Microcirculation: More questions than answers*

Until recently, microcirculation was a sort of black box between the arterial and venous compartment. Pulmonary artery catheters and associated techniques can investigate the upstream part whereas the downstream part is estimated using organ function, Svo_2 or lactate. This black box played a key role in exchange with tissues and is considered the motor of disease, especially in septic shock. Except using invasive animal experiments such as *in vivo* cremaster microscopy, little data were available to see inside the black box. Ten years ago, laser Doppler allowed to measure red blood cell velocities in the small arteries and capillaries oriented toward the probe, such as in the digestive tract. Orthogonal polarization spectroscopy, further refined in sidestream dark field (SDF) microscopy allows to visualize directly the blood flowing in a thin mucosa (1). By using a wavelength absorbed by hemoglobin, red blood cell appears dark and this allows us to measure the diameter of the capillaries, the type and velocity of flow. The explored area corresponds to roughly 0.7 mm^2 (940×750 μm). Numerous investigations are published, showing the effect of specific pathology or therapeutic intervention on microcirculation. Interestingly, changes in the microcirculation can occur without changes in macrocirculation (1), the latter being defined as flow/pressure/oxygen content through the aortic valve. Persistent alterations in microcirculations, despite correction of "macrocirculatory" parameters, are associated with worse prognosis on septic shock (2). Microcirculatory alteration in the early postoperative period is associated with an increased risk of complications, despite no changes in cardiac output or oxygen transport (3).

Table 1. Microcirculation research program

Get more: How can we get more information from the microcirculation images?
Vascular beds: Have all the vascular beds the same pattern, reactivity?
Pathologies: Have all pathologic processes the same effect on microcirculation? Adaptive or pathologic changes?
Therapeutic intervention: Effect of various therapeutic interventions on the microcirculation. Vasoactive drugs, sedative drugs?
Outcome: Do therapeutic intervention improving the microcirculation improve organ function or outcome?

Need for More Data and Analysis

SDF images under the tongue are easy to acquire in patients in the intensive care unit, can be repeated frequently, and are noninvasive. Provided some technical pitfalls, such as pressure artifacts, are controlled, SDF images are almost self explaining. An experienced investigator can at the first glance tell if the "*microcirculation is OK*" or not. From this first impression, a numerical functional capillary density and a semiquantitative microvascular flow index were derived and standardized (4). Recently, a software package has become available that enables automated image analysis. Although the actual versions of the software requires time-consuming manual corrections and vessel detection, this product opens the door to automated bedside assessment of microcirculation. Refined numerical data must be obtained from the SDF images: Objective measurement of capillary density, capillary diameter and distribution, capillary repartition, and objective measures of flow heterogenicity should be obtained (Table 1).

Will Microcirculation Change Outcome?

Microcirculation is a monitoring tool, as is the pulmonary artery catheter. This tool is like a little hole in the black box between the arterial and venous compartment. By being able to see inside the box, we hope to be able to understand the missing link between macrocirculatory parameters and organ function/failure. Will we be able, with this piece of information, to change outcome? In the 1970s with the advent of the pulmonary artery catheter, we hoped to be able to improve the outcome of intensive care unit patients. After 30 yrs of debate and controversy, the pulmonary artery catheter is not definitively improving outcome. The chain from a monitoring device to outcome has several hurdles: This includes 1) proper signal detection and analysis; 2) proper interpretation of the information; 3) selection of the adequate and efficient therapeutic tool; and 4) clinical response to these therapeutic interventions. Trzeciak and co-workers recently investigated septic shock patients during early goal therapy. Patients showing an improvement in early microcirculatory parameters between admission and 3 to 6 hrs later had an improvement in organ function (Sequential Organ Failure Assessment scores) in the first 24 hrs (5). Based on the previous pulmonary artery catheter studies, it will be probably impossible to show that monitoring the microcirculation will change patient outcome. In an era of evidence-based medicine, what is the level of evidence required for monitoring techniques? Among the dozens of monitoring techniques available, only pulse oxymetry and capnography have been shown to improve perioperative outcome—not because these techniques are superior—but because these techniques permit simple interpretation of supplemental data and easy application of highly efficient therapies like oxygen or endotracheal tube repositioning.

*See also p. 2333.

Key Words: shock; microcirculation; organ failure; oxygen delivery

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Adaptive Versus Pathologic?

Several investigators demonstrated that there was a correlation between sublingual microcirculatory disturbances and outcome in septic patients. We think these changes are the result of the pathologic process (septic shock, cardiogenic shock). One can also argue that these changes could also be adaptive: The closure of the microcirculation in septic shock or in patients with postoperative complication may be a physiologic response to redistribute flow to more vital organs. The organism has a (to-be-discovered) mechanism to close the sublingual microcirculation to promote flow to more important vascular beds, such as the brain or the liver. As lactate was considered a pathologic process and waste product of shock state, there is evidence that lactate is an adaptive phenomenon to shock providing high octane fuel to the cell and promoting survival (6). In this issue of *Critical Care Medicine*, Wan and colleagues (7) add an important piece to the microcirculation puzzle. In a clean animal model of reduced cardiac output, they measured sublingual and cerebral microcirculation. They showed that, with the reduction of cardiac output, there is a closure of the sublingual but not the cerebral microcirculation. This work extends their previous work showing that not all forms of shock have an equal impact on microcirculation. Septic shock seems associated with worse microcirculatory alterations (8). In the present investigation, they induced cardiogenic shock by aortic banding. They observed a 50% decrease in cardiac output and perfusion pressure but no changes in cerebral microcirculation. This opens the door to further investigations looking at other vital organs, like the heart, liver or kidney, investigations in other physiopathological states, and the effect of hemodynamic therapies on microcirculations. The data from Wan et al are welcome but blur the picture a little bit more. From a good to bad scale of 0 to 3, we know now that not all physiopathological processes are equal and not all vascular beds are equal. The more we look inside the black box, the more complex it looks.

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Estrogen therapy for trauma/hemorrhage: The heart follows suit*

Therapies aimed at improving outcomes in patients with hemorrhagic shock continue to be at the center of resuscitation science research; however, the development of any pharmacologic agent or resuscitation strategy that achieves this goal continues to elude investigators and clinicians. The use of clinically relevant animal models in combination with *in vitro* investigations aimed at improving our understanding of both genetic and intra- and extracellular signaling mechanisms that take place in response to hemorrhage is essential to guide the development of therapeutic agents. One therapeutic agent in development that continues to hold great promise is estrogen. In this issue of *Critical Care Medicine*, Hsu and colleagues (1) present further support of 17β-estradiol as therapeutic agent for trauma with hemorrhagic shock and describe signaling mechanisms that lead to decreased inflammation in cardiac tissue and improved outcomes in cardiac function.

Despite inconsistent and confounding clinical studies that have examined the influence of gender on outcomes from a myriad of disease processes (2–4), including sepsis, burns, or hemorrhage, the use of estrogen as a therapy in such clinical conditions continues to show potential and requires more investigation. Work in experimental models of sepsis or hemorrhage convincingly illustrates acute intracellular signaling effects of estrogen that result in improved outcomes (5–7). The work by Hsu and colleagues (1) continues to tell this evolving story, most of which has been developed through investigations from Dr. I.H. Chaudry's laboratory.

The recognition of estrogen as a potential therapy for shock was born out of an observation that females tolerated sepsis better than males in an experimental model (8). Work on hemorrhagic shock soon followed (9). Subsequent work demonstrated survival benefits in females during the time of proestrus, when high circulating endogenous levels of 17β-estradiol are present (10). These initial investigations challenged the paradigm of estrogen as a hormone that primarily operated through genomic modifications, and the authors recognized the potential acute signaling consequences of estrogens in the context of acute injury and

*See also p. 2338.

Key Words: 17β-estradiol; trauma; hemorrhage; Akt; heme oxygenase-1; cardiac

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Microcirculation in distress: A new resuscitation end point?*

Sepsis is a disease of the microcirculation. The orchestra of pathogenic mechanisms unleashed during sepsis targets almost every aspect of the function of the microcirculation, leading to distress of the tissue cells and ultimately to organ dysfunction. Cellular properties of immune cells, red blood cells, and endothelial cells, as well as the functional properties of subcellular structures such as membranes and mitochondria, change dramatically under the influence of hypoxia and inflammation occurring during sepsis.

This pathology adversely affects vascular autoregulatory mechanisms and alters rheologic properties of blood (1, 2), thereby causing pathologic heterogeneous flow distribution of blood (3). This results in weak microcirculatory units becoming shunted and hypoxic, causing mismatch between oxygen need and oxygen supply of the cells by the microcirculation (4). Mitochondrial dysfunction has been demonstrated in septic patients (5) and is thought to contribute to disturbances in cellular oxygen utilization seen in sepsis (6). An intact functioning microcirculation, however, is an essential prerequisite for efficient oxygen delivery to the tissues cells. That is why correction of microcirculatory function is attributed to the beneficial effects of resuscitation procedures (7). It is thereby conceivable that the microcirculation itself may provide the needed (micro)hemodynamic end point for resuscitation from septic shock.

