mortality = 16% in patients receiving the enriched formula and 25% in patients receiving the unenriched formula; p = .165). The study by Singer and colleagues (2) randomized 100 patients at a single center. Patients receiving the enriched formula showed better oxygenation (at day 4, PaO2/FIO2 = 317.3 vs. 214.3; p = .05) and lung compliance; there was no difference in mortality. The study by Pontes-Arruda and coworkers (3) enrolled 165 patients, of whom 103 were evaluable (an adequate feeding period of 4 days, etc.). All patients were ventilated and had severe sepsis (15 patients in the enriched group and only six in the standard group were in shock). The patients receiving the enriched formula experienced significantly better oxygenation, more ventilator-free days (13.2 vs. 5.8; p < .001), fewer organ failures, and lower 30-day mortality (22.7% vs. 52.1%; p = .037). Although an intent-to-treat analysis was not planned or provided, some of the available data suggests that the main conclusions might generally hold up. For example, in the 62 nonevaluated patients, there were 13 deaths before day 4 in 38 patients randomized to the unenriched formula and eight deaths before day 4 in 29 patients randomized to the enriched formula.

Based largely on these three studies, at least one expert panel recommended the use of enteral formula enriched with fish oils, borage oils, and antioxidants for patients with acute lung injury (4). It seems that this approach was never widely adopted, perhaps in part because the critical care community was aware of new studies being planned.

In this issue, the article by Stapleton et al (5) reports on an important investigation, which was aimed at testing whether fish oil (EPA and DHA) alone, without the additional supplements used in the other studies (γ-linolenic acid and antioxidant vitamins), could demonstrate efficacy. By design, this was a small phase II study powered to detect changes in biomarkers rather than assess clinical outcomes. The primary end point was bronchoalveolar lavage fluid interleukin-8 levels. Patients were randomized to receive either fish oil (n = 41) with an EPA dose approximately 25 greater than that received in the previously mentioned studies or placebo (n = 49) delivered every 6 hrs. All regular enteral or parenteral feeding, including substrate and timing, was fully at the discretion of the treating physician. No data are provided on what was actually given, but it is implied that formulas now used commonly in critically ill patients, rather than the high-fat preparations used in the mentioned studies, were selected (an explicit statement to that effect would have been welcome). In the treated group, serum EPA concentration increased to levels associated with efficacy in earlier trials. However, there was no no improvement in bronchoalveolar lavage fluid interleukin-8 levels, other bronchoalveolar lavage fluid and plasma biomarkers, organ failure score, ventilator-free days, or hospital mortality (22.0% in the fish oil group vs. 20.4 in the control group; p =

*See also p. 1655.

Key Words: acute lung injury; acute respiratory distress syndrome; fish oil; borage oil; antioxidants

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.65). Of course, the small sample size limits the ability to detect differences. Furthermore, there is an issue of generalizability, because approximately 40% of the patients had trauma as the risk factor for acute lung injury/acute respiratory distress syndrome. Despite these limitations, this study provides very useful information, particularly when the results are viewed in conjunction with a study performed by the National Heart, Lung and Blood Institute ARDS Network.

The results of the ARDSnet’s “OMEGA” trial (Clinical Trials Registry # NCT00609180) are currently available in abstract form (6). In this trial, patients with acute lung injury/acute respiratory distress syndrome were randomized to receive twice-daily supplementation with EPA, DHA, γ-linolenic acid, and antioxidants vs. control. Enteral nutrition was provided by the physician’s choice of a standard nonenriched formula. The primary outcome was ventilator-free days; secondary outcomes included mortality and biomarker levels. The target enrollment was 1000 patients, but the trial was stopped at 272 patients when the Data and Safety Monitoring Board concluded, during a planned interim analysis, that the treatment was unlikely to show benefit. Patients who received the supplements experienced fewer ventilator-free days (14.6 vs. 17.4; \( p = 0.03 \)) and a higher 60-day mortality rate (26.6% vs. 16.3%; \( p = 0.05 \)). Mortality adjusted for baseline characteristics (there was nominally higher proportion of shock [55% vs. 48%] and more severe hypoxemia in the supplement group) was 24.6% in the treatment group and 17.9% in the control group (\( p = 0.14 \)). Clearly, adding EPA, DHA, γ-linolenic acid, and antioxidants did not improve outcomes in these patients. However, I believe it is unwarranted based on this single study (with its low mortality in the control group, etc.) to conclude that the supplements may be harmful when added to currently used enteral preparations. Nevertheless, an open mind should be maintained. The data in the study by Stapleton et al (5) did show that trauma patients who received EPA and DHA had higher bronchoalveolar lavage fluid levels of interleukin-8 and higher plasma von Willebrand factor than those that received placebo. Additional analyses and future studies will be needed to judge whether the signals of possible adverse effects of supplements seen in these two studies represent random effects or reflect actual pathophysiology.

For completeness, the study by Moran and coworkers (7) merits discussion despite the fact that it appeared only in abstract form with somewhat limited description of methods and outcomes. Some additional outcome data were subsequently obtained from the author (4). The trial enrolled 198 ventilated sepsis patients in 20 Spanish intensive care units. Patients were randomized to fish oil, γ-linolenic acid, and an antioxidant-enriched enteral formula vs. an isocaloric, isonitrogenous, high-protein formula (not the high-fat control used in the studies by Gadek et al, Singer et al, and Pontes-Arruda et al). There was no difference in 28-day mortality or ventilator days.

In summary, I believe that the body of evidence regarding the effect of supplementation with fish oil, borage oil, and antioxidants in acute lung injury/acute respiratory distress syndrome can be reconciled. The three studies that demonstrated a beneficial effect of such supplementation (1-3) used a nonstandard “control” formula, which is high in fats and low in carbohydrates. This formula has approximately 50% of calories resulting from fat compared with approximately 30% fat calories in enteral formulas commonly used in intensive care unit patients. Furthermore, the high-fat control formula consists of a relatively high concentration of n-6 and n-9 fats, which tend to be proinflammatory. Compared with this, a high-fat formula supplemented with anti-inflammatory n-3 fats (and with a higher n-3:n-6 ratio) could show benefit. This might be especially true when baseline lung inflammation may have been more severe during the time before lung protective ventilation became common practice (1). In contrast, three recent studies failed to show a benefit of adding fish oil (and in two of those studies, DHA and antioxidants as well) to standard low-fat enteral formulas currently in common use for critically ill patients (5-7). Based on this evidence, there is no role for supplementing standard enteral feeding with fish oil, borage oil, or antioxidants in the treatment of patients with acute lung injury/acute respiratory distress syndrome.

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REFERENCES
Innovative research on end-of-life decision making*

Although all research studies have considerable value, every now and again an investigation clearly stands out. The study by Barnato and colleagues (1) in this issue of Critical Care Medicine is exceptional in terms of novel methodology and promise for advancing the practical science of research, while at the same time having gained timely and clinically relevant insight into end-of-life decision making for use not only in the United States but other countries.

The stated purpose of this study was to determine the relationship between patient race and physician treatment decisions using high-fidelity simulation. Trained actors were used to enact realistic bedside care vignettes where physicians were asked to make treatment or palliative decisions for older terminally ill African (Black) Americans and European (White/Caucasian) Americans. Additional research complexity was introduced by having these “patients,” who were previously diagnosed with end-stage pancreatic or gastric cancer, experiencing acute hypoxia or hypotension, with major healthcare decisions thus needing to be made. Concealment was used so that physicians were not aware that race-based decision making was the primary research focus.

The practicing hospital-based physicians who provided the data for this study were asked about their knowledge of race-based patient preferences for life support, with these data subsequently revealing the commonality of life support in hospitals is often cure oriented (3). A retrospective chart review by Paice et al (4) for instance, revealed diagnostic and therapeutic procedures were common in the final 2 days of life for patients at a Midwestern US hospital. Research studies in other countries, such as Taiwan, Japan, Singapore, and Germany, have also revealed the commonality of life support over palliative care in hospitals (5–8). It is perhaps not surprising then, given this legacy, that the physicians in the study by Barnato et al (1) overestimated patient preferences for life support.

Although it is normally thought that people would want to live longer in health and even in sickness, years of access to increasingly sophisticated life-supporting technologies has revealed that futile cure-oriented treatment is often burdensome to patients and their families (3, 7). The diversion of attention from a good death, to chasing a cure at all costs (4, 7), is one of the most unfortunate outcomes of the healthcare sophistication that has occurred since penicillin began to be widely used in the mid-1940s to save lives. The Barnato et al study (1) illustrates that American physicians are now more accepting of the fact that death is inevitable in some cases, and that palliative care is both clinically and socially appropriate in these cases. This acceptance of impending death and related decisions will undoubtedly become more evident in the future, with increased end-stage chronic illness and accelerated population aging (9). Furthermore, personal preferences for or against life support are likely to become more prominent as exposure to dying persons increases. Deaths could as much as double in number as the large baby-boom generation ages (10).

