N E W S L E T T E R

Society of Critical Care Anesthesiologists SOCCA

INTERCHANGE

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President's Message

Counting the Value

Michael F. O'Connor, M.D., F.C.C.M., President

We practice medicine in an era where the intensive care unit (ICU) is referred to as a "cost center." What does this mean? It means that as accountants track the flow of money and supplies through the hospital, a substantial amount of both are allocated to and consumed by the ICUs. From the accountant's perspective, anything that might be done to reduce the flow of either would be good for the organization, its bottom line and its financial health. Many intensivists now find themselves summoned to discussions where the focus is to do exactly this. The intensivist is compelled to defend the apparently staggering consumption of resources by their operation, often to people who receive a bonus proportionate to the amount they reduce "expenses." One of the reasons that, collectively, we find ourselves on the defensive in these discussions is because we have allowed others to frame them.

Critical care medicine (CCM) is relatively new. Unlike most specialties (but like the ER), it is defined by the direction and coordination of care of patients in a specific location, rather than diseases of a specific organ system (e.g., cardiology or cardiac surgery), a particular approach to the management of disease (medicine or surgery), or a specific population of patients (e.g., pediatrics). By taking the metrics that others had developed and applying them to our circumstances, we failed to develop metrics appropriate to capture our contributions.

Since its beginning, critical care has been outcome-driven. The literature of CCM is a narrative of unfunded or minimally funded explorations into how to improve outcomes and reduce resource utilization. Industry supports some research, as does the National Institutes of Health, but CCM remains ridiculously underfunded relative to other medical specialties. "Resource starved" would not be an exaggeration. In spite of this, critical care has made as much or more progress than other specialties. Why? The short answer is this: since its inception, the clinical question for CCM has been, "How should we deliver care?" The literature of critical care is largely an iterative exploration of this question. By and large, the progress we have made in improving outcomes has been from using the same tools better, not from new technology or drugs. The clinical literature and practices of CCM have been exported to the practice of medicine outside the ICU. Critical care has failed to claim credit for adding this value.

Long before the rest of medicine understood the importance of preventive medicine, intensivists had already made substantial progress preventing thromboembolic disease. While other specialties floundered in their efforts at prevention, critical care made substantial progress at preventing the complications of mechanical ventilation, sedation for mechanical ventilation and transfusion; and it is presently making substantial progress on reducing other complications of critical care medicine (e.g., central line-associated infections). There have been blind alleys too (glycemic control), but the healthy debate in our community allows us to recognize them over time. Most importantly, our community made these great strides absent any regulatory mandate or P4P incentive.

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Ironically, critical care may have been the first adult medical specialty in the modern era

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EDITORIAL NOTES

Editorial Policy

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A Note from the Editor to SOCCA Members:

If you would like to contribute a review for a Fellowship Program at your institution in a future issue of the SOCCA Interchange, please contact Chris Dionne at **c.dionne@asahq.org**.

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President's Message

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to rediscover patient autonomy, compassion and family-centered care. In many hospitals, the ICUs led the movement to keep the family at the bedside with their loved ones and the engagement of the family in the care of the patient. Across medicine, intensive care began the era of shared decision-making and initiated the first discussions about withholding life-sustaining therapy. As a specialty, critical care medicine has failed to claim credit for these critical improvements in the social structure of medicine.

Hospitals and health care systems are dismal at tracking value and understanding how it is created. Intensivists enable other physicians – surgeons, oncologists, etc. – to spend their time in their specialty activities, rather than being distracted into inefficiency by the necessity of generating care for a patient in an ICU. Intensivists are present and available to patients and their families, and thus dramatically improve patient and family satisfaction. All of this is unrecognized but is obviously value added.

In spite of so many advances, intensivists have failed to take the credit for the value we add for our patients, our organizations and our health care system. We have failed to develop metrics that illuminate the value we add. Until we can quantify the value we add, our conversations will be centered on the costs we incur.

On a separate note, the FDA has convened a group of experts to generate guidance about sedation, and SOCCA members **Pratik Pandharipande, M.D.** and **Avery Tung, M.D.** will be among the experts for sedation in the ICU.

SOCCA board member **Miguel Cobas, M.D.** has faithfully spearheaded SOCCA's collaboration with the ASA for Maintenance of Certification (MOC) in Critical Care. This is an undertaking that consumes a substantial amount of time and energy; a small number of people will generate every component of MOC for CCM. SOCCA is fortunate that many intensivists are also leaders in simulation. **Randy Steadman**, **M.D.**, who chairs the ASA Committee on Simulation, has helped recruit two SOCCA members, **Manny Pardo, M.D.** and **Elizabeth Sinz**, **M.D.** , who have crafted a proposal that will allow accredited sim centers to offer simulation experiences for those seeking maintenance of certification in CCM via the ABA. The proposal has been approved by both SOCCA and the ASA, and we anticipate that a number of sim centers will offer this opportunity sometime in this calendar year. See future newsletters for news about progress on other aspects of MOC in CCM.