This microcirculatory view of the sequel of events in the pathogenesis of sepsis has until now largely been supported by experimental and indirect measurements in clinical investigations. The role of the microcirculation in the treatment of septic shock has been more a theoretical aim than a practical component of resuscitation of patients: that is, until now.

In the current issue of *Critical Care Medicine* Dr. Sakr and colleagues (8) present a study in which they examined the behavior of sublingual microcirculation of septic shock patients during the time course of their treatment and related these to the changes seen in global hemodynamic and oxygenation variables and to outcome.

The authors applied the orthogonal polarization spectral imaging technique to directly observe the flowing blood cells in the microcirculatory network of the sublingual microcirculation. Most important for their study, this technique allowed observation and evaluation of the blood flow in the smallest vessels of the microcirculation, the capillaries. Dr. Sakr and colleagues (8) investigated the sensitivity and specificity of the perfusion of these capillaries to predict outcome. They asked the important question: Is a persistent deficit in microcirculatory perfusion associated with poor outcome? If the answer would be yes, it would identify the microcirculation and the preservation of its function as a key component in the pathogenesis of sepsis and multiple-organ failure. It could further allow identification of patients who might benefit from resuscitation interventions aimed at recruitment of the microcirculation.

In previous sublingual orthogonal polarization spectral imaging studies in septic patients, De Backer et al. (9) as well as ourselves (10) observed that impairment of perfusion of sublingual capillaries but not of the larger microvessels characterized the microcirculation in septic shock patients, indicating the presence of shunting pathways in sepsis (4). De Backer demonstrated the importance of this impairment of capillary perfusion in sepsis by showing that it was related to poor outcome (9). In this study, however, sublingual microcirculatory measurements were only made early in the disease. To identify the central role of microcirculation in the pathogenesis of sepsis leading to multiple-organ failure, the authors would need to follow the progress of microcirculatory alterations in time, day by day. In the present study, Dr. Sakr and coworkers did just that.

Their carefully conducted study revealed three important findings: a) that capillary perfusion remains depressed in nonsurvivors, whereas in survivors capillary perfusion recovers within the first 24 hrs of treatment; b) that global hemodynamic and oxygen variables as well as the type and amount of therapeutic drug did not discriminate between survivors and nonsurvivors; and c) that persistent loss of capillary perfusion was the most sensitive and specific hemodynamic predictor of survival from septic shock in comparison to all variables measured with the exception of lactate.

The importance of assessing peripheral circulation in the management of septic shock was already appreciated in the late 1960s when Joly and Weil (11) presented their publication, "Temperature of the great toe as an indication of the severity of shock." Values obtained from gastric tonometry and recently also for strong ion difference measurements have been reported to provide more sensitive indicators for outcome in critically ill patients than do global hemodynamic and oxygenation variables (12–14). It would be interesting to compare the sensitivity and specificity of these indicators in the setting of Dr. Sakr and coworkers (8).

Besides the detail obtained about the heterogeneity in the microcirculation with respect to capillary and venule perfusion, the study by Dr. Sakr and coworkers (8) is distinguished by their investigation into the effect and role of time. Their finding that capillary perfusion, if not restored within 24 hrs, predicts bad outcome underscores the importance of early resuscitation and the conclusions of the Rivers et al. study (15). It also emphasizes that time itself is a pathogenic factor. De Backer et al. (10) showed previously that perfusion deficit of the capillaries could be reversed by topical application of acetylcholine. In an orthogonal polarization spectral study, we found that administration of the vasodilator nitroglycerin was able to reverse the stop-flow

*See also p. 1825.

Key Words: microcirculation; sepsis; orthogonal polarization spectral imaging; outcome; sublingual

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perfusion of the sublingual capillaries seen in septic patients (9). It would be interesting to know whether these procedures to recruit the capillaries are less effective later in time as microcirculatory dysfunction becomes irreversible.

The study of Dr. Sakr and coworkers (8) together with studies on the mitochondrial dysfunction in septic patients (5, 6) suggests that resuscitated sepsis should be regarded as a "microcirculatory and mitochondrial distress syndrome," where despite correction of systemic variables, microcirculatory and mitochondrial distress persist. In this model, time and therapy form part of the hit and define the pathogenesis and severity of disease. As the authors point out, trials with goal-directed therapeutic interventions targeting recruitment of the microcirculation are now needed.

With this important study, Dr. Sakr and coworkers (8) have truly identified the microcirculation as an important target organ in the pathophysiology of sepsis and its progress to multiple-organ failure. They have also shown that the microcirculation can be effectively monitored over days and that sustained capillary perfusion predicts survival. Will resuscitating the microcirculation provide a new, more sensitive end point for treatment? Future research will tell. But one thing is for sure: With this study, microcirculatory hemodynamics is here to stay.

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Do cultural differences in communication and visiting result in decreased family desire to participate in decision making?*

Dr. Azouley and colleagues (1) follow up on a long line of intriguing and important work related to family needs, family communication, and decision-making models in French intensive care units (ICUs) (2–6).

It has been demonstrated that anywhere from 10% to 50% of patients are not competent to make their own decisions in the ICU. Therefore, whether the family should be included in the decision making of an incompetent patient is important and timely (2, 4, 7–11).

The work of the FAMIREA group illuminates cultural and societal differences with which communication and decision making are handled. Canada, England, Sweden, France, and the United States all approach the issue differently (4, 12, 13). We are a mobile society, and the significance of societal/cultural differences is far from academic. Physicians from a country where the paternalistic method of decision making is widely accepted (such as France) may very well emigrate to a society where a shared decision-making model is favored (such as Canada or the United States). If a physician uses the paternalistic model, works as the guardian for the patient, and dictates care according to one's own values, we can envision the battle that would ensue when the physician is challenged by the staff, patients, or family accustomed to a more autonomous role. Conversely, patients emigrate from one society to another. In the United States, immigrants from Asian cultures present in the ICU requesting that the elderly competent patient not be burdened with or informed of the diagnosis of a terminal illness. The ethical question then arises: Do we respect the children's request to withhold information because it is the normative value in their culture? Or do we follow our own American societal value of the

*See also p. 1832.

Key Words: decision-making models; competence; communication

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inflammation. The work from the Chaudry laboratory that followed these initial observations has helped to illustrate these nongenomic signaling effects of estrogens and unravel the therapeutic potential of this hormone. In this latest investigation, the group pursues the potential benefit of 17β-estradiol in cardiac inflammation and function in the setting of trauma and hemorrhage.

The findings by Hsu and colleagues (1) are not wholly novel or unique when scrutinized as an individual work but should be viewed in the context of the entire body of work from this group investigating the pharmacologic delivery of exogenous 17β-estradiol as a therapeutic agent. To this end, the protective effects of 17β-estradiol in the setting of trauma and hemorrhage have been previously demonstrated, including beneficial effects on limiting cardiac inflammation and preserving cardiac function (7). Furthermore, the authors have previously illustrated that the salutary effects of this drug on trauma/hemorrhage-induced hepatic injury are dependent on activation of AKT (protein kinase B) and associated with the up-regulation of heme oxygenase (HO)-1 (11). Although the cell signaling pathway defined in the current work of Hsu and colleagues (1) is not unique from that previously demonstrated in the liver under the same experimental conditions, these findings provide new and specific insight into the signaling of this therapeutic agent in the heart. Based on disparate signaling in many tissues in response to like stimuli, it cannot be assumed that the signaling effects of a drug would be similar in different organs/tissues even under the same experimental conditions. These unlike responses can be multifactorial in origin and include factors such as differential expression of receptors/signaling molecules and the context of the local environment of the cell.

A reoccurring theme in the work from Dr. Chaudry's laboratory has been the important role of the inducible enzyme HO-1 in mediating the protective effects of 17β-estradiol in many of the tissues and cell types previously investigated. HO enzymes are the rate-limiting enzymes in the catabolism of heme into carbon monoxide, iron, and biliverdin (12). HO-1 expression is usually protective in the setting of inflammation and is known to be protective in the setting of hemorrhagic shock (13). Data suggest that HO-1, perhaps via the generation of carbon monoxide or via modulation of intracellular heme, is central in preventing and resolving inflammation and regulating homeostasis in cells under inflammatory stimuli. Dr. Hsu and colleagues (1) demonstrate that HO-1 protein is increased in the heart in response to trauma/hemorrhage and that this increase in HO-1 protein is exaggerated by 17β-estradiol. Furthermore, 17β-estradiol-induced HO-1 in the setting of trauma/hemorrhage is reversed by the PI3-K inhibitor wortmannin. The induction of HO-1 in response to trauma/hemorrhage has been shown by this group to be increased in proestrus females compared with other phases of the menstrual cycle (14). Previous work illustrates that 17β-estradiol fails to protect against cardiac injury and dysfunction from trauma/hemorrhage when HO activity is pharmacologically inhibited, suggesting at least a partial dependence on estrogen-regulated induction of HO-1 (7). These data should be carefully interpreted, because HO-1 itself is induced in response to trauma/hemorrhage in the absence of 17β-estradiol, and pharmacologic inhibition of HO activity alone in this setting can exacerbate injury, thus making it difficult to determine the dependence of 17β-estradiol on HO signaling. Although the group has illustrated in trauma/hemorrhage that pharmacologic inhibition of HO does not worsen cardiac dysfunction, these investigators have also shown exacerbated hepatic injury with HO inhibition compared with vehicle-treated subjects in this trauma/hemorrhage model (7). Interestingly, in the intestines, where 17β-estradiol has also been shown to be protective against trauma/hemorrhage-induced gut inflammation, there is an induction of HO-1 via p38 MAPK activation as opposed to PI3-K/Akt-dependent signaling (15). Together, these data suggest that HO-1 signaling is vital for 17β-estradiol to exert its protective effects. The mechanism by which this estrogen regulates HO-1 expression or activity in the setting of trauma/hemorrhage requires further tissue-specific investigation. Current investigations indicate that HO-1 signaling may represent a rudimentary, nonspecific intracellular response of cells that endogenous signaling pathways or pharmacologic therapies can converge upon to limit inflammation.