To conclude, the simulation study by Barnato et al (1) is a welcome advancement over past studies that used paper vignettes highlighting brief hypothetical cases or retrospective chart reviews to gain insight into complex end-of-life decisions. Although the current study finding of an absence of race-based end-of-life medical decision making is mostly relevant to Americans, future studies will hopefully use high-fidelity case scenarios to advance knowledge of the impact of gender, age, and many other possible influences on end-of-life decision making.

REFERENCES


2. Johnson KS, Kuchibhatla M, Tulsky JA: What explains racial differences in the use of...
Resuscitation from cardiac arrest: Can we do better?*

The successful resuscitation of patients who suffer out-of-hospital cardiac arrest (OHCA) and the subsequent in-hospital care of those who survive resuscitation efforts present major challenges to healthcare delivery systems. In the United States, estimates of the incidence of OHCA are 166,000–310,000 yearly, although not all of these will receive attempts at resuscitation (1, 2). It is sobering to realize that the likelihood of surviving OHCA to hospital discharge has not changed during the past 25 yrs, remaining at around 6% to 8% (2). Improvements in cardiopulmonary resuscitation (CPR) techniques, public education, CPR training of laypersons, improved advanced life support training of emergency response personnel, availability of automatic external defibrillators, and new treatment protocols for cardiac arrest survivors, such as hypothermia, have not yet resulted in better outcomes. Factors that impede successful resuscitation include the absolute necessity for rapid institution of chest compressions and defibrillation necessary to restore blood flow to the brain to prevent irreversible cerebral damage, increasing age and complex medical comorbidities of patients receiving CPR, and a higher proportion of patients now with initial rhythms associated with poorer outcomes, i.e., asystole or pulseless electrical activity (3).

External chest compression for resuscitation of in-hospital cardiac arrest was first described in 1960 (4), and soon thereafter was combined with mouth-to-nose ventilation and defibrillation (5). These techniques have been extended from treatment for patients dying as a complication of myocardial infarction in-hospital, to the outpatient population with heterogeneous medical conditions, including respiratory illnesses, and differing modes of cardiac arrest rhythms, including asystole, as well as ventricular fibrillation. Analyses of large databases of CPR efforts consistently show that the following factors improve the chance of successful resuscitation with meaningful survival (2, 6, 7): 1) a witnessed event; 2) bystander-initiated CPR in under 5 mins; 3) early defibrillation in under 8 mins; 4) the presence of ventricular tachycardia or ventricular fibrillation as the initial rhythm; 5) cardiac arrest occurring in a public place rather than in the home setting; and 6) return of spontaneous circulation before transport to hospital.

Recent studies have reported ventricular tachycardia/ventricular fibrillation as the initial rhythm in 23% to 40% of OHCA, and the incidence may be decreasing relative to “nonshockable” rhythms (3). The likelihood of survival to hospital discharge is 3–10-fold worse if asystole is the initial rhythm. Survival to hospital discharge increases from 8% in all arrests to 34% if an automatic external defibrillator was applied by a bystander and delivered an appropriate shock (7). After successful return of spontaneous circulation, rates of survival to hospital discharge are 20% to 50% (2).

In view of these data, it would seem that several initiatives should yield better outcomes. Public education about CPR and training in the use of automatic external defibrillators would be expected to narrow the gap between the rates of bystander-witnessed arrest (46% to 53%) and bystander-initiated CPR (only 31% to 32%) (2, 8, 9). Improvement in training and allocation of emergency medical service personnel could shorten response times and time to first defibrillation. Increased availability of automatic external defibrillators in public places and in home settings should also show benefits. In a report from Lick et al (10), a comprehensive effort to address these issues improved survival from OHCA to hospital discharge from 8.5% to 19% over a 4-yr period.

Of those patients who are successfully revived to be admitted to hospital, only a minority will survive with no or only modest neurologic impairment. Assessing the prognosis of an OHCA survivor is essential to provide family members with realistic expectations as well as to provide appropriate intensity and duration of critical care services. In this issue of Critical Care Medicine, Hunziker and colleagues (11) validated a score to predict in-hospital death or survival with poor neurologic function, incorporating five simple clinical factors: initial rhythm, time to initiation of CPR (“no-flow interval”), duration of CPR (“low-flow interval”), and admission levels of serum creatinine and lactate. This score was first proposed by Adrie et al (12) and validated in a population in Europe. In the present study, 77% of patients had a poor outcome (death or survival with severe neurologic impairment); 100% of patients with a score in the highest quartile had poor outcomes, and 97% of patients with

*See also p. 1670.

Key Words: out-of-hospital cardiac arrest

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a score in the second highest quartile also did poorly. It is important to note that this score did not perform well in predicting good results, since those with scores in the lowest quartile still had a 40% to 50% chance of poor outcome.

Other groups have reported prehospitalization criteria that reliably predict poor outcomes and that may be used to stop resuscitation efforts. If all three of: 1) arrest not witnessed by emergency medical service personnel, 2) defibrillation was not used, and 3) absence of return of spontaneous circulation before transport were not present, successful survival did not occur (13).

How can these and similar prognosis scores be best utilized? First, after initial stabilization and assessment of every patient, noting individual characteristics may define a unique setting, the use of these scores to inform family members of a very poor overall prognosis may obviate inappropriate, seemingly limitless and futile intensive care therapies. Second, the effectiveness of new therapies, including hypothermia, can be assessed more meaningfully when prognosis at hospital admission can be defined. Third, reporting risk scores in survivors of CPR in population-based studies can help gauge the effectiveness of community-wide resuscitation programs.

Ongoing efforts to apply CPR protocols in more effective ways, to improve in-hospital care, and define cases where intensive care will not improve survival will allow us to allocate and apply resuscitation resources more meaningfully.

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REFERENCES

Prognosis of sepsis: Lessons from epidemiological studies*

Sepsis is a worldwide ever-increasing condition, representing a leading cause of death and a significant healthcare burden (1–3). Failure to promptly initiate effective antibiotics being associated with increased morbidity and mortality (4, 5), broad and regularly updated epidemiologic data on factors likely to help physicians choose the right antibiotic regimen such as causative microorganisms and antibiotic susceptibility are of paramount importance. However, although numerous large epidemiologic studies from developed countries are currently available (1–3), there is a striking paucity of data from other parts of the world.

The study by Rodriguez et al published in this issue of Critical Care Medicine (6) constitutes a remarkable effort to characterize the epidemiology of sepsis in a developing country. Over a 6-month period, the authors prospectively recruited 2681 septic patients in ten hospitals of the four main cities of Colombia corresponding to a cumulative monthly incidence rate of sepsis of 3.61 per 100 admissions per hospital. The predominance of Gram-negative bacteria, making the current epidemiology of sepsis in Colombia resemble the one in the United States 25 yrs ago, and the high mortality rate in an otherwise relatively young and healthy population were the two main findings.

From a microbiologic point of view, the results of the study by Rodriguez et al are not surprising because significant differences in epidemiology across countries (and across treatment sites in a given country) have long been known (7). Nevertheless, this study adds evidence that guidelines for empiric antibiotic therapy based on up-to-date local epidemiologic data should be preferred to general recommendations to reduce the risk of therapeutic failure.

More relevant are the results regarding mortality. Although mortality rates accord-

*See also p. 1675.
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In their complex interactions make it clear that current strategies focusing on therapeutic aspects, despite being of value, are probably insufficient. Conversely, global and coordinated strategies may substantially improve the prognosis of patients.

To establish efficient strategies, both general and patient-specific considerations matter.

From a general perspective, medical, economic, organizational, and educational aspects have to be simultaneously taken into account. Of note, general recommendations should share a universally accepted framework but should also be customized to local conditions to improve their applicability and efficiency. In a way, recommendations should vary from one geographic area to another just like patients and micro-organisms do. Thus, in addition to general guidelines for the early diagnosis and treatment of sepsis, local surveillance programs need to be promoted to serve as a basis for customized protocols for antibiotic therapy and for both rationale and patient-specific considerations.

From the patient-specific perspective, the inability to include an individual dimension in the management of sepsis is a major limit of current recommendations. Developing general guidelines that are supposed to apply to all patients while each individual is genetically unique is, at least to some extent, paradoxical. Actually, various genetic polymorphisms have been shown to be associated with an increased susceptibility to sepsis and poor outcomes. Examples of these polymorphisms involve genes coding for cytokines, cell surface receptors, angiotsin-converting enzyme, plasminogen activator inhibitor, or caspases. Undoubtedly, the list will continue to grow, providing new potential therapeutic targets and opening the way to a “patient-tailored” approach.

In the near future, the elaboration of multifaceted strategies encompassing the entire spectrum of sepsis, from “basic” microbiology to genetic epidemiology, will probably be the key step toward a better prognosis.