Ultrasonography in Critical Care Series Recent Guidelines and Meeting Announcement: The ACCF 2011 Appropriate Use Criteria for Echocardiography

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The American College of Cardiology Foundation (ACCF), along with the American Society of Echocardiography (ASE) and other key subspecialty societies, recently updated its appropriate use criteria for echocardiography.[1] The first iteration of these guidelines for transthoracic (TTE) and transesophageal (TEE) echocardiography use was published in 2007.[2] The purpose was, and still is, to provide a framework for the "rational [read 'reimbursable'] use of imaging services." Although the guidelines do *not* address intraoperative use, they are relevant to all perioperative physicians, particularly with the growing demand for efficient allocation of health care resources.

The 2011 criteria fittingly reflect the increased utilization of echocardiography in a variety of clinical situations. Whereas the 2007 guidelines covered 59 common scenarios for TTE and TEE, the updated document covers a whopping 202. However, 89 of these are actually updates for contrast and stress echocardiography appropriateness criteria originally published in 2008 under a separate paper,[3] so the actual increase for listed TTE and TEE scenarios is from 59 to 113. Much of the expansion is due to extended use of echocardiography in patients with adult congenital heart disease, patients with pulmonary hypertension, and the increased role of echocardiography for evaluating implanted devices such as pacemakers for cardiac resynchronization therapy, defibrillators and ventricular assist devices. It is interesting to note that the 2007 guidelines rated 44/59 (74.5 percent) of the indications as "appropriate," while the 2011 guidelines rate 78/113 (69.0 percent) as "appropriate." In general, TTE and TEE indications for initial diagnosis of cardiac conditions were positively received, while routine testing for asymptomatic surveillance was considered "inappropriate."

So why should critical care physicians be interested in guidelines written predominantly by cardiologists for patients in their clinics? For starters, the use of echocardiography in the acute care setting is increasingly being recognized as something of tremendous value. The new guidelines acknowledge the use of TTE/TEE as "appropriate" for several common ICU scenarios: hypotension of unclear etiology, potential myocardial ischemia and respiratory failure of unclear etiology, among others. With proper training, the ICU physician can quickly obtain information him/herself about these conditions that can directly impact patient care. Additionally, the 2011 criteria list "assessment of volume status in a critically ill patient" as a new situation where echocardiography might be utilized. While this is classified as an "uncertain" (versus "appropriate" or "inappropriate") indication, it potentially opens the door for using echocardiography not just as a diagnostic test, but as a monitoring tool as well. Indeed, there are already reports of using miniature, disposable TEE probes for ongoing monitoring of cardiac function and filling in the ICU.[4]

Critical care physicians, particularly those with a background in anesthesiology, may be more familiar with the 2010 Practice Guidelines for Perioperative TEE written by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists.[5] Nevertheless, it is comforting to know that other societies are endorsing the expansion of TTE/TEE into the ICU. It certainly encourages intensivists from all backgrounds to pursue education in echocardiography.

Information for the SCA's Introduction to Transesophageal Echocardiography (iTEE) course to be held in Philadelphia on September 9-10, 2012 can be found at: **http://www.scahq.org/Education/ContinuingMedicalEducation/meetingsEvents.html.**

The 2012 iTEE course will have special emphasis on TEE use outside of the cardiac O.Rs.

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Does Recombinant Factor VIIa (rFVIIa) Have an "Off-Label" Role in Critical Care?

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Recombinant factor VIIa (rFVIIa) (NovoSeven®, Novo Nordisk, Denmark) was originally developed and described by Hedner and Kisiel in 1983 for use in treating two patients presenting with hemophilia, a complication with high titer allo-antibodies.[1] In 1999, the U.S. Food and Drug Administration (FDA) licensed rFVIIa to treat bleeding episodes in patients with hemophilia A or B with inhibitors (antibodies) to factor VIII or IX, respectively. Subsequently, the license for rFVIIa was extended in 2005 to include use in surgical procedures in hemophilia A and B patients with inhibitors, congenital Factor VII deficiency and Glanzmann's thromboasthenia.[2] Complying with its role, the FDA did an excellent job in analyzing the reported adverse events of rFVIIa use for all patients in the first five years following the initial licensure in 1999. Thrombo-embolic complications, including serious myocardial and cerebral infarctions and pulmonary embolism, happened in about 90 percent of these reports due to "off-label" use of rFVIIa in patients, most of which (68 percent) were actively bleeding at the time of administration. Furthermore, 72 percent of the reported deaths were proved to be due to these thrombo-embolic events, and 52 percent of these events happened in the first 24 hours, proving a temporal association.[2]