Hsu and colleagues (1) have added another chapter to the mounting story of this innovative treatment strategy that was born out of keen observation. Although the current literature suggests a pivotal role for HO-1 in mediating the protection afforded by 17β-estradiol in experimental models of shock, further investigations are sure to provide more insight into the beneficial effects of this therapy. We all look forward to further translational investigations and trials involving this promising therapeutic agent.

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Before we go too far: Ultrasound-guided central catheter placement*

One never goes so far as when one doesn't know where one is going.—Johann Wolfgang von Goethe (1749–1832)

An estimated 5 million central venous catheters (CVCs) are placed annually in the United States in a variety of settings, including intensive care units, emergency departments, operating rooms, and even outpatient settings. The frequency of mechanical complications during placement of CVC ranges from 5% to 19%, with such complications including arterial puncture, arterial cannulation, malposition, hematoma, and pneumothorax (1). In 1984, Legler and Nugent (2) published a brief report describing the use of Doppler ultrasonography to locate the internal jugular vein for cannulation. Since that time, two-dimensional ultrasound guidance has become an accepted, and now required, tool to improve success and to reduce the number of attempts required for venous cannulation. Ultrasound guidance is particularly helpful for novice operators.

In this issue of *Critical Care Medicine*, Blaivas and Adhikari (3) conducted a single-institution study to prospectively investigate the frequency of posterior wall penetration during ultrasound-guided CVC placement by emergency medicine residents with prior ultrasound training and CVC placement experience. The study protocol used a transverse approach with dynamic guidance for internal jugular cannulation on a life-size torso model (Blue Phantom, Kirkland, WA). The authors found a 64% occurrence rate of posterior venous wall puncture, a 20% occurrence rate of carotid penetration, and significant correlations with both years of training and experience using ultrasound for CVC placement (3).

This well-designed study provides four important messages. First, complications during ultrasound-guided CVC placement can occur. Second, an understanding of how these complications can occur under ultrasound guidance provides the operator with a mechanism to prevent their occurrence. Third, operator training and experience are important in determining the complications associated with this procedure. Fourth, simulations offer procedural practice that ultimately improves staff proficiency and enhances patient safety.

In regard to the first point, the rate of posterior complications in this study seems unusually high. Prior studies using real patients reported CVC complication rates of 4.6% (4). Sadler et al (5) reported a single venous wall puncture rate of 13.4% in real patients in contrast to the 64% found in simulated patients in the current study. It is our supposition that this complication, exemplified by getting a "flush of venous blood" upon withdrawal of the needle, is very common and perhaps even nearly universal in hypovolemic patients, although the clinical consequences remain entirely unclear. We expect that the number of posterior venous wall penetrations would be higher in patients who are dehydrated, are under respiratory distress, experience internal jugular vein collapse, or have a vein diameter <4–5 mm, but none of these conditions were found in the simulated procedures performed here (6). This high complication rate may be related to the inexperience of the operators (highlighting the need for additional practice), the failure to detect this complication in real life, or the simulated environment, which may in some way alter the operator's "feel" and increase the complication rate.

The second point is important particularly because these complications occurred under dynamic ultrasound guidance. One explanation for their occurrence is that the ultrasound beam is narrow (0.2–1.2 mm) and although the operator appears to be following the tip of the needle into the vessel, the tip has actually passed out of the ultrasound beam, and a cross section of the proximal part of the needle is now seen in the view (Fig. 1). In this circumstance, the tip may have already penetrated the contralateral wall of the vessel (Fig. 1). The authors discuss the benefits of using a longitudinal real-time approach for internal jugular cannulation, and this approach is also recommended by the American College of Emergency Physician (7). However, the ultrasound plane thickness compared with the needle diameter also makes it difficult to visualize the entire needle longitudinally. Partial visualization can occur and makes one vulnerable to the same phenomenon described previously for the posterior wall; namely, the operator is following the tip of the needle into the vessel, although the tip has actually passed out of the ultrasound beam, and a cross section of the proximal part of the needle is now seen in the view (Fig. 1). Only now, the lateral vessel wall has been unknowingly penetrated. Keeping the entire needle within the view is important and requires skill and practice, belaboring the procedure and causing frustration among novice and seasoned operators alike.

***See also p. 2345.**

Key Words: critical care; intensive care; central venous catheter; ultrasound guidance; bedside ultrasound; training; simulation in health care; patient safety

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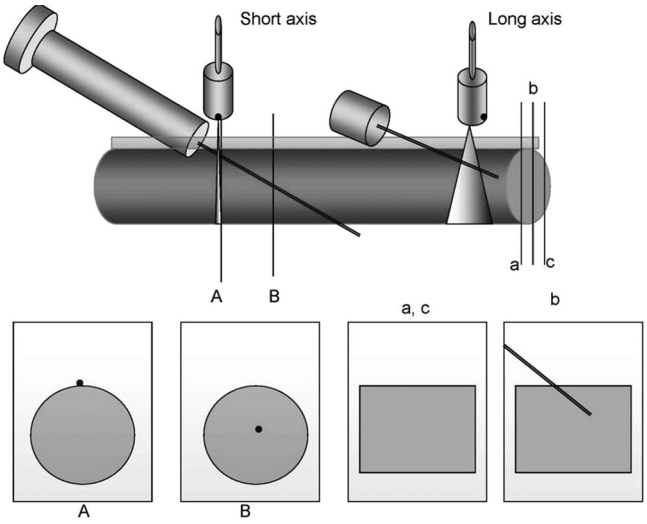

Figure 1. Difference between long- and short-axis guidance for central venous catheter placement.

Regarding the third point, multiple studies have demonstrated a negative correlation between the frequency of complications and operator experience (8). Attempts to look for new techniques to avoid those complications and to improve the efficiency and accuracy of CVC placement failed until the relatively recent introduction of ultrasound guidance. As the use of ultrasound at the bedside matures, best-practice guidelines regarding technique that are informed by well-designed studies will supplant our reliance on personal preferences. One of the most important points made by Blaivas and Adhikari (3) is the need to establish recommendations on training, competence, and proficiency in ultrasound use for diagnostic and therapeutic procedures including ultrasound-guided CVC placement. Our approach uses an educational program with three levels of competency that provides learners with the knowledge, skills, and aptitudes to effectively perform ultrasound at the bedside (9). In the absence of accepted guidelines, however, training will be highly variable and will introduce unnecessary variation into clinical practice, ultimately affecting our patients' safety. At least for now, the choice of axis for the guidance of CVC placement still depends mainly on the location of the vessel, operator experience, and personal preference.

As regards the fourth point, we appreciate the authors' use of simulation as a technique to teach and improve the skills of trainees of all different skill levels, while keeping our patients safe for high-risk procedures. Alternatives, including the possibility of performing such procedures on unembalmed, specially prepared cadavers in a manner similar to the protocol by Blaivas and Adhikari (3), will minimize patient exposure and provide the necessary information to inform and establish best-practice recommendations for ultrasound use. Pioneering efforts to validate the impact on simulation in health care, specifically CVC placement, are underway and will provide useful tools as we enhance the educational experiences of our trainees (10) and ensure adequate preparation before patient exposure.

Bedside ultrasound, as a component of the augmented physical examination, is an essential tool to improve the diagnostic and therapeutic activities in a number of venues. Its role in improving the safety and efficiency of CVC placement and other commonly performed intensive care unit procedures is increasingly being demonstrated. The contribution by Drs. Blaivas and Adhikari (3) helps us to improve our effectiveness as we establish best-practice recommendations, training requirements, and competency guidelines that will further improve safety for critically ill and injured patients.

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Cytomegalovirus reactivation and mortality during critical illness: A $64,000 question*

The pathogenicity of cytomegalovirus (CMV) has been appreciated for many years in immunosuppressed patients, but its potential in nonimmunosuppressed patients has only recently been recognized. From the time we and others first became interested in CMV during critical illness in the early- to mid-1990s, significant progress has been made. In this issue of *Critical Care Medicine*, Kalil and Florescu (1) present an intriguing meta-analysis of available data that provides several important insights into this potential disease process.