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Leading an intensive care unit – we need more than medical knowledge!* 

Intensive care units (ICUs) are growing more and more from small units with 6 to 10 beds, quite often in only one medical subspecialty and only few doctors and nurses, to highly complex interdisciplinary units or even departments. Specialization in intensive care medicine and economic pressure are forcing hospitals to concentrate ICU beds in large units or divisions with up to 100 or more beds.

Most commonly, leaders of ICUs receive their jobs due to personal medical skills and/or qualification, but hardly one has been trained specially in leadership, management skills, or communication. But is this sufficient for people quite often responsible for the medical treatment of thousands of patients per year? Is this sufficient for doctors who are responsible for budgets of millions of dollars in one of the most expensive areas of the hospital? And is this sufficient for someone leading a multiprofessional team of hundreds and more employees? Even if there are some examples in history of people who were very successful moving from the role of a worker to managerial tasks like Frederick Winslow Taylor (1856–1915, who developed the Scientific Management = Taylorism), just applying knowledge and experience from the basics seems not to be sufficient in modern times. A leader must lead other people or a team. He or she needs to develop a vision and communicate this vision. He needs a strong commitment to his unit and his vision. And last but not least, differentiated skills are necessary to put visions into practice.

Hence, team leadership became a very important issue for successful units over the last decade. While this has been recognized in industrial areas already for some years, hardly anyone is focusing on this important issue in the medical community. Although 12 yrs ago Baggs and coworkers (1) could show that leadership skills do have an important influence on mortality and outcome, this topic did not become a favorable field for further research. This explains the relevance of the manuscript from Reader and colleagues (2) in this issue of Critical Care Medicine.

Reader et al (2) examined the team leadership in the ICU from the perspective of specialists. Using a semistructured interview, they asked 25 senior physicians about their estimation for important functional and team development behaviors. After transcription, these behaviors were grouped into a theory-based framework for ICU team leadership. They concluded that the preliminary framework they developed, and which needs further validation, could be a tool to train the next generation of ICU leaders and, from my point of view, of course to improve the team leadership skills of the current generation of ICU team leaders.

The functional leadership behaviors Reader et al (2) were elaborating seem to be quite obvious on the first glance, like gathering information on new patients, planning and decision making on patient management, and managing team members, like training of young colleagues and deploying staff dependent on their skills. However, it is important to name these leadership skills and to stress the importance to train these skills. Leading an ICU is no longer just a medical commitment, but a managerial task (3, 4). Beside medical knowledge and experience, communication in and outside the team (5), and team member coordination is very important and takes a great amount of our daily time on the ward (6). Loss of information due to organizational mismanagement or neglecting boundaries of human capacities may have detrimental effects on patient outcome and mortality (7).

The study of Reader et al (2) is well designed and grounded on theory and research on team leadership mostly in areas other than medicine (8). However, even using a structured interview and a test for coding reliability, it would have been nice to obtain data about the factors of team leadership from the team’s point of view. I am sure we would see “client-professional gaps” between the leaders and team members as we see client-professional gaps in the estimation of patient satisfaction between patients and staff (9). We do not know whether the interviewed ICU seniors are good or bad leaders. And so we cannot differentiate between good and bad, and useful and useless functional behaviors. We just know that 25 seniors feel, from their daily work, that this is important.

An extended examination of team members’ estimation will reduce bias further – and maybe highlight other key leadership skills than those assessed by the leaders themselves. As noted by the authors themselves, it needs to be explored and validated whether each behavior of the framework, as elaborated in their study, has important influence on the outcome of the patients, the risk management, the team satisfaction, and last but not least, the process development in the ICU. But in the manuscript it is striking as well that organizational skills are only mentioned by the seniors a few times, which implies that most of the ICU leaders are not aware (and not trained?) of the importance of these skills.

However, this fact sounds like an urgent call for systematic implementation of management skills into the training of intensive care residents, who become the next generation of ICU team leaders. Reader et al (2) gave us the first tool, but further research on the influence of team leadership skills on team performance, patient safety, and outcome is necessary to validate good leadership skills in intensive care medicine. Let’s start to reduce the gap in managerial and organizational training and research between industrial
D epression of myocardial function during severe sepsis, which currently accounts for approximately 200,000 deaths/year in the United States (1), is characterized by a decrease in contractility and a poor response to fluid therapy (2). Since the mid-1980s, it has been recognized that the decreased cardiac function, which undoubtedly contributes to the overall pathophysiology of the septic state, does not arise from factors that are intrinsic to the myocardium, but instead results from the presence of circulating myocardial depressant factors (3, 4). Because much of the massive inflammation and multiorgan dysfunction in sepsis result from the secretion of various cytokines, it was long suspected that these proteins were also responsible, at least in part, for the observed myocardial dysfunction, although their identification and the molecular basis for their effects on myocyte function were poorly understood.

A study by Pathan and colleagues (5) recently showed that the cytokine interleukin-6 is a major factor responsible for modulating myocardial depression in children with meningococcal septicemia. In this issue of *Critical Care Medicine*, a study by Pathan et al (6) used an *in vitro* cardiac myocyte cell culture system to investigate the signaling pathways (and potential drug targets) that modulate and/or are modulated by interleukin-6. They report that the stress activated p38 mitogen-activated protein kinase (p38 MAPK) pathway controls interleukin-6-induced myocardial depression and that this can be reversed using a specific chemical inhibitor of this kinase (SB203580). The authors go on to look at gene expression changes in a small cohort of pediatric patients with meningococcal sepsis and find a number of differences between septic patients and healthy control subjects. Among the genes that show differential expression are a number of upstream and downstream regulators of p38 MAPK signaling indicating that this pathway is deregulated in this cohort of patients. However, the mechanism by which such a large group of genes involved in p38 MAPK signaling could be deregulated remains to be determined. In addition to the work of Pathan et al there is a number of observations that link p38 MAPK and one of its downstream kinases, MK2 (MAPKAPK2) to the control of interleukin-6 biosynthesis (7). For example, during lipopolysaccharide-induced inflammation, p38 MAPK activates MK2, which in turn controls interleukin-6 production by stabilizing the interleukin-6 messenger RNA (8). Therefore, the p38 MAPK/MK2 pathway appears to lie both upstream and downstream of interleukin-6 in inflammation and sepsis.

These observations are of obvious clinical relevance because p38 MAPK and its downstream effectors are under intense scrutiny as viable drug targets for the treatment of a number of diseases from colitis to cancer (7, 9, 10). The current study further highlights the potential use of p38 MAPK inhibitors in the specific management of sepsis-associated cardiac dysfunction. p38 MAPK, however, activates a variety of downstream effectors that affect a wide variety of other cellular responses during sepsis in addition to cytokine secretion and myocardial contractility, including effects on apoptosis and neutrophil function (11, 12). In this regard, drugs that target the specific components of the p38 MAPK pathway that are central to its interleukin-6 effects such as MK2 or its substrates may also show promise in the clinical treatment of sepsis by preventing interleukin-6 production, thus inhibiting myocardial depression, while having fewer effects on other p38 MAPK-dependent responses.
this regard, emerging new drugs targeting interleukin-6 itself such as interleukin-6 blocking monoclonal antibodies (13) may also show use in this setting. Importantly, the use of these drugs will not be limited to myocardial dysfunction in sepsis because the p38 MAPK/MK2/interleukin-6 pathway appears to be a major determinant of response to chemotherapy in certain cancers (14, 15). For example, p38 MAPK-dependent interleukin-6 secretion from thymic endothelial cells mediates drug resistance and relapse in a mouse model of Burkitt’s lymphoma (16). Therefore, new drugs targeting the p38 MAPK/MK2/interleukin-6 signaling pathway may have broader use in cancer treatment as well as for the treatment of conditions in which chronic inflammation is a major driving force of the diseased state such as sepsis. If such drugs prove useful, it will be yet another example of how agents that were developed to prove useful, it will be yet another example of how agents that were developed to treat inflammation such as cyclo-oxygenase inhibitors can have a double life in clinical oncology. That indeed would be quite a lot of heart to salvage.

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REFERENCES

1. Lukaszewicz AC, Payen D: The future is pre-determined in severe sepsis, so what are the implications? Crit Care Med 2005; 33(Suppl): S512–S517

Endothelial damage after resuscitation: Reactive oxygen species as possible therapeutic targets?

The resumption of spontaneous circulation after cardiopulmonary resuscitation (CPR) is a complex pathophysiological state (1). Since the very first description of closed chest compressions as a method for out-of-hospital resuscitation >50 yrs ago, the lives of many thousands of patients could be saved (2, 3). However, despite multiple attempts to optimize CPR and post-CPR guidelines, overall mortality rates of those patients who regained sufficient circulation remain high, ranging between 50% and 80% depending on the population and study methods (4). Cardiac arrest, which causes systemic hypoxia and ischemia, and the subsequent reperfusion after successful CPR lead to multiorgan dysfunction in the scope of a general ischemia/reperfusion situation. The respective syndrome has been named “postresuscitation disease” in the study by Negovsky and colleagues from the specific treatment of the precipitating pathology and selective hypothermia, no other therapeutic strategy has been reported over the past decades. Modulation of endothelium-dependent modalities and endothelial injury might
serve as powerful bystander therapies in this context.