The mechanism of action of rFVIIa consists of:

1. A tissue factor (TF)-dependent mechanism in which rFVIIa mimics the action of nFVIIa by forming a complex with TF leading to factor X activation, thrombin production and platelet activation, the net result of which is enhanced platelet-derived thrombin production.
2. A TF-independent mechanism in which rFVIIa binds to the surface of activated platelets and, in doing so, directly activates factor X in the absence of the requirement of TF, the result of which is to increase thrombin production. This TF-independent mechanism is what explains the ability of rFVIIa to bypass factor VIII and IX deficiency in hemophiliac patients.
3. The ability of rFVIIa at pharmacological doses to potentially escape the inhibitory effect of nFVIIa on coagulation.
4. The potential for rFVIIa to down-regulate the fibrinolytic system *via* activation of thrombin activation fibrinolysis inhibitor (TAFI).[3]

This should be considered in the light of the changing concept of the coagulation system to become a "cell-based" model, where coagulation occurs on different cell surfaces, such as TF bearing cells and activated platelets, in three overlapping steps of initiation, amplification and propagation. Furthermore, this "cell-based" model may also explain differences observed between the *in vitro* effects of rFVIIa and those that occur in the more complex *in vivo* environment.[4]

The likelihood of the "off-label" usage of rFVIIa in critical care patients will be mainly in relation to three different types of patients: hepatic, cardiac and trauma, in which hemorrhage is a major and frequent complication that can be detrimental to the procedure and patient survival. The use of rFVIIa in surgical procedures in hemophiliac or other coagulopathic critical care patients is already indicated, licensed and proven to be effective.[5] The controversy mainly comes from its "off-label" use in bleeding patients without predetermined coagulopathy. The timing of rFVIIa administration appears to be an equally important determinant of its efficacy. However, as with many of the facets of the use/potential use of rFVII, it remains unclear and controversial as to how early it should be administered during the management of 'intractable hemorrhage" due to its questionable risk-benefit profile.[6]

"In hepatic patients, coagulopathy resulting from progressive liver disease is no longer considered being solely a form of bleeding tendency as one might expect, but is now regarded as being considerably more complex in nature."

In hepatic patients, coagulopathy resulting from progressive liver disease is no longer considered being solely a form of bleeding tendency as one might expect, but is now regarded as being considerably more complex in nature. Clinical evidence demonstrated that

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Does Recombinant Factor VIIa (rFVIIa) Have an "Off-Label" Role in Critical Care?

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cirrhotic patients, despite prolonged coagulation tests, show paradoxical signs of thrombosis as determined by thromboelastography (TEG). In fact, more recent evidence suggests that cirrhotic patients may suffer from a state of hypercoagulability due to endothelial activation, an event that leads to increased levels of thrombin-antithrombin complexes, TF and homocysteine in comparison to non-cirrhotic subjects.[7]

In cardiac surgery patients, the apparent "post-CPB coagulopathy" is multifactorial in origin (e.g., varying degrees of hypothermia, acidosis, hypocalcemia, anemia, hyperfibrinolysis, platelet dysfunction, inflammatory reaction, etc.), and when these patients bleed, they do so due to different combinations of underlying factors. As a result, these patient populations will likely respond differently to the same treatment regimens, if they respond at all. The result of this from the clinical standpoint is that the likelihood of a single "universal haemostatic agent" emerging seems oversimplistic and remote. The "Canadian Consensus Conference on the Emerging Role of rFVIIa in On-pump Cardiac Surgery" has recently convened in an attempt to address the lack of recommendations for the use of rFVIIa. They weighed all evidence available to date with the view to decide on recommendations at three levels of rFVIIa use, including prophylactic use, routine use and the use for refractory hemorrhage after on-pump cardiac surgery. The panel recommended against the prophylactic and routine use of rFVIIa in cardiac surgery, and, however, made the weakest (grade 2C) recommendation.[8]

Three placebo-controlled randomized trials exist to date assessing the efficacy of rFVIIa in prophylaxis of bleeding after cardiac surgery. The first two trials were in non-coronary adult cardiac surgical patients who had major limitations, including being underpowered; essential differences between the two compared groups and the use of other haemostatic factors.[9-11] The third trial was in infants and concluded no difference.[12]