Although it is now indisputable that CMV reactivation can occur during critical illness, the actual incidence of reactivation has been confounded by several factors. First has been use of variably sensitive monitoring techniques. For example, during our early work, we felt that it was critical to demonstrate live virus, using less sensitive but highly specific culture methods (2, 3). The current meta-analysis confirms what we know from immunosuppressed patients: cultures grossly underestimate the incidence of viral activity. Thus, similar to immunosuppressed patients, CMV antigen or DNA methods seem comparable and most sensitive to monitor CMV in intensive care unit (ICU) patients.

A second confounder confirmed by the authors is timing of monitoring. It is now known that CMV displays delayed kinetics in both transplant patients (4) as well as ICU patients (5). In animal models, CMV transcriptional reactivation can be detected as early as 1 wk after stimulation, but these approaches utilize whole organ homogenates (6). It is therefore not surprising that, when monitoring is performed <5 days after ICU admission, detection of reactivation is extremely infrequent (~1%). Unfortunately, there are insufficient data for the authors to determine how frequently patients should be monitored for reactivation, but the proposal for twice-weekly monitoring of CMV antigen or DNA seems reasonable.

A final confounder of incidence relates to defining who is at risk. Previous data have suggested that *de novo* CMV infections in critically ill patients are quite uncommon (2, 5). Because CMV infections are lifelong and most adults harbor latent CMV (7), it has been hypothesized that most CMV in ICU patients is reactivated virus. Data from the current report show that latently infected patients identified by serology (IgG) and monitored with sensitive techniques have CMV rates of 26% to 47% (1). This is substantially higher than general ICU populations containing both CMV positive and naïve patients. Thus, the current report helps solidify the hypothesis that most CMV during critical illness is reactivated from latency, and emphasizes that roughly one third of latently infected patients reactivate during their ICU stay.

In addition to latent infection, there were several additional risk factors associated with CMV reactivation. The current study suggests that patients with sepsis/severe sepsis are at increased risk for reactivation. This association is consistent with previous reports as well as animal data that show CMV reactivation after bacterial sepsis or inflammation (6, 8, 9). Further, there seems to be an important association with severity of illness, as patients with "high" severity show significantly higher reactivation rates than those with "low" severity. It therefore seems reasonable to direct future attention at patients at highest risk for reactivation, particularly those with sepsis or high severity of illness as the authors and others have suggested.

The most important observation in the current report is the association of CMV reactivation with mortality in ICU patients. With the exception of recent data from Limaye et al (5), previous studies have been too small to demonstrate convincingly an associated mortality influence (2, 3, 10–14). Nonetheless, when raw mortality rates from these small studies are plotted, there is a striking consistency in mortality, despite differences in methods of detection (Fig. 1). This gross relationship is confirmed by proper statistical analyses in the current report, showing nearly doubled mortality risk for patients with reactivation (1). When one considers the myriad potential pathogenic mechanisms associated with CMV, including pulmonary injury (15) and immune modulation (16), the possibility that CMV contributes to poor outcomes in very sick ICU patients becomes very plausible.

We are therefore at a crossroads and must determine our next step: proceed with yet another epidemiologic trial in an attempt to further narrow down the "at-risk" population as Kalil and Florescu suggest (1), or begin testing pathologic causality with antiviral therapy. Can an at-risk group be further narrowed to prevent treatment in some patients not destined to reactivate? It is interesting to note that, after identifying latently infected patients by IgG screening, narrowing the field further by including severely ill or septic patients did not appreciably improve detection of reactivation (1). It is, therefore, our opinion that sufficient "due diligence" has been done and that further epidemiologic studies will only delay answering the important causality question.

It must be emphasized that, despite animal data suggesting that sepsis-induced reactivation can be prevented with antiviral therapy (15), there are currently no good data to support or refute antiviral treatment in nonimmunosuppressed ICU patients. Thus, for now, there is clinical equipoise. Of significant concern, the recent flurry of manuscripts on this topic both in this journal and

***See also p. 2350.**

Key Words: cytomegalovirus; cytomegalovirus; reactivation; infection; critical illness

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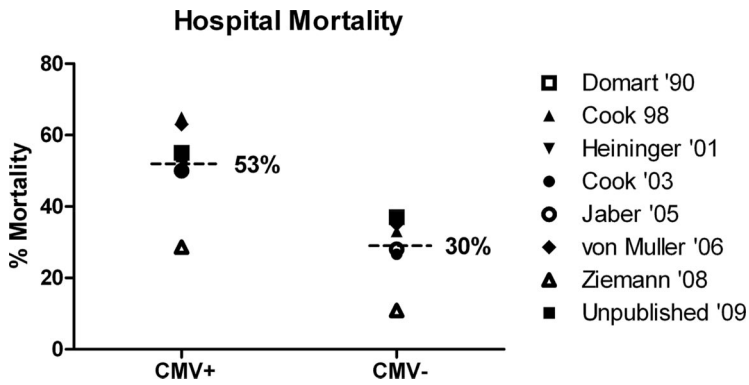

Figure 1. Raw hospital mortality in critically ill patients with cytomegalovirus (*CMV*).

others (1, 5, 13, 14, 17, 18) may soon prompt practitioners to take matters into their own hands and begin filling this void with anecdotal treatment data. Although Kalil and Florescu raise valid arguments that treatment trials at this juncture may expose approximately two of three patients to unnecessary antiviral therapy, this rationale alone would preclude many currently accepted but far less efficient therapies for sepsis. Unfortunately, properly controlled trials may be the only way to determine risks and benefits of antiviral treatment in this patient population.

In conclusion, although there may be some disagreement as which direction to proceed, it is clear that CMV can no longer be ignored as a potential pathogen in nonimmunosuppressed patients during critical illness. In the old game show, $64,000 Question, questions posed became progressively more difficult to answer. With the current report, many easier questions of CMV reactivation during critical illness have now been firmly answered. It seems that the $64,000 question remaining is how much of the mortality associated with CMV reactivation, if any, is attributable to CMV. It is this author's opinion that the time has come to answer this question by carefully performed treatment trials.

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Regional occult hypoperfusion detected by lactate and Sequential Organ Failure Assessment subscores: Old tools for new tricks?*

The significance of persistent occult hypoperfusion in the development of multiple system organ failure and death has been described and, no doubt, needs further elucidation.

Visible hypoperfusion, either as shock or as hypotension, and visible hypovolemia have been treated actively in critically ill patients during the past decades to decrease the incidence of multiple organ dysfunction syndrome (MODS), although not always with great success (1). Therefore, an increasing number of researchers have proposed a role for occult hypoperfusion in the pathophysiology of MODS, especially in those cases where visible hypoperfusion has been treated correctly (2).

Occult hypoperfusion has been associated with an increased mortality rate despite the normalization of visible hypoperfusion (2, 3). It is well known that MODS, an important cause of morbidity and mortality, occurs despite correction of visible hypoperfusion in many conditions, including sepsis (4) and systemic inflammatory response syndrome induced by multiple trauma, burns, severe acute pancreatitis, bypass, and other conditions (5). Blood lactate level has been associated with the occurrence of organ failure using several organ failure scales and is potentially a reliable marker of persistent occult hypoperfusion (6). Nevertheless, the relationship between lactate levels and the Sequential Organ Failure Assessment (SOFA) score (7) has not been studied until now, particularly in occult hypoperfusion.

In this issue of *Critical Care Medicine*, Jansen and colleagues (8) hypothesize that blood lactate measurement may act as a real-time marker for the severity of organ failure compared with SOFA, because SOFA is scored over a period of 24 hrs and comprises subscores from six different organ systems. As a consequence, it would be possible to evaluate the association of lactate with the separate organ subscores, including the cardiovascular subscore. The final aim of Jansen and colleagues' study was to evaluate whether the level and duration of increased blood lactate levels (represented by the area under the lactate curve) were associated with daily SOFA score and its separate organ subscores in order to evaluate whether these associations were also time-dependent. The investigators concluded that both the duration and the level of hyperlactacidemia estimated the risk of organ failure. Furthermore, the authors concluded that of all individual SOFA organ systems, the respiratory and coagulation subscores were most strongly associated with lactate.

The study by Jansen and colleagues (8), although very well conducted in terms of both methodology and adjustment for confounding factors, has certain important limitations. The design is observational and retrospective, thereby rendering the conclusions more suggestive than truly definitive, and the intensive care population studied is heterogeneous. No measurements are presented of regional lactates that could further confirm the relationship between individual organ systems and global lactate, and no mention is made of metformin use in any patient, a documented cause of lactic acidosis that is certain to influence measured lactate values. Furthermore, the authors did not try to correlate lactate with other markers of global or regional occult hypoperfusion. Several recent investigations have suggest that strong ion gap (SIG) could be a better marker of regional occult hypoperfusion than is lactate (9, 10). Although recovery from cardiac arrest may differ from recovery after severe shock, there are certain similarities and therefore the studies on SIG after cardiac arrest (9, 10) can be taken into account in this comparison. SIG is possibly useful not only for measurement of anions but also as a surrogate marker for tissue damage (sometimes very locally) and as well an early and more specific predictor of outcome compared with traditional acid-base quantification and even lactate. Recent studies in general intensive care populations have demonstrated SIG to be an independent prognostic factor for mortality even in the presence of a normal acid-base status as traditionally described using the Henderson-Hasselbalch equation (11).