**ROS in Resumption of Spontaneous Circulation: Possible Target for Bystander Therapies?**

The role of ROS in myocardial, cerebral, and several other organ-specific ischemia/reperfusion settings has been avidly examined in animal and human investigations over the past decade. During myocardial ischemia/reperfusion, the rapid increase of oxygen leads to dysfunctional mitochondrial respiration and an increase in cellular ROS levels (9, 10). This is, at least in part, reversible through increases in myocardial nitric oxide levels during reperfusion after the administration of sodium nitrite, the oxidation product of nitric oxide (11). It remains elusive if these beneficial effects are entirely attributable to hypoxic nitric oxide signaling, preservation of ROS decomposition systems, or through a direct interaction of nitric oxide with ROS.

In the current issue of *Critical Care Medicine*, the study by Huet and colleagues (12) investigates the role of ROS for endothelial damage after successful resuscitation, a general state of ischemia/reperfusion. Using plasma from post-CPR patients incubated with cultured human endothelial cells, the authors demonstrated a remarkably high average cell death of as much as 65.5% as compared with 34% in patients with septic shock and 21% in healthy volunteers, of which 50% were smokers. The authors attribute these differences to significantly higher levels of ROS as measured by total fluorescence. The detrimental effects were partially reversible under scavenging of hydroxyl radicals. Notably, increased ROS levels were accompanied by lower activity of cellular ROS decomposition systems, namely the superoxide dismutase and the glutathione reduct system. Additionally, the study describes a much impaired mitochondrial respiration. The study has certain limitations such as the number of included patients, which does not allow ruling out an influence of standard medications on the present findings. The authors did not define the specific mediators of increased ROS levels after incubation of patient plasma with endothelial cells. Also, a direct *in vivo* demonstration of ROS-dependent impaired endothelial functions has not been conducted, e.g., by means of flow-mediated vasodilation, presumably the gold standard of endothelial function assessment *in vivo* (13). This present contribution is, however, the first demonstration that systemic changes after CPR promote severe damage of the endothelial layer. This could be attributed to increased ROS levels and an impaired ROS decomposition.

It is now widely acknowledged that reperfusion can cause a burst in free radicals in postischemic tissues (14). Less agreement exists for a possible modulation of ROS. In this context, some authors have related organ protection to decreased ROS, whereas others measured unaffected levels or even an increase in ROS despite a general organ-protective effect of the respective intervention (15). The question remains whether ROS represent a therapeutic target and whether a modulation of ROS in patients after resuscitation leads to an improvement in the overall morbidity and mortality.

**Possible Therapeutic Directions: Potential Role for Nitrite?**

The administration of sodium nitrite might provide such a novel therapeutic approach. Nitrite is the oxidative product of nitric oxide. A large part of the bodily provision of nitrite derives from dietary sources, whereas the rest has been attributed to endogenous enzymatic nitric oxide synthesis (16). Nitrite reduction to bioactive nitric oxide occurs selectively under hypoxic/ischemic or acidic conditions (17–19). This mechanism is not only relevant for physiological mechanisms such as the regulation of blood flow (18), but has also been suggested to exert protection under pathophysiological conditions. In this context, it could be demonstrated that a postischemic burst in ROS can be prevented through an increase in cellular levels of exogenous nitrite and subsequent reduction to nitric oxide (11). This has been linked to myocardium-specific organ protection and a reduced infarct size. A study by Dezfulian and coworkers (20) was able to extend this view to the setting of CPR and resumption of spontaneous circulation. Using a murine model of cardiac arrest and resuscitation, they demonstrated that intravenously administered nitrite on inception of CPR: 1) reduces cellular ROS; 2) restores mitochondrial respiration; 3) improves postcardiac arrest myocardial function (myocardial stunning) as well as neurologic measures; and 4) reduces mortality. In their study, the authors focused primarily on the harmful ROS-attributable effects on mitochondrial functions in cardiac tissues. However, considering this demonstration and the submission by Huet et al (12), one might speculate that ROS contribute to systemic endothelial damage as well as to organ-specific injury and that inhibition of ROS formation effectively modulates these circumstances. Studies examining the clinical relevance are therefore crucial, but at this point still missing. It would nevertheless be intriguing to use nitrite for selective nitric oxide delivery to ischemic sites vulnerable for ischemia/reperfusion injury such as the heart, the brain, and the endothelium.

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**REFERENCES**


7. Cerchiarì EL, Safar P, Klein E, et al: Vis-
Recruitability, recruitment, and tidal volume interactions: Is biologically variable ventilation a possible answer?*

Nowadays, recruitment and recruitment maneuvers are among the most fashionable topics related to acute respiratory distress syndrome (ARDS) despite any clear evidence that interfering with these phenomena is of some benefit. On the other side, the “6 mL/kg IBW low tidal volume” approach, which is in reality the “normal tidal volume approach,” is a recognized cornerstone of setting mechanical ventilation in acute lung injury (ALI) or ARDS (1). Interestingly, recruitability, recruitment maneuver, and tidal volume are usually treated as separate issues, whereas they are deeply intertwined. Recruitability, in fact, is a condition in which a given amount of lung regions is collapsed but still openable. In ALI/ARDS, the primary reason for lung collapse is the increased lung weight resulting from edema, which compresses the most dependent lung regions (2); other possible causes of atelectasis are the lack of surfactant or regional hypoventilation leading to gas reabsorption. Up to 90% of the recruitable tissue opens up in a range of inspiratory pressures that are reached during normal tidal ventilation (20–25 cm H2O) as demonstrated in both experimental animals (3) and humans (4). Therefore, normal tidal volume may be viewed as a “tidal recruitment maneuver.” To fully recruit the lung, higher tidal volumes are required, which generate higher inspiratory pressures. Indeed, the relationship between inspiratory recruitment (function of tidal volume/inspiratory pressure) and the lung regions that remain open at end expiration, at a given positive end-expiratory pressure, is straightforward and well documented both in experimental animals (3) and human ALI/ARDS (4): the greater the amount of tissue opened at end inspiration, the greater the amount that remains open at end expiration. In summary, at a given positive end-expiratory pressure, the extent of lung opening at end inspiration depends on the interaction between recruitability (i.e., the amount of collapse, whatever may be its cause) and the size of tidal volume (i.e., recruitment maneuver).

The article by Graham et al (5), in the current issue of Critical Care Medicine, presents a series of experiments in pigs in which ALI/ARDS was induced by oleic acid. In a carefully conducted study, the authors compared conventional mechanical ventilation with biologically variable mechanical ventilation in the presence or absence of surfactant, for which they investigated the anatomic distribution. The recruitability of this pig model appeared to be unusually low (approximately 10% of the lung mass); nonetheless, the biologically variable mechanical ventilation improved systemic arterial oxygenation and respiratory system compliance while decreasing the physiological dead space and the amount of nonaerated lung tissue. Most of these findings have been previously reported in animal models (6, 7) and the interpretation of the underlying mechanism is straightforward (8): a biologically variable mechanical ventilation, in fact, includes a certain number of high tidal volumes. Tidal volumes of such size, when mechanical ventilation began to be applied worldwide in the early 1960s, were called “sighs.” The old ventilators incorporated a “sigh” function to prevent progressive atelectasis, because

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*See also p. 1721.

Key Words: acute respiratory distress syndrome; mechanical ventilation; surfactant replacement; biologically variable ventilation; experimental model; recruitment maneuver

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monotonous low tidal volume ventilation during anesthesia and paralysis was commonly known to cause resorption atelectasis (9). Therefore, the “sigh” was equivalent to what we call now “a recruitment maneuver.” In the middle 1970s, it was clearly recognized that greater tidal volume in ALI/ARDS was associated with a better compliance as a result of greater lung recruitment (10). In the 1990s, with the application of more sophisticated techniques, it has been confirmed that few sighs per minute even could better maintain lung mechanics and oxygenation in severe ARDS (11). Not surprisingly, the biologically variable mechanical ventilation, with its periodic deep inflation, reproduces the effects of “sigh” ventilation. The safety of higher tidal volumes, even applied at low rates, remains to be proved, especially when used during long-term ventilation.