Jansen and colleagues (8) suggest that lactate can be seen as a marker for ongoing inflammatory disease, especially in the lung rather than for tissue hypoxia itself (8). Along the same lines, Funk et al (10) suggested that unmeasured anions constituting SIG may be seen as surrogates of tissue damage even before lactate, when lactate was generated through tissue hypoxia. Jansen and colleagues postulate that regional lactate could be seen as a surrogate marker reflecting metabolic adaptation in response to inflammatory mediators (8). Other authors have tried to correlate local inflammatory mediators with surrogates markers like lactate and even unmeasured anions (10), although, until now, the relationship between metabolic acidosis, unmeasured anions, and mediators released has been unclear (12).

Several authors have studied other scores for early detection of occult hypoperfusion. Schulman et al (13), conducting a prospective cohort study, demonstrated that the Injury Severity Score in patients with multiple trauma was an independent predictor of occult hypoperfusion and subsequent higher risk of MODS and death. More recently, it has been shown that a high Injury Severity Score in patients with multiple trauma and in occult hypoperfusion lasting >12 hrs is an independent risk factor for infection, another potential source of MODS and in

*See also p. 2369.

Key Words: occult hypoperfusion; lactate; scores; multiple organ dysfunction syndrome; organ failure; hemofiltration; review

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some cases a cause of death (14). Jansen and colleagues have (8) shed more light on the interesting idea that each organ should be treated individually regarding organ failure risk associated with occult hypoperfusion via adequate regional volume loading in order to avoid excessive volume in the lung or in the abdominal compartment, although for now this remains hypothetical.

In the absence of an accurate tool to detect occult underresuscitation, aggressive treatment of occult hypoperfusion without minimizing the risk of excessive volume loading in some organ targets remains the clinical practice. Recent studies using continuous monitoring systems, such as the Licox polarographic tissue (muscle) oxygen monitor and the InSpectra near-infrared spectrometer, demonstrated that myocardial Po_2 and hemoglobin oxygen saturation were promising candidates for the early detection of occult underresuscitation (15, 16).

The study by Jansen and colleagues (8), although retrospective in nature, sheds new light on the role of lactate and SOFA subscores as markers of outcome after severe shock, especially in multiple organ dysfunction syndrome. Other markers like SIG or scores like the Injury Severity Score might be worthwhile candidates for early detection of occult hypoperfusion. Markers such as lactate and SIG could also be viewed as indicators of regional damage in persisting inflammation rather than occult hypoperfusion solely. However, these conclusions should be challenged in further controlled and well-conducted studies. An era of novel use of established markers and scores is upon us and may be seen as a revolutionary step in the early detection of occult hypoperfusion, while we await the development of new tools to monitor occult underresuscitation continuously. The speed of change that we can expect is unknown.

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Grading intensive care unit performance—Does one size fit all?*

The Institute of Medicine report, "To Err Is Human" (1), has been a transformative force in health care, and has placed quality measurement and quality improvement at the center of healthcare reform in the United States. The healthcare system has been characterized as "fragmented, unsafe, and inefficient" (2). Quality measurement will play a critical role in redesigning health care for the 21st century. As the emphasis placed on performance measurement has grown, improving the quality of quality measurement has moved to the top of the research agenda (2).

Risk adjustment is at the heart of quality measurement. It is impossible to compare the performance of intensive care units (ICUs) without accounting for differences inpatient case mix. The three major ICU risk adjustment models—Acute Physiology and Chronic Health Evaluation (APACHE) (3, 4), Simplified Acute Physiology Score (SAPS) (5–7), and Mortality Probability Models (MPM) (8, 9)—were all designed for use with heterogeneous patient populations. In other areas such as cardiac surgery, separate condition-specific models are used, depending on the surgical procedure (coronary revascularization vs. valve surgery). Intuitively, it is reasonable that the selection of patient-level risk factors and the weighting of risk factors in a risk-adjustment model would be expected to vary across different patient populations. Previous work has shown that the predictive performance of ICU risk-adjustment models—model calibration—deteriorates when they are tested in homogeneous patient populations (10). In particular, ICU risk-adjustment models tend to either over- or underestimate mortality when they are applied to specific patient subgroups (10). When a model overestimates the predicted mortality rate for a particular patient population, such as elective surgical patients, ICUs with a higher proportion of such patients will have a higher expected mortality rate, and thus, a lower observed-to-expected mortality rate ratio. In theory, it is possible for ICUs with case-mixes different from the average ICU to seem better or worse than their comparison group simply because of the performance of the risk-adjustment model, unrelated to actual differences in quality of care.

In this issue of *Critical Care Medicine*, Nathanson and colleagues (11) have explored whether the quality ranking of ICUs in the Project IMPACT database changes when subgroup models based on MPM-III, but customized to specific subgroups of patients (e.g., trauma, neurosurgical patients), are used for risk adjustment instead of a single general mortality probability model (MPM-III). As have others, they find that MPM-III also overestimates mortality in certain patient groups, and underestimates mortality in other groups. For each ICU in this sample of 135 ICUs and nearly 125,000 patients, they calculated the expected mortality rate by either using MPM-III on all patients, or using the subgroup models to predict the expected mortality rates for patients in each of the subgroups. They found that the use of subgroup models yields virtually identical observed-to-expected mortality ratios, irrespective of whether MPM-III or subgroup models based on MPM-III are used to assess overall ICU quality. This is a striking finding which has broad implications for quality measurement in general ICUs. In theory, hospital performance measurement may be biased, even after risk-adjustment, by differences in case-mix across hospitals. In practice, Nathanson and colleagues have shown that MPM-III does not lead to case-mix bias in this large sample of ICUs.

Although considerable emphasis has been placed on risk-adjustment, the Achilles heel of quality reporting may be the problem with sample size and the rarity of outcome events—hospital caseloads may actually be too low to detect clinically important quality differences across hospitals. Annual hospital caseloads for many of the most common high-risk surgical procedures are inadequate to detect even a doubling of mortality rates across hospitals (12). These findings suggest that quality measurement is a very blunt instrument for detecting quality problems. The elegant study by Dimick and colleagues (12), based on a simple power analysis, suggested that even with "perfect" risk-adjustment, we may be incapable of identifying the worst hospitals. This has led to the search for outcomes with event rates that are higher than simple mortality (e.g., complications or composite end points, such as mortality and complications) to be better able to distinguish between high- and low-quality hospitals. The problem with this approach is that the use of complications as an outcome measure is much less reliable than mortality because variation in hospital performance based on complication rates may reflect differences in coding practices across hospitals, rather than true differences in quality.

An alternative approach to solving the "case load problem" is to construct a composite mortality measure based on mortality outcomes for several high-risk procedures. Reasoning that the unobservable object of interest, quality, is likely to be similar in a single ICU, we group together many different patient populations for the purposes of quality measurement. Nathanson and colleagues show that the use of subgroup ICU models leads to the same quality assessment obtained with a single ICU model. Outside the ICU, where the use of a single risk adjustment model for diverse surgical procedures may lack face validity, separate risk-adjustment models can be used to estimate the expected mortality rates for patients undergoing high-risk procedures (e.g., coronary artery bypass graft surgery, aortic valve surgery, mitral valve

*See also p. 2375.

Key Words: outcome assessment; quality of care; quality assurance; statistical models; health services research; report card

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surgery, major vascular surgery, neurosurgery, esophageal surgery). Using separate risk-adjustment models provides the flexibility of including different risk factors, depending on the surgical procedure. The observed and expected mortality rates could then be aggregated to create a single observed-to-expected mortality ratio to produce jointly a hospital quality metric for several high-risk procedures. The work of Nathanson and colleagues challenges us to explore the feasibility of such an approach to quality measurement. From the group which championed the use of surgical volume as a proxy for hospital quality (13, 14), we are told that "operations for which surgical mortality has been advocated as a quality indicator are not performed frequently enough to judge hospital quality" (12) using conventional quality metrics. The work by Nathanson and colleagues suggests a simple solution to the problem posed by small sample sizes for patient populations outside the ICU.

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Ministering to the dead in critical care medicine: Has its time come?*

The occurrence of brain death unleashes a catecholamine surge, resulting in intense vasoconstriction, hypertension, tachycardia, and an increased myocardial oxygen demand (1, 2). Subsequently, there is loss of sympathetic tone and secondary cardiovascular collapse, which are further compounded by hypovolemia. Aggressive resuscitation is required to maintain adequate tissue perfusion and organ function. Furthermore, experimental and clinical data show that an intense inflammatory response occurs rapidly after brain death. This systemic inflammatory response further compromises cardiovascular stability and is also implicated in poor recipient outcomes (3). The association of hemodynamic instability and an increased inflammatory response observed in deceased donors demands further investigation into the mechanistic aspects of this response (4, 5). Such investigations would have the potential to improve organ donor management and ultimately provide more and better quality organs from deceased donors. In this issue of *Critical Care Medicine*, Murugan and colleagues (6) address this area. Following their earlier observation that increased circulating levels of interleukin-6 in deceased donors were associated with shorter hospital-free survival after transplantation (7), Murugan and colleagues (6) investigated whether preload (volume) responsiveness is associated with increased inflammation and decreased organ yield per donor. Earlier data from animal experiments showed that uncorrected hemodynamic instability could hasten and worsen immune activation (5). The observations from the current pilot study support the notion that hypovolemia in deceased donors might aggravate the systemic inflammatory response.