In our opinion, the new and unexpected finding of this article is that the exogenous surfactant given at dosage of 4 mL/kg body weight, i.e., 60–80 mL per pig, both in conventional and biologically variable mechanical ventilation worsened systemic arterial oxygenation and lung mechanics without significant changes of quantitative lung computed tomography variables. Not surprisingly, exogenous surfactant was primarily located in the most dependent lung regions (because gravity always wins) but, apparently, it behaved more as a foreign liquid leading to airway obstruction/alveolar occupation instead of working as surfactant should. The authors postulated surfactant inactivation in the most dependent lung regions. As an alternative explanation, it is conceivable that exogenous surfactant in this oleic acid model has been simply useless. We know, in fact, that surfactant workers in a model of lung lavage, where it substitutes the surfactant lost with lavage fluids. In human ARDS, the lack of surfactant, and the need for its substitution, is far more questionable. In fact, a bulk of data from both experimental and human ALI/ARDS strongly suggests that the intrinsic mechanical characteristics of the residual ventilatable lung are normal (the baby lung concept (12)) as indicated by normal values of specific lung elastance/compliance (13). This suggests that the lack of surfactant, if any, is insufficient to change the intrinsic characteristics of the lung parenchyma. In the present article, the respiratory system compliance normalized to the well- aerated tissue weight (a rough surrogate of specific compliance) averaged, after 4 hrs from injury, 0.13 ± 0.02 mL/cm H2O−1·gr−1 in the four groups of pigs and was not different from what we found in healthy pigs of similar weight (0.13 ± 0.03 mL/cm H2O−1·gr−1) (14). Taken together, these findings further support the idea that the exogenous surfactant replacement may be ineffective in ARDS and should be limited to a subgroup of patients in which a surfactant deficit could be clearly demonstrated (15).

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REFERENCES


Does positive end-expiratory pressure improve CO\textsubscript{2} exchange in controlled ventilation of acute airflow obstruction?*

Although positive end-expiratory pressure (PEEP) clearly reduces triggering effort, work of breathing, and cycling dysynchrony in mechanically ventilated patients with chronic obstructive pulmonary disease who experience flow limitation during tidal breathing, its value for those with asthma, first challenged more than two decades ago, remains less clear (1, 2). Also contested is the value or detriment associated with adding PEEP during passive ventilation of patients with air flow obstruction of any type (3). An animal study of bronchoconstriction induced during controlled ventilation that appears this month provides high-quality scientific data that help to address selected aspects of both issues (4). Using sophisticated imaging methodology, a low level of PEEP was demonstrated to even the distribution of ventilation in the histamine-challenged lungs of rabbits positioned upright, albeit at the apparent cost of distending some lung units into a range associated with overdistention (at least by imaging criteria). These elegant experiments, although seemingly far removed from the clinical setting, would appear to support the potential value of low-level PEEP in a passive model more analogous to the bronchoconstriction of acute asthma than to the functional expiratory airway collapse of advanced chronic obstructive pulmonary disease.

Alveolar dimensions within the geographically separated lung units that comprise the normal lung—as well as their relative ventilations during tidal breathing—vary in a fashion that relates inversely to regional lung volume (5). As inflation proceeds from functional residual capacity toward total lung capacity, regional differences of dimension and of incremental ventilation both decline as transpulmonary pressures become more evenly distributed and mechanical interdependence is more forcefully expressed. Lung volume bears a strong relationship to the distribution of ventilation within the diseased lung as well, where pathologic topography is heterogeneous (5). For example, during exacerbations, the lung units of patients with asthma and chronic obstructive pulmonary disease exhibit a range of mechanical properties that vary impressively with lung volume and position. The reasons for this variation include local differences of transalveolar pressure, of tissue compression, of bronchomotor tone, and of secretion retention and drainage.

Although only a single value for auto-PEEP can be measured at the airway opening, it, too, varies regionally and that variance is certain to change with changes of body position. Dependent airways, subjected to greater compressive forces, close relatively early in expiration and therefore trap gas at higher pressures. For similar reasons of declining transpulmonary pressure, patients with chronic obstructive pulmonary disease trap gas in moving from upright to recumbent positions (6). Lateral decubitus positioning favors gas trapping within the dependent lung; in emphysema, this phenomenon may lead to reduced ventilation that can be restored by modest levels of PEEP (7). The upper lung, stretched by greater transpulmonary pressure, remains open and relatively well ventilated. Interestingly, easily reversible auto-PEEP has also been reported in acute respiratory distress syndrome (8), presumably as a consequence of external airway compression of dependent airways by the weight of the overlying lung rather than by inherent narrowing or bronchoconstriction within feeder airways. Avoidance of airway closure by the application of PEEP at least partially restores ventilation to the most compromised areas.

A consistent theme of published work in these diverse experimental and clinical settings is that adding PEEP redistributes ventilation in a way that favors more homogeneous ventilation. How best might this be explained? The answer would almost certainly depend on whether PEEP acts by preventing closure of unstable or compressed airways or by narrowing the pressure gap separating the most and least obstructed units; i.e., by replacing intrinsic with extrinsic PEEP in some air channels as it raises the alveolar pressure within others. The accompanying PEEP-generated rise in central mean airway pressure is usually—but not invariably (9)—associated with further lung distention. Whether PEEP directly alters the distribution of bronchomotor tone, for example by reflex stimulation or inhibition, is an intriguing but as yet unstudied possibility. Improved distribution of inhaled bronchodilator after PEEP application has also been suggested (10). For completeness, it must be recognized that PEEP is unlikely to improve the distribution of ventilation if plugged airways predominate as the cause for obstruction.

One somewhat surprising finding of the current article by Porra and colleagues (4) is the detection of technique-defined overdistention in some lung units exposed to only 5 cm H\textsubscript{2}O PEEP and tidal volumes of 6 mL/kg. Extreme flexibility of the rabbit chest wall provides a partial but unsatisfying explanation. Two other possibilities come readily to mind. First, redistribution of blood flow away from expanding tissue may reduce alveolar image density without the need to invoke excessive stretch of the alveolar tissue itself (which seems unlikely at these relatively low alveolar pressures). Second, the upright position technically required to implement synchrotron radiation imaging is unnatural for the rabbit, whose cone-shaped lungs would be subjected to regional stresses in this position for which they are not anatomically designed. Whatever the explanation, we...
cannot assume that similar levels of airway pressure would result in excessive strain within the lungs of larger animals (or patients) ventilated in positions that are customarily used at the bedside. It must not be forgotten that variations of body position can powerfully influence the functional residual capacity and the distribution of ventilation within the diseased as well as normal lung. In my view, clinicians often remain unaware of the use of positioning as a therapeutic complement or alternative to manipulations of airway pressure.

In the end, is reducing the heterogeneity of ventilation by applying PEEP beneficial to the welfare of the passively ventilated patient with bronchoconstriction? Intuitively, the answer must depend on disease type and severity, the cause of ventilation heterogeneity, body position, minute ventilation, and the magnitudes of applied PEEP and end-inspiratory plateau pressure. Furthermore, improving the evenness of ventilation of itself does not directly address gas exchange efficiency, which must depend on the coexisting distribution of perfusion. Studies of the effect of PEEP on CO2 elimination suggest that the competition between airway/alveolar recruitment and overdistention of open airways subjected to a higher mean airway pressure determines whether dead space falls or rises as PEEP is applied (10–12). In the specific setting of the ventilated patient with well-established asthma, in which the lung is already grossly distended and many air channels are stubbornly plugged by mucus, it is uncertain that raising mean airway pressure further would redistribute perfusion in a beneficial manner. Therefore, adding PEEP to the passive patient must be done cautiously with close attention to plateau pressure and delivered tidal volume. Like with many problems we confront in critical care, the longstanding question of whether PEEP is of therapeutic value to the passively ventilated patient experiencing bronchoconstriction deserves a nuanced and highly qualified reply.

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REFERENCES

1. Tuxen DV: Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. Am Rev Respir Dis 1989; 140:5–9

Microparticles have macro effects in sepsis*

*See also p. 1739.

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Organs failure represents one of the causes of high mortality during sepsis, in spite of the many advances made in medicine. Although the mechanisms involved in organ failure are not completely

known, imbalances between inflammatory mediators and oxidative and nitratve stresses have been proposed at the cellular level. Growing experimental evidence indicates that circulating microparticles (MPs) may regulate vascular cell function (1). MPs are small vesicles shed from the surface membranes of cells during apoptosis and activation. Due to their protein, lipid, and cytoplasmic contents (e.g., miRNA, mRNA), MPs can also serve to transfer a large number of messages between cells. Importantly, it has been shown that circulating levels of MPs are elevated during sepsis (2, 3) and that levels of circulating MP inversely correlate with survival of septic patients (4).

In this issue of Critical Care Medicine, Mastronard and colleagues (5) hypothesize that MPs from septic patients can contribute to organ dysfunction observed in these patients. The authors describe the effects of injection of human MPs from septic patients into experimental animals to track the expression of proteins related to nitratve and oxidative stresses in the heart, lungs, liver, and kidneys. The main findings reported are that: 1) MPs from septic patients exert pleiotropic and differential effects de-
pending on target tissues; 2) MPs from septic patients mainly induce changes in the expression of enzyme systems related to inflammation, nitrative, and oxidative stress; and 3) heart and lung tissues are affected to a greater degree by MPs from septic patients. These authors previously reported that circulating MPs from septic patients can exert a protective role against vascular hyporeactivity induced by lipopolysaccharide in mice (3). This protective effect of MPs from septic patients was associated with increased production of the vasoconstrictor thromboxane A2, possibly serving to compensate for the hyporeactivity that accounts for the hypotension in patients with septic shock.

The tissues analyzed (heart, lungs, liver, and kidneys) in the study by Mastronardi et al (5) constitute the main targets of sepsis-associated organ failure. In sepsis, cardiac depression is, in part, the consequence of the attenuation of the adrenergic responses of the cardiomyocytes (6). Acute respiratory failure initiated by sepsis increases alveolar epithelial-endothelial permeability and so reduces lung compliance (7). In addition, the early phases of sepsis sees decreases in portal and hepatic blood flows that lead to hepatic dysfunction. Finally, sepsis is the most common cause of acute renal failure, where there is a pronounced deterioration of glomerular and tubular function, often leading to prolonged patient stays in intensive care units that usually requires immediate medical attention (8). Of the several mechanisms proposed to explain systemic organ failure in sepsis, an increase in nitrosative and oxidative stresses as well as the upregulation of proinflammatory proteins are leading contenders for possible therapeutic targeting. Related to this, Mastronardi et al (5) show that circulating MPs from septic patients induce alterations in the expression of nitric oxide synthases and of cyclooxygenases—changes that are likely associated with large increases in cardiac superoxide anion production. Although similar findings related to the expression of nitric oxide synthases and cyclooxygenases were also evident in the lungs from mice treated with MPs from septic patients, there were, however, no corresponding changes in nitric oxide and superoxide anion levels. In addition, MPs from septic patients enhanced the nitration of proteins in pulmonary tissue but not in other tissues. These observations suggest new roles for MPs during sepsis. However, there are some limitations to the conclusions that can be drawn. Other enzymes related with nitrative and oxidative stresses were not studied. Also, interactions (e.g., immune, etc) between MPs from humans and MPs from mice are possible. Finally, another criticism is related with the fact that the authors did not analyze changes in the function of target organs. Regarding this latter point, other studies report that injection of control rats with MPs from septic rats reproduced hemodynamic changes and septic inflammatory responses that were associated with oxidative and nitrosative stresses, at least in the heart (effects of these MPs on other tissues were not analyzed) (9). Nonetheless, the findings of Mastronardi et al (5) provide new insights into the effects of MPs in the pathogenesis of sepsis. Indeed, based on the results described in cardiac and pulmonary tissues, one can hypothesize that while MPs from septic patients act as true vectors of untoward inflammation, these effects can occur in organ-specific ways.

Thus, although circulating MPs from septic patients may exert a protective role at the vascular level by compensating for attendant hyporeactivity (3), these MPs could also participate in the genesis of mutilorgan failure in sepsis by inducing deleterious protein changes in target tissues.

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REFERENCES

Inactivity-induced diaphragm dysfunction and mitochondria-targeted antioxidants: New concepts in critical care medicine*

Over the past decade, the Powers lab has contributed a remarkable series of publications (1–4) indicating that controlled mechanical ventilation (MV) in the rat—according to a standardized protocol carried out for 12–18 hrs—predictably elicited diaphragm inactivity that was accompanied by the triad of oxidative stress, myofiber atrophy, and contractile dysfunction. The clinical relevance of these studies became apparent in 2008, when we (5) reported that 18–72 hrs of MV and human diaphragm inactivity—in brain dead organ donors—elicited some evidence of oxidative stress and dramatic (i.e., 50%) atrophy of both slow and fast diaphragm myofibers. Furthermore, we noted increased activity of caspase-3, a cytosolic serine protease, and increased expression of messenger ribonucleic acid coding for atrogin-1 and MuRF-1, key components of the ubiquitin–proteasome proteolytic pathway (UPPP), and we suggested that increased proteolysis played a major role in producing the myofiber atrophy. Additionally, on the basis of the data in our article, we calculated that maximum transdiaphragmatic pressure of these diaphragms would be dramatically decreased to <50% of control concentrations, and this provides one possible mechanism for the postulated contractile dysfunction. More recently, Jaber et al (7) used cervical magnetic phrenic nerve stimulation to directly demonstrate progressive decreases in diaphragm peak twitch tension (assessed by airway occlusion pressures) in patients on prolonged MV; additionally, their biopsy data indicated myofiber atrophy, increased UPPP activity, and increased protein expression of the calpains (i.e., calpains I, II, and III), another family of serine cytoplasmic proteases. We presume that these increases in calpain expression represented an increase in calpain activity; this inductive leap is important since the UPPP cannot degrade intact actinomysin complexes that are attached to the myofiber lattice. Indeed, recent work by Whidden et al (4) and others (8) indicates that increased activity of both the calpains and caspase-3 in conjunction with oxidative stress cleaves structural proteins such as titin (9) and thereby affects the release of actin, myosin, and other myofibrillar proteins from the lattice for further degradation by the UPPP.

Other recent work by Hussain and colleagues (10) demonstrated that the diaphragms of brain dead organ donors—exposed to prolonged MV and inactivity—also exhibited autophagy, and this mechanism can account for the degradation of cytosolic organelles (e.g., mitochondria) that occur during the myofiber atrophy process. Equally important, Hussain et al (10) were the first to directly demonstrate that, in human diaphragms exposed to prolonged MV and inactivity, increased protein carbonylation and increased 4-hydroxyynonenal–protein adducts are manifestations of oxidative stress. In summary, both human and rat studies indicate that the combination of prolonged MV and diaphragm inactivity elicits a pathologic triad characterized by oxidant stress, myofiber atrophy, and contractile dysfunction.

How do we prevent this syndrome from developing in patients on prolonged MV? Prior work from the Powers lab demonstrated that antioxidant therapy with Trolox (an analogue of vitamin E that is not approved for clinical use) attenuated the oxidant stress, myofiber atrophy, and contractile dysfunction that predictably occur in their rat MV model (2, 4, 11). After exploring several possible oxidant generating pathways, these workers postulated that mitochondria were the major source of oxidants in the MV rat model, and the experiments of Kavazis et al (12) demonstrated that diaphragm mitochondria from their MV rats—in comparison to control rats—generate increased reactive oxidative species (ROS) during both states 3 and 4 respiration. The seminal paper by Powers et al (13) in this issue of Critical Care Medicine suggests that the systemic administration of mitochondria-targeted antioxidants may represent future preventive treatment for patient diaphragms exposed to prolonged MV and inactivity. Specifically, these workers administered the “mitochondria-targeted antioxidant”—Szeto–Schiller peptide 31—to one group of rats that were undergoing MV according to their standard protocol; they noted that, despite presumed inactivity, these rat diaphragms did not exhibit the expected increase in mitochondrial generation of ROS, as well as any myofiber atrophy, or contractile dysfunction. In contrast, control rats that were pretreated with saline—and underwent the same MV protocol—exhibited increased mitochondrial ROS production, myofiber atrophy, and contractile dysfunction. Therefore, we believe that the data in the paper by Powers et al strongly support the concept that mitochondria are the major source of ROS in diaphragm inactivity and this increase in diaphragm ROS appears to be necessary for development of the pathologic triad of oxidative stress, myofiber atrophy, and contractile dysfunction.

Conceptually, we view the type of oxidative stress—manifest in the diaphragms of both the MV rat model and human studies in the literature—as an increase in the generation of ROS that is initiated in close proximity to the inner

*See also p. 1749.

Key Words: contractile dysfunction; diaphragm disuse atrophy; humans; mechanical ventilation; mitochondria-targeted antioxidants; myofiber atrophy; oxidative stress

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mitochondrial membrane (where the respiratory complexes are located); this increase in ROS then spreads throughout the mitochondria and diffuses to all areas of the myofiber, producing oxidant damage to proteins, lipids, and deoxyribonucleic acid. This model suggests that the increase in ROS will be greatest in the inner mitochondrial membrane, resulting in progressive damage to the respiratory complexes that in turn will cause progressive increases in ROS production. A major problem in treating this pathology is that the only currently Food and Drug Administration approved antioxidant (i.e., N-acetylcysteine) is thought to lack the ability to effect adequate concentrations in the mitochondria. Therefore, the theoretical advantage of this new class of mitochondria-targeted antioxidants is that, following systemic administration, the ratios between mitochondrial matrix concentrations and those in plasma range from 500:1 to 1000:1 (14, 15). (We recognize that a recent paper in this journal by Agten et al (16) casts some doubt on this concept; however, a detailed discussion of this paper is beyond the scope of this editorial.) The members of this new class of drugs are Szeto-Schiller peptide 31 (15), which has completed phase I studies, and the extensively studied drug mito-Q (14), which has completed phase I as well as some phase II studies.