Given that overzealous fluid administration could compromise cardiopulmonary function in some donors, accurate identification of who needs additional fluids and who does not is paramount. Conventional static cardiovascular monitoring variables, such as central venous

***See also p. 2387.**

Key Words: preload responsiveness; donor resuscitation; deceased donors; donor inflammation; organ recovery; organ transplantation; critical care

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pressure and pulmonary artery occlusion pressure, may not provide an accurate assessment. Cardiac preload is quite sensitive to changes in intrathoracic pressure brought about by mechanical ventilation, and these variations translate into systolic and pulse pressure variations. The accuracy and utility of measuring pulse pressure variation as an indicator of the need for volume resuscitation are well substantiated in the literature. The threshold value of >13% variation chosen by the investigators appears to be in line with the literature (8). They provide evidence that preload responsiveness was associated with the systemic inflammatory response as characterized by cytokine release, predominantly interleukin-6 and to a lesser degree tumor necrosis factor-α. More important, they show that preload responsiveness and increased interleukin-6 levels were associated with decreased organ yield per donor. The potential ramification of their observations is that appropriate fluid resuscitation in deceased donors could decrease systemic inflammation and result in increased organ recovery.

As is often the case with clinical investigations, some important confounders must be considered. Increasing donor age and hypertension are associated with decreased organ yield. Donor age ≥60 by itself characterizes an extended criteria kidney donor. Similarly, donor age is an important component of donor risk index for liver donors (9). Furthermore, aging is associated with a heightened inflammatory state (10). Using univariate analyses the investigators show an association between preload responsiveness and cytokine levels. On the other hand, donor age bore no association despite the preload responsive donors being nearly 10 yrs older than unresponsive donors. Could this be an effect of sample size rather than a true lack of association? The multivariate analyses provided by the authors in Table 4 of their article brings into focus the potential quadrangular association between donor age, inflammatory cytokines, preload responsiveness, and organ yield. It is hard to resist asking whether increasing donor age, which decreases organ yield and could heighten the inflammatory state, could be a confounder. It would have been easier to discount the effect of donor age as a confounder had preload responsiveness emerged as a significant independent variable in the investigators' multivariate analyses. Nevertheless, their findings in this small pilot study are very provocative and merit substantiation by additional and larger studies.

This brings us to the future. Like several good research studies, the work of Murugan et al (6), while answering some questions, raises additional questions for further enquiry. An important question is whether hypovolemia is important in initiation and/or perpetuation of the ubiquitous inflammatory response in deceased donors. Perhaps even more important is whether attenuation of the inflammatory response in deceased donors ultimately increases organ yield and quality. Thus, additional prospective and adequately powered, controlled studies are needed that include fluid resuscitation as an intervention and measure outcomes in terms of inflammatory response variables, organ yield, and organ function after transplantation. It is encouraging to note that in a recent clinical trial, high-dose steroids not only ameliorated the donor inflammatory response but also decreased liver graft reperfusion injury and acute rejection (11). Thus, mounting evidence indicates that aggressive and judicious donor resuscitation along with other evidence-based interventions after brain death is vital to the organ donation and transplantation effort. Yes, the time has come.

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Optimizing the shape of defibrillation shocks*

To work efficiently, the cardiac pump relies on a coordinated electrical activation of its contractile components. Optimal timing of the contraction and relaxation of the cardiac chambers is achieved by sequential electrical activation of the constituting cardiomyocytes, starting from a group of autonomic pacemaker cells in the right atrium, spreading over the atria, and propagating to the ventricles with appropriate delays by the specialized system of conducting fibers. However, the normal electrical activation pattern may be disturbed and replaced by a rapid, seemingly irregular, and unsynchronized pattern commonly referred to as *fibrillation*. Fibrillation may be limited to the atria, a rather common form of arrhythmia that is often asymptomatic and not life-threatening (although an unfavorable condition, particularly given the increased risk of stroke). Much more severe is ventricular fibrillation that causes acute pump failure, cessation of blood circulation, and death within minutes (sudden cardiac death). Although ventricular fibrillation in most cases occurs secondary to myocardial infarction and in patients with existing cardiac conditions, this lethal arrhythmia may also occur in apparently normal hearts (idiopathic ventricular fibrillation), presumably is related to specific ion channel abnormalities.

Pharmacologic remedies to terminate ventricular fibrillation are not available, and defibrillation by electric shock remains the only effective therapy. Starting with early experiments using high-voltage shocks applied directly to the myocardium and large capacitor discharges across the closed chest, the search for the most effective defibrillation strategy is still ongoing (1). The main aim of shock delivery obviously is successful defibrillation (2). Preferably this should be achieved with rapid and stable return of normal contraction-relaxation and with minimal permanent myocardial damage. With the advent of implantable defibrillators, minimizing energy requirements also became a highly relevant issue. Ideally, optimization of defibrillation shocks should be based on, or at least guided by, a clear understanding of the mechanism of defibrillation. However, multiple, partly conflicting theories exist (3, 4), and although recent technical advances such as optical mapping (5) and sophisticated computer modeling (6) provided better insights and tools to test the various hypotheses, the debate is not closed (7). In practice, the search for optimal shock strategies has been largely empirical, via testing of numerous defibrillator waveforms in animal experiments and clinical studies. Efficacy is defined by the ability of a shock to terminate an (induced) episode of ventricular fibrillation and is typically measured as the number of successful shocks divided by the total number delivered. Most studies implicitly assume that shock-induced contractile dysfunction and myocardial damage scale with total delivered energy and therefore minimize energy by limiting the amplitude or the duration of the shock. In this issue of *Critical Care Medicine*, Tsai and colleagues (8) describe their efforts to unravel which specific component of the defibrillator shock relates most closely to postshock contractile impairment. To address their hypothesis, which is that peak current rather than total energy is the main factor, they applied biphasic triangular and square waveforms with varying amplitudes and durations (10 or 20 msecs) to isolated, beating cardiomyocytes from adult male rats. To this end, the isolated cells were placed in a Tyrode's solution bath and paced at 0.5 Hz. The mechanical function of the cells was monitored by a microscope video system and quantified by percentage length shortening. In addition, recordings reflecting intracellular Ca^{2+} concentration were obtained by the Fura-2 method (9). Postshock, the cell (a) were dead, (b) had irregular beating and/or reduced shortening, or (c) had been rapidly restored to regular beating and baseline function. The latter was defined as length shortening more than half of baseline. The authors tested 10 different shocks with triangular or square waveforms and peak voltages ranging from 25 to 100 V. Each different shock was applied in approximately 30 cells (each cell was shocked only once). As main outcomes, the authors reported the percentage of cells that died or showed loss of regular beating; the percentage of cell length shortening at 10 secs, 2 mins, and 4 mins postshock; and the associated intracellular Ca^{2+} abnormalities. By comparing shocks with the same energy but different peak currents on the one hand and shocks with the same peak current but different energies on the other hand, the authors reached the conclusion that peak current plays a more determinative role in postshock contractile dysfunction than does energy.

The authors are to be complimented for an original and carefully performed study. Their effort to isolate one part of the complex defibrillation puzzle and to solve it in a series of well-controlled experiments is highly appreciated. However, there are some limitations that seem worth mentioning to put the findings in better perspective. First, by using single-cell preparations, the authors obviously could not address questions regarding defibrillation efficacy of the studied waveforms. The authors argued that these isolated cells were subjected to similar conditions as cells in the intact heart during "normal" effective defibrillation shocks by showing that the applied voltage gradients were in the same range. However, it remains questionable whether a single cell floating in a well-conducting Tyrode's solution experiences the same transmembrane currents and disruptive forces as a cell embedded in the myocardium. Another related issue is that the orientation of the cells was not controlled in this study: It is very conceivable that cell orientation longitudinal or transverse to the applied electric field greatly modulates the harmful effects (10). Second, the authors only tested triangular and square waveforms and thus could not optimally assess independent effects of waveform "shape" because comparing shocks with the same energy but different peak currents also implied comparing different shapes (dV/dt), and vice versa. More in gen-

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eral, clinical practice more complex waveforms such as truncated exponentials are used (11) and may be substantially more effective (12). Third, temporary postshock dysfunction and temporary abnormalities in calcium transients were used as outcome variables. Ultimately, what counts is whether successful defibrillation is obtained with shocks that avoid or limit permanent damage. Although it may seem plausible, it was not proven that these outcome variables were associated with the occurrence of permanent damage.

Despite these limitations, the study by Tsai and colleagues (8) provides useful information in the quest for more effective and less harmful defibrillation strategies, which are of critical importance in daily clinical practice.