In 2004, in a prophetic perspective article, Vassilopoulos and Petrof (17) introduced the term “ventilator-induced diaphragm dysfunction” to describe the pathologic changes (noted above) in human and experimental animal diaphragms exposed to prolonged MV. On the basis of this concept, they suggested that partial ventilator support modes would be less likely to be associated with this syndrome. Indeed, this has now become accepted clinical practice in patients who are suitable for this ventilator modality. However, at the present time, we believe that the term “inactivity-induced diaphragm dysfunction” may be a more useful concept because regardless of the settings on the ventilator, early observations by Powers et al (3) indicate that the diaphragms of MV rats were inactive (as assessed by electromyographic observation) and the human diaphragms of brain dead organ donors reported by our group (5, 6) as well as Hussain et al (10) were also inactive. Furthermore, the two signaling pathways (i.e., IGF1-PI3K-AKT, NF-κB) that have been demonstrated to play a role in eliciting the increase in UPPP activity in these diaphragms are known to be activated by disuse (6, 7).

In summary, we hope that the inactivity-induced diaphragm dysfunction concept will stimulate human studies on therapeutic modalities that either eliminate prolonged diaphragm inactivity (i.e., periodic electrical stimulation for short periods of time [18]) or drugs that will prevent the diaphragm mitochondrial pathology associated with inactivity (i.e., mitochondria-targeted antioxidant drugs).

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REFERENCES

Thromboprophylaxis in critically ill children: How should we define the “at risk” child?*

The need for thromboprophylaxis in hospitalized adults deemed to be “at risk” for venous thromboembolic events (VTEs) is well recognized (1, 2). However, there is no consensus regarding a similar need in pediatric patients. A major factor contributing to this lack of consensus is undoubtedly the lack of data available to guide clinical practice. While there are a number of recent studies that document the increasing incidence of VTEs in children admitted to pediatric intensive care units (PICUs) in North America and in Europe (3–5) that also identify risk factors for VTEs in children, these reports have not resulted in the widespread adoption of evidence-based recommendations regarding which of these children would most likely benefit from pharmacologic thromboprophylaxis. Whether this is due to a lack of confidence in the data, an inability to coherently apply the literature to actual patients, a belief that kids do not require thromboprophylaxis because their hemostatic physiology is different from adults, or to practice “inertia” is not known. In the absence of such data, the “default” position for a large number of PICUs appears to be not to consider pharmacologic thromboprophylaxis due to the accompanying risk of bleeding. What is needed are data that would facilitate the development of a set of guidelines that might assist the intensivist in developing a consistent, rational approach to thromboprophylaxis in critically ill children. The first step in this process is to catalogue what the current practices are in order to identify areas of potential consensus on which to build.

The report by Faustino and colleagues (6) in this issue of Critical Care Medicine is just such a step. They surveyed 151 North American PICUs as to their pharmacologic thromboprophylaxis practices using standard patient clinical scenarios. Their 62.2% response rate (97 of the 151 units queried) suggests that the nature and practice of the responding units is likely to be representative of PICUs throughout North America. At least two conclusions can be drawn from their data: first, practices vary across PICUs, and second, many “at risk” children, as defined by current descriptive studies (e.g., children <1 yr or >14 yrs of age, children on mechanical ventilation, and children with central venous catheters) do not appear to be considered for pharmacologic thromboprophylaxis in many PICUs. Indeed, a recent survey of PICUs in England and Wales reached a similar conclusion that most PICUs do not have a standard approach to VTE prophylaxis in children (7). Whether this failure to initiate pharmacologic thromboprophylaxis results in harm to these patients is not addressed in the study by Faustino et al (6), and such data cannot be extracted from those studies reporting on the incidence of VTEs in children. Consequently, it is difficult to call for a uniform policy similar to that prescribed by our adult medicine colleagues in the absence of such outcome data. While it may seem logical to surmise that children who fall into defined risk groups are indeed “at risk” and should receive such therapy, there may also be reasons to believe that the risk-benefit relationship of pharmacologic thromboprophylaxis may not favor such therapy in children because the physiology affecting hemostasis in children may be different from that in adults. Maybe we need look no further than the endothelium for insights. A child’s endothelium is not the same as an adult’s. As we age, our endothelium appears to become less nonthrombogenic, but there are multiple factors that affect the pace of this endothelial “aging,” including exercise and obesity during childhood (8–11). Indeed, in those studies reporting on the incidence of VTEs in adult patients that stratify results by age cohorts, most show that risk of VTEs increases with age, with the mean age of patients experiencing VTEs in the mid-60s (12, 13). However, these statistics may be misleading given that most admissions to medical/surgical ICUs and hospital units are of older individuals. Studies of VTE incidence that include children, adolescents, and young adults have demonstrated a greater relative risk for VTEs in younger patients, even though the VTE incidence increases with age (14, 15). As the hospitalization of children, particularly sicker children, increases, the need to address VTE prophylaxis in this population may become more acute.

In the United States, VTE prophylaxis for hospitalized adult patients has become a major patient safety issue and adherence to VTE prophylaxis guidelines in adult patients is tracked on a regular basis. While these guidelines consider several different factors, including patient age, the push is to move toward more rather than fewer patients receiving prophylaxis. Pediatricians have largely been spared from this push, although when confronted with an obese, ventilated, immobilized adolescent patient we must, and generally do, ask the thromboprophylaxis question. Faustino et al (6) have shown us that how we answer is largely a matter of personal opinion and experience rather than being grounded in data. Previous studies have enabled us to identify populations of children who are at an increased risk of developing VTEs but do not help us to predict in which, if any, of these groups of children pharmacologic thromboprophylaxis would be appropriate. The results of this study may be useful to pediatricians as they develop a general approach to thromboprophylaxis that is rational and has the chance to be widely accepted. Given that our patients are different from adult ICU patients in many important ways, it is unlikely that our pediatric VTE prophyl-
Steroids for respiratory syncytial virus: Is it finally time to just say “no”?*

An estimated 2 million children require medical care because of respiratory syncytial virus (RSV) infection, and approximately 57,500 children are hospitalized annually (1, 2). Of those previously healthy children who are hospitalized with RSV, 10% to 20% will require admission to the intensive care unit (ICU), and nearly half of these ICU admissions will require mechanical ventilation (3–5).

Children admitted to the ICU with respiratory failure secondary to RSV have one of two types of lower respiratory tract infection (LRTI), bronchiolitis or a more severe form of RSV-induced pneumonia. The inflammatory response to RSV-infected epithelium results in acute bronchial inflammation and edema. In severe cases, the resultant tissue damage, cellular debris, altered surfactant composition, and proteinaceous mucus production can contribute to airway obstruction and to airway hyperresponsiveness (6). Although the host immune response leads to clearance of the virus during RSV-LRTI, it is unclear how much of this inflammatory process may also be contributing to the clinical disease severity.

Differences in the extent of airway inflammation and airway hyperresponsiveness may underlie the severity of clinical disease in critically ill patients with RSV. Based on the severity of gas exchange abnormalities present within 24 hrs of mechanical ventilation, Tasker et al (4) identified two clinical subgroups of mechanically ventilated patients with RSV-LRTI. Stratifying the groups by mean airway pressure and alveolar-arterial oxygen gradient, they found a significantly longer length of ICU stay in the severe group. Physiologically this makes sense, in that patients in the mild group have predominantly small airway obstructions whereas those patients in the more severe subgroup demonstrate significant parenchymal lung disease, a small degree of increased airway resistance, and meet the clinical criteria for acute respiratory distress syndrome (7). Studies have shown that 25% to 30% of children mechanically ventilated with RSV-LRTI have this more severe pneumonia type (8–10). This has led to the use of these subgroups for stratification in clinical trials and to test hypotheses that the pathogenesis of RSV bronchiolitis and RSV pneumonia may be different and require different therapeutic approaches.

The therapeutic potential of corticosteroids as immunomodulators of RSV pathogenesis has been investigated for over 40 yrs producing mixed results. A systematic review by the Cochrane col-

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laboration, which excluded studies with intubated or ICU patients, demonstrated no significant differences between corticosteroid and placebo groups for respiratory rate, oxygen saturation, admission rates, length of stay, or readmission rates (11). A systematic review of the effect of corticosteroids in hospitalized nonintubated infants demonstrated a statistically significant, yet clinically unsatisfying, 0.5-day decreased duration of hospital length of stay (12). Finally, for the mechanically ventilated patient population, a systematic review of the three published trials found that corticosteroids had no overall effect on the duration of either mechanical ventilation or hospitalization (13). Given that these studies were each underpowered to detect a true difference, it remained unclear whether steroids could have a beneficial effect in the critically ill. Certainly, the use of corticosteroids in clinical practice remains high, with 60% of patients hospitalized with RSV and 30% of those intubated with RSV receiving steroids (14, 15).

In this issue of Critical Care Medicine, van Woensel and colleagues (16) present an international, multicenter, randomized, double-blind, placebo-controlled trial of dexamethasone or placebo for 48 hrs in 145 mechanically ventilated children <2 yrs of age. Patients were enrolled across 12 sites from December 2003 through January 2008 and block randomization occurred by site and within strata for disease severity (mild: PaO2/FIO2 >200 mm Hg and/or mean airway pressure <10 cm H2O; and severe: PaO2/FIO2 <200 mm Hg and/or mean airway pressure >10 cm H2O). The primary outcome was duration of mechanical ventilation. The study design and analyses were performed to take into account data derived from the authors’ previous work in 2003 using a similar stratified population of mechanically ventilated patients with RSV-LRTI (8). Although no overall treatment effect was seen in this prior study, a post hoc analysis demonstrated the average length of mechanical ventilation was shorter, by up to 4 days, within the mild subgroup of patients treated with dexamethasone vs. placebo, whereas no evidence of effects of steroid in the severe subgroup was detected. Therefore, in this current study, the study design incorporated a superiority approach to detect the benefit of steroid over placebo in the mild subgroup, and a noninferiority approach to analysis of the severe subgroup. Further, planned interim analyses were performed and reviewed by an independent data monitoring committee to monitor for early dramatic effects or harmful effects of dexamethasone treatment vs. placebo. The trial was stopped for futility after the third interim analysis with no evidence of benefit from treatment with dexamethasone on the duration of mechanical ventilation in those patients with mild oxygenation abnormalities.

Post hoc analyses generate hypotheses for further study. So it is appreciated that, given the author’s intent to pursue an investigation of these post hoc analysis results, the study design, level of analyses, and use of the data monitoring committee created an academically strong paper despite the ultimately negative results of the trial. Post hoc analyses are notoriously misleading and, as the authors submit, the failure to find a difference in measured outcomes between the dexamethasone- and placebo-treated patients with mild oxygenation abnormalities in this present study may indicate that these results in 2003 had been spurious findings. The futility of dexamethasone to have an effect on the duration of mechanical ventilation may also represent the difficulty with using this as an outcome measure. There were no extubation protocols used in this study; each site was left to use their routine management. Weaning and extubation protocols are not well established in the pediatric ICU population, but certainly, clinical trials have attempted to reduce the effect of this variability in practice on the outcome measure by employing a commonly applied weaning and extubation practice during study participation (17). Several studies have shown wide variation in the management of bronchiolitis, and the length of mechanical ventilation in these studies varies significantly.

Further, when considering the difficulties in studying this important problem in critically ill children, previous work has demonstrated that slow enrollment and small sample sizes limit the ability to determine statistically significant results. By employing this type of study design and using the mild and severe disease subgroups in the stratification, these authors have made the attempt to maximize the efficiency of finding a measurable effect.

Treatment remains largely supportive for the patient with RSV-LRTI. Dexamethasone has not shown measurable effects on airway inflammation or on clinically important outcomes (13, 18). Given the significant burden of disease in previously healthy children who are admitted to the ICU with RSV-LRTI, how to affect the airway inflammation and the degree of airway hyperresponsiveness remains an important problem for future study. Ongoing research in this area continues to identify the contribution of both cellular and neurogenic inflammation in the lung after RSV infection (6). These findings suggest that it may take a combination of therapeutic approaches to modulate the severity and duration of RSV in the critically ill patients.

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REFERENCES

Antibiotics in intensive care: Too little or too much?*

It remains a challenge to strike a reasonable balance when prescribing antibacterial chemotherapy (ACT) to patients in intensive care. Invasive bacterial infections occur frequently and are a leading cause of death. Unfortunately, a state-of-the-art diagnostic armamentarium is often not able to timely identify the presence, let alone the specific type, of the responsible bacteria. Were modern technology able to resolve the latter, we would be able to rationally target and standardize the use of ACT and at the same time ensure that the specific type of bacterial infection was effectively eradicated.

Until such a technology has been invented, however, we are unfortunately left in a situation in which many patients admitted to the intensive care unit receive empiric broad-spectrum ACT for extended periods of time. There is a natural reluctance to reduce or even stop ACT in critically ill patients until there is clear evidence that any possible infection is not contributing to morbidity. If the ACT is stopped before the bacterial infection has been sufficiently treated, it is likely that the bacterial infection will re-emerge making the prospect of recovery more difficult. Conversely, extensive use of broad-spectrum ACT leads to the selection of resistant bacteria and a more restrictive policy will tend to reduce this selection pressure for resistance.

There is a fairly extensive body of literature comparing efficacy and safety of various antibiotics regimens given for fixed and predefined periods of time. Conversely, the literature informing the required duration of use of ACT to treat various types of infections is more limited.

It has been proposed that biomarkers would be helpful to guide appropriate use of ACT in the intensive care setting. Biomarkers could potentially either lead to earlier initiation of treatment after the onset of the infection, avoid using ACT in persons not infected, and/or guide premature interruption of ACT once the bacterial infection has been eradicated. The table outlines the current status on all three fronts of this research area on one biomarker, namely procalcitonin. Procalcitonin levels increase rapidly after onset and clear quickly after resolution of bacterial infection. In this issue of the Journal, Heyland and colleagues (1) argue that routine use of procalcitonin can lead to a 2-day mean reduction in use of ACT without affecting hospital mortality or length of stay in the intensive care or in the hospital.

This is an appealing observation that likely will lead many colleagues focused on ACT stewardship to consider introducing regular procalcitonin monitoring in their units to guide their efforts further. Some important considerations are, however, relevant in this context.

First, the data show convincingly that strict adherence to a protocol of stopping ACT in case of low procalcitonin levels can lead to reduced use of ACT in the intensive care setting; this observation has also been made in other settings and is most likely widely applicable (2–4). Physicians tend to work with prespecified standards for duration of use of ACT, and if you introduce an intervention that challenges this routine to physicians who are willing to adopt their prescription behavior, then you will likely see this result. It would, however, be important to better understand how much of this benefit is driven from a mere change in the behavior of the physicians, where it is otherwise obvious that ACT is no longer required; ie, the introduction of stricter antibiotic stewardship (5). Focused stewardship has been shown to cause a similar reduction in duration of ACT use when managing, eg, ventilator-associated pneumonia (6). Conversely, the added value of also measuring procalcitonin as part of such a strategy is less clear and the present meta-analysis is not providing clarity on this point. How frequently did the results of this biomarker lead to interruption of ACT in situations in which one would not have interrupted ACT otherwise as part of an optimized antibiotic stewardship approach?

Second, it is critical to ensure that the meta-analysis provides compelling data that exclude a situation in which a clini-
Avoid using ACT in patients who are not infected (reduce side effects).

Stop ACT as early as possible after infection has been eradicated (reduce side effects and resistance).

Aim of Strategy | Current Evidence
--- | ---
Initiate empiric ACT as early as possible after infection onset (reduce harm from infection) | No benefit from proactively initiating and expanding ACT on the basis of procalcitonin increase in one randomized trial (n = 1200) (13)
Stop ACT as early as possible after infection has been eradicated (reduce side effects and resistance) | Maybe possible, although the noninferiority of clinical outcome has not yet proven (1); ongoing trials may clarify this (11, 12)
Avoid using ACT in patients who are not infected (reduce side effects) | Seems not possible; published randomized trials observe equal proportion (>95%) of patients in intensive care on ACTs on days 1–2 irrespective of strategy applied

ACT, antibacterial chemotherapy; PCT, procalcitonin.

*Only systematically investigated by Bouadma et al (14). In this study, >95% patients received ACTs on days 1–2 in both arms, although the PCT algorithm at baseline would have ruled out ACT in 65 of 321 (20%) in the PCT-arm (ie, the protocol was overruled).

Table 1. Strategies for using the biomarker procalcitonin to guide use of ACT in intensive care

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<th>Aim of Strategy</th>
<th>Current Evidence</th>
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<td>Initiate empiric ACT as early as possible after infection onset (reduce harm from infection)</td>
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<tr>
<td>Avoid using ACT in patients who are not infected (reduce side effects)</td>
<td>Seems not possible; published randomized trials observe equal proportion (&gt;95%) of patients in intensive care on ACTs on days 1–2 irrespective of strategy applied</td>
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A quick way to understand whether a study has demonstrated noninferiority is to compare the 95% confidence limits exceed 10%, respecting authorities would not accept a study with a statistical difference of 10% between the groups. Relevant to the present discussion, this may help to clarify this further (10, 11). An alternative and likely favored approach would be to reinforce the effectiveness of antimicrobial stewardship and, in doing so, apply multisciplinary teams including infectious disease-trained physicians to ensure that appropriate ACT is provided to patients in intensive care.

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REFERENCES