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Sepsis, ghrelin, the cholinergic anti-inflammatory pathway, gut mucosal hyperpermeability, and high-mobility group box 1*

Ghrelin is a 28-amino acid orexigenic (appetite-stimulating) peptide hormone that is secreted mainly by a distinct subset of cells lining the gastric mucosa (1). Initially discovered by Kojima et al (2) in 1999, the peptide's odd-sounding name comes from an Indo-European root, *ghre*, which means "to grow" and the suffix, (*l*)*in*, commonly used for polypeptide hormones (e.g., insu*lin*, moti*lin*, vasopress*in*). Two forms of ghrelin circulate in the bloodstream: acyl ghrelin, which is esterified with an O-*n*-octanoyl moiety linked to the serine residue in position 3 of the peptide, and des-acyl ghrelin, which lacks the post-translational modification (2). Most of the ghrelin in the circulation is the des-acyl form (1).

Ghrelin, in its acylated form, is an endogenous ligand for the growth hormone secretagogue receptor 1a (GHS-R1a) (3). Although it is a potent secretagogue for growth hormone (GH) in both animals and people, ghrelin also possesses other notable biological activities. For example, circulating ghrelin increases appetite in humans and feeding behavior in animals, an effect that depends on the activation of vagal afferents in the stomach as well as two key orexigenic mediators in the central nervous system: neuropeptide Y and agouti-related peptide (3). Ghrelin also increases gastrointestinal motility, and down-regulates the expression of key proinflammatory mediators, including interleukin-1β, interleukin-6, and tumor necrosis factor, by immunostimulated monocytes and T cells (4).

Ghrelin is a hot topic in biology and medicine. On March 1, 2009, a PubMed search, using *ghrelin* as the only key word, yielded 3,370 articles. Given its known activities, it is not surprising that ghrelin is hugely interesting to scientists and clinicians interested in obesity, anorexia, cachexia, or derangements of gastrointestinal motility. In addition, ghrelin is becoming an important topic for biologists of all stripes who care about sepsis as a clinical problem. In this issue of *Critical Care Medicine*, Wu and colleagues (5) from the Department of Surgery at North Shore University Hospital and Long Island Jewish Medical Center and the Feinstein Institute for Medical Research, provide the latest addition to this burgeoning field.

Using a well-accepted model of sepsis in rodents, namely cecal ligation and puncture, Wu and colleagues (5) obtained data that support the following conclusions: 1) sepsis is associated with gut epithelial barrier dysfunction, as evidenced by increased mucosal permeability to a hydrophilic tracer and increased bacterial translocation to mesenteric lymph nodes; 2) sepsis is associated with increased circulating levels of the cytokine-like protein high-mobility group box 1 (HMGB1);

***See also p. 2421.**

Key Words: ghrelin; orexigenic peptide hormone; acyl ghrelin; des-acyl ghrelin

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3) treatment with ghrelin, whether administered peripherally by intravenous infusion or directly into the central nervous system by intracerebroventricular injection, decreases circulating HMGB1 levels in septic rats and ameliorates sepsis-induced gut barrier dysfunction; and 4) truncal vagotomy abrogates the salutary effects of ghrelin on circulating HMGB1 levels and gut barrier function in septic rats.

It is worthwhile to review what is not new—and then what is—in the article by Wu and colleagues (5):

First, the notion that sepsis is associated with derangements in gut barrier function already is well-accepted based on results from studies carried out using reasonable animal models (6–8) as well as data from clinical investigations (9, 10).

Second, it is well-established that circulating HMGB1 levels are significantly elevated in septic patients (11–13) as well as septic rodents (14–16). As the readers of *Critical Care Medicine* undoubtedly know, HMGB1 is a small DNA-binding protein that is passively released by necrotic cells (17) and actively secreted by immunostimulated macrophages and monocytes (18, 19), pituicytes (20), endothelial cells (21), and enterocytes (22). HMGB1 is an *alarmin*, meaning it is an endogenous compound that serves as a danger signal to activate the innate immune system (23). Therapeutic agents that inhibit the secretion of HMGB1 (14, 24, 25) or neutralize its effects (15) have been shown to improve survival in septic animals, even when treatment is started as long as 24 hrs after the onset of infection.

Third, in two previous, important reports, Wu and his colleagues (26, 27) showed that treatment with exogenous ghrelin down-regulates the release of certain proinflammatory cytokines (tumor necrosis factor and interleukin-6), ameliorates organ system (lung) injury, and improves survival in rodents with sepsis induced by cecal ligation and puncture. Furthermore, this group previously documented that vagotomy abrogrates the anti-inflammatory effects of exogenous ghrelin administration in the setting of severe sepsis (27). In other words, the *in vivo* anti-inflammatory effects of ghrelin seem to be mediated via the vagus nerve. This latter notion is entirely plausible given the seminal work of Kevin Tracey (28), who has shown that the central nervous system plays a pivotal role in the regulation of immune responses by means of a vagally mediated system called the "cholinergic anti-inflammatory pathway." Indeed, we now know that a number of agents, including CNI 1493 (semapimod) (29, 30), anisodamine (31), and galantamine (32), exert anti-inflammatory effects *in vivo* by stimulating vagal efferent firing.

Fourth, recent work by Chorny et al (16) established that administration of exogenous ghrelin down-regulates circulating HMGB1 levels in rodents with acute endotoxemia or cecal ligation and puncture-induced sepsis.

From the preceding, it is apparent that some of the findings in the current article by Wu and colleagues (5) merely confirm earlier work from this same group of investigators or other research laboratories. But these investigators make two key observations that are entirely new and quite important. The first is the link between ghrelin's ability to activate the cholinergic anti-inflammatory pathway and its ability to suppress HMGB1 secretion. The evidence supporting this link is robust and the finding is completely novel.

The second key observation by Wu and colleagues (5) is that sepsis-induced gut barrier dysfunction is significantly ameliorated by administration of ghrelin, irrespective of whether the peptide is infused into the bloodstream or injected directly into the central nervous system. Because we know that HMGB1 is capable of increasing intestinal epithelial permeability (22, 33) and we know that ghrelin inhibits sepsis-induced HMGB1 release (5, 16), it is tempting to conclude that ghrelin prevents gut barrier dysfunction in sepsis by blocking the secretion of HGMB1. But drawing this conclusion would be moving too far out in front of the data. Although down-regulated secretion of HMGB1 might be one factor contributing the salutary effects of ghrelin on intestinal epithelial barrier function, it is entirely reasonable to hypothesize that blunted secretion of other cytokines is also important. Because the gut is vagally innervated, a direct effect of the cholinergic anti-inflammatory pathway is a potential mechanism as well.

Although ghrelin is a naturally occurring ligand for GHS-R1a, a large number of synthetic compounds are also GHS-R1a agonists. One of these compounds, KP-102 (*GHRP-2*: pralmorelin), is being evaluated clinically in Japan as a treatment for short stature in children. Does it make sense to carry out a clinical trial of the ghrelin mimetic, KP-102, as an adjuvant treatment for severe sepsis? The answer to this question is perhaps. At a minimum, however, we should be cautious about undertaking such a study, because ghrelin and ghrelin mimetics stimulate GH secretion and because treatment with exogenous GH worsens outcome for critically ill patients (34). Rather than using KP-102 or some other ghrelin mimetic (or authentic human acyl ghrelin) as a single agent, we might be better advised to use a combination of a GHS-R1a agonist with thyroid-releasing hormone. In an elegant single-center trial, van den Berghe et al (35) showed this approach to have beneficial effects on metabolism and body composition in critically ill patients, although immunologic responses to this hormonal therapy were not studied. Based on this and other work by van den Berghe and her associates, recently published work from studies of ghrelin infusion in animal models of sepsis, and the current article by Wu and colleagues (5), it seems likely that GHS-R1 will emerge as an important drug target in critical care medicine and that intensivists eventually will add ghrelin, or perhaps a ghrelin mimetic, to their therapeutic armamentarium.

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Studies in hypothermia-treated cardiac arrest patients are needed to establish the accuracy of proposed outcome predictors*

A critical issue when treating cardiac arrest patients after return of spontaneous circulation is when and how to decide to withhold further treatment, knowing that the patient cannot be brought back to useful life. This decision raises many issues. With patient focus, setting aside other stakeholders (relatives, treatment team, and the best use of limited intensive care and other resources), there are at least two issues: How do we define useful life and how certain do we have to be? How high specificity for negative outcome is required?

Most will categorize severe brain damage with permanent coma as not useful life, and would wish for predictive criteria with close to 100% specificity, perhaps accepting confidence intervals down to 97% to 98%. Due to the use of limited resources, there has also been a search for predictors with the required specificity as early as possible after cardiac arrest so futile treatment can be terminated (1). If such predictors were available, it must be remembered that this will become a self-fulfilling prophecy; no patient filling the criteria will survive. Whatever predictors we use, it is therefore important that somebody at times challenges those truths, particularly when changes in therapy occur.

Over the last few years, such changes in therapy have occurred, which dramat-

***See also p. 2427.**

Key Words: heart arrest; hypothermia; induced; prognosis; resuscitation orders; sensitivity and specificity

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ically change the outcome of patients with return of spontaneous circulation after cardiac arrest. Therapeutic hypothermia has increased the likelihood of survival with an intact brain (2). In one study, therapeutic hypothermia combined with percutaneous coronary intervention and control of hemodynamics, blood glucose, and seizures doubled 1-yr survival rate with good brain function from 26% to 56% (3).

A significant number of papers from the prehypothermia era reported prognosticators for poor outcome with 100% specificity and tight confidence interval 48 to 72 hrs post arrest (4–8). Absence of corneal reflexes, pupillary light reflexes, motor response to pain no better than extension, or bilateral absence of N20 in somatosensory-evoked potentials after 48 to 72 hrs have therefore been used to withdraw active treatment (9).

As hypothermia affects neurologic signs and pharmacokinetics and alters the progression of neurologic injury (9), it is therefore of utmost importance to reevaluate prognosticators after its implementation (10, 11). In this issue of *Critical Care Medicine*, Wennervirta and colleagues (12) have done just that by examining quantitative variables of electroencephalogram suppression and epileptiform activity in 30 patients, of whom 21 had good neurologic results and nine had bad neurologic outcome. They report threshold values with 100% specificity for poor result after 24 and 48 hrs for some electroencephalogram variables and the biochemical markers neuron specific enolase and protein S-100B. Unfortunately, no connected sensitivity was >33%. Thus, if these thresholds were valid and used to determine futility, treatment would be terminated in only every third patient with ultimate poor outcome. Adjusting the thresholds to maximize the number of correctly predicted outcomes gave no positive prediction value for poor outcome of >64%.

Al Thenayan et al reported that, of 37 consecutive adults treated with hypothermia post arrest, no patient without corneal or pupillary reflexes on day 3 regained awareness, although motor response no better than extension no longer was prognostically reliable (13). As in the present study (12), no patient who developed myoclonic status epilepticus regained awareness (13). The confidence interval for the latter prognosticator is slightly larger than for the other clinical signs even without therapeutic hypothermia (6, 9); and in two case reports, hypothermia-treated patients with myoclonic status epilepticus have been reported to awaken eventually and return to normal life (11, 14).

At American Heart Association Sessions 2008, Friberg and Rundgren reported that, of hypothermia-treated patients still unconscious 72 hrs after rewarming (96 hrs post arrest), all eight patients with continuous pattern electroencephalogram, neuron specific enolase <27 μg/L, and cortical response on somatosensory-evoked potentials woke up neurologically intact, although one of these three markers was negative in 27 of 29 patients who never regained consciousness (15). This study indicated that prognostication must not be done too early.

The present report by Wennervirta et al (12) is a valuable contribution to the search for prognosticators after cardiac arrest. As in the study by Al Thenayan et al (13), the number of patients is small; thus, these studies only indicate where to conduct further studies. A more important caveat is that whereas Al Thenayan et al tested previously determined predictors (13), the present study falls in the same category as most post cardiac arrest prediction studies (1); the predictor threshold values are set to fit the data (12). That will usually give too high predictive accuracy. As with any other diagnostic tests, a predictor must be verified on a separate group of patients, and to be extrapolated to other institutions, the predictor must also be tested in other institutions.

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Gram-specific quantitative polymerase chain reaction for diagnosis of neonatal sepsis: Implications for clinical practice*

Sepsis in neonates, particularly those with low gestational age and birth weight, is a serious disease that is associated with high morbidity and mortality (1). The outcome of sepsis depends, to a great extent, on early identification of affected infants and rapid initiation of appropriate antimicrobial agents against causative organisms (2). The standard of care for infants suspected to have sepsis is to give combination broad-spectrum antimicrobials to cover potential pathogens at a given age or clinical setting. The type and duration of antimicrobials are usually based on results of cultures and other laboratory markers of sepsis, and the clinical condition of the affected infant. The gold standard for the microbiological diagnosis of a bloodstream infection is a positive blood culture. In small infants, the sensitivity of blood culture is low despite the presence of clinical indicators of sepsis (2–11). This may be due to intermittent seeding of bloodstream with low numbers of bacteria, suppression of bacterial growth by prior antibiotics given to the mother or infant, and insufficient volume of blood samples as is common in neonates (3).

In recent years, there have been several reports (4–13) on the use of polymerase chain reaction (PCR)-based assays for early and accurate identification of bacterial deoxyribonucleic acid (DNA) in the blood of neonates suspected or confirmed to have sepsis. These assays rely on PCR amplification of the 16S rRNA gene, a highly conserved gene present in all bacterial species, but absent in humans. As the gene has a number of divergent regions nested within it, PCR has also been targeted for species-specific detection of bacteria in clinical specimens. When compared with blood cultures, the range of the sensitivity of the PCR assays in various studies (5–7, 9, 10) was 66.7% to 100%, specificity was 87.5% to 97.85%, positive predictive value was 47% to 95.4%, and negative predictive value was 75% to 100%.

The impetus for the development of such assays is to improve the rate of microbiological diagnosis of neonates presenting with signs and symptoms of sepsis and decrease the time for identification of a pathogen. As a result, the expectation is to influence the utilization of antibiotics in such infants.

In this issue of the *Critical Care Medicine*, Chan and colleagues (14) report the results of an evaluation of a quantitative (q) PCR test for identification of Gram-negative and Gram-positive bacterial infections in 218 episodes of suspected late-onset sepsis in preterm infants. The positivity rate of blood culture was 42/176 (23.86%) and qPCR was 33/176 (18.75%). Compared with blood culture, the sensitivity and specificity of the qPCR for Gram-positive infections were 73.7% and 98.5%, and for Gram-negative infections 86.4% and 99.5%, respectively. The qPCR identified correctly the Gram-specific causative pathogens in negative blood cultures in five infants who had intra-abdominal sepsis. The results of the PCR assay were available more rapidly than blood cultures (5–29 hrs vs. 17.2–127 hrs). These results are in line with previous studies (5–7, 9, 10).

Jordan et al (5) compared the performance of a 16S rRNA gene PCR and blood cultures in 548 neonates with suspected sepsis. Twenty-five infants had positive blood cultures (4.6%) and 27 had positive PCR (4.9%). Compared with blood culture, the sensitivity, specificity, positive predictive value, and negative predictive values of the PCR were 96%, 99.4%, 88.9%, and 99.8%, respectively. The turnaround time for PCR results was around 9 hrs. In another study, Jordan et al (8) evaluated 16S rDNA PCR in 1233 near-term infants with suspected or confirmed sepsis. The blood culture positivity rate was 17/1233 (1.38%) and PCR 37/1233 (3%). Compared with culture, the sensitivity of PCR was 41.2%, specificity 97.5%, and negative predictive value of 99.2%. The low sensitivity was attributed to suboptimal sampling and preparation techniques. Shang et al (7) examined blood cultures, and 16S rRNA gene PCR amplification and microarray analysis in 172 neonates with suspected sepsis. The positivity rate of the PCR assay was significantly higher than that of blood culture (9.88% vs. 4.65%). Compared with blood culture, the sensitivity of the PCR was 100%, specificity was 97.8%, positive predictive value was 47%, and negative predictive value was 100%. The results of the PCR assay were available within 6 hrs.

Wu et al (9) studied the performance of Gram-negative stain-specific-probe-based real-time PCR representing 53 Gram-positive and Gram-negative clinically important bacterial strains in blood samples of 600 neonates with suspected sepsis. The positivity rate of the PCR assay was 50/600 (8.33%) and the blood culture 34/600 (5.67%). Compared with blood culture, the sensitivity, specificity, and index of accurate diagnosis for the PCR were 100%, 97.17%, and 0.972%, respectively. In a recent study (10) of 48 neonates with signs and symptoms of sepsis, the positivity rate of a broad range 16S-DNA PCR was 9/31 (29%), and blood culture was 6/31 (19.3%). Compared with blood culture, the sensitivity, specificity, and positive and negative predictive values of PCR were 66.7%, 87.5%, 95.4%, and 75%, respectively.

Molecular assays may be potentially useful adjunct tests in microbiological diagnosis of septic neonates. These assays (5–10, 14) have the following advantages over blood cultures: 1) they utilize smaller volumes of blood; 2) the results are available within a shorter turnaround time; 3) they can detect a small amount of bacteria; and 4) they are unlikely to be

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affected by prior antibiotic therapy. However, these assays are associated with a potential for false-positive results due to contamination from bacterial DNA, which is widespread in the environment, and false-negative results in patients who are infected with pathogens that are not targeted in the assay. Additionally, these tests are not yet readily available in all hospitals. A real-time PCR LightCycler SeptiFast Test MGRADE Kit (Roche Molecular Diagnostics, Penzberg, Germany) is available commercially in some countries (15). It detects and identifies 25 bacterial and fungal pathogens commonly associated with bloodstream infections directly in 1.5 mL of blood in <6 hrs. However, the diagnostic accuracy of this test has not been validated in neonates.

The microbiological diagnosis of infants who present with signs and symptoms of neonatal sepsis remains a challenge. Although molecular assays may improve the detection of pathogens causing sepsis, the positivity rate of PCR (range from 3% to 29%) in various studies of septic neonates is still low (5–10, 14). Further studies are needed to define the role of molecular assays in the identification of septic infants, their impact on physician management decisions regarding antibiotics, and their effect on clinical outcome.

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