In trauma patients, a report of two parallel randomized placebo-controlled trials from blunt and penetrating trauma patients concluded that rFVIIa significantly reduced blood transfusion in blunt but not penetrating trauma patients.[13] The investigators, setting an example of self-criticism, stated in a separate report that despite making every effort to standardize the practice across the 32 hospitals in eight countries that contributed to the trial, it remained possible that the centers were not uniform in their transfusion polices, and yet the chosen surrogate marker of bleeding, blood transfusion, was the only significant primary end point in the study in one of the two trauma groups that the trial was set out to study.[14] In addition, the investigators did not report which, if any, surgical procedures were performed on patients during the 48 hours of the study and did not include any details of additional blood components transfused alongside red blood cells. While impossible to predict the exact effect of these factors, both these variables seem likely to be significant in affecting outcome. On looking more in depth into the study's reported results, the investigators stated that the primary end point studied was the total number of RBC units transfused within 48 hours of rFVIIa administration. In their analysis, however, they chose to eliminate any subject who, after enrollment, randomization and treatment with rFVII, died within the first 48 hours, which undoubtedly profoundly affected the conclusions of this trial. If one looks at all patients enrolled, according to the intention-to-treat principle, it is clear that in the blunt trauma group, actually the placebo group, required significantly fewer RBCs (Table 2 in the published manuscript), which is the designated primary end point of the trial. That is in addition to the fact that there was no statistically significant difference between the placebo and intervention arms in the penetrating trauma group. Nevertheless, this trial is frequently cited as being a "positive" trial in favor of rFVIIa use in trauma.

> "In trauma patients, a report of two parallel randomized placebo-controlled trials from blunt and penetrating trauma patients concluded that rFVIIa significantly reduced blood transfusion in blunt but not penetrating trauma patients.[13]"

The role of rFVIIa in medicine, in general, will continue to be investigated. The critical care community must remain vigilant and patient in pursuing the evidence of efficacy of rFVIIa and determining its role in coagulopathy in critical care patients. The problem is probably not deficient evidence but rather a defective or unclear concept of how the hemostatic system functions in different disease processes and how to manage it in these different and variable clinical settings. Furthermore, due to the questionable risk/benefit profile of rFVIIa, there is no choice but to follow the conventional hierarchy of medical evidence in evaluating its safety and efficacy in the different applications in question. Any obtained evidence should be scrutinized carefully and patiently in order not to waste lives when we attempt to save them.

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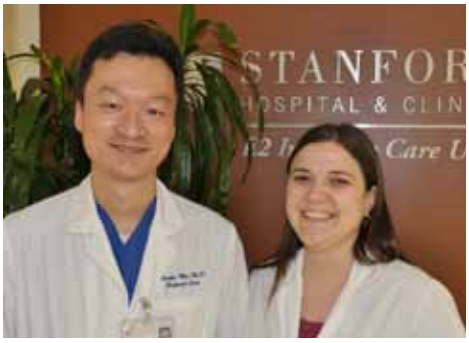
Multiple-choice Question:

Mechanisms of action of rFVIIa include:

A. A tissue factor-*dependent* enhancement of platelet-derived thrombin production
B. A tissue factor-*independent* enhancement of platelet-derived thrombin production despite factors VIII and IX deficiency
C. Escaping the inhibitory effect of native FVIIa
D. Down-regulation of the fibrinolytic system *via* activation of thrombin activation fibrinolysis inhibitor (TAFI)
E. All of the above.

Answer: E

Fellowship Review: Stanford University Medical Center Critical Care Fellowship



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The critical care medicine training at Stanford Medical Center offers an ACGME-accredited, 12-month multidisciplinary experience for anesthesiology fellows at the beautiful Stanford University campus in Palo Alto, California.

A Truly Multidisciplinary Experience

The critical care teams are directed by attending intensivists from Pulmonology, Anesthesiology, Emergency Medicine, Surgery, and Neurology. Our 15 fellows also come from the disciplines of Internal Medicine, Neurology, Anesthesiology and Emergency Medicine. Each fellow brings a unique knowledge base and set of strengths that contributes to the learning environment of all. The critical care medicine fellows work closely with consultant colleagues from all fields and are strongly supported by a team of excellent nurses, respiratory therapists, pharmacists, nutritionists and speech pathologists, as well as physical and occupational therapists.

Home Base

The fellowship year begins with a one-month rotation as a critical care medicine *resident*, referred to as the "resi-fellow" month. During that time, the fellow takes in-house call as a resident, allowing the fellow to assimilate into the Stanford environment and discover the acuity of the patients admitted to our ICU. During the next several months, fellows supervise patient care provided by residents and students. Progressive independence during the fellowship gives our fellows more opportunities to direct patient care and teaching. Near the end of the year, each fellow will be assigned as a junior attending in our Medical-Surgical Intensive Care Unit, in which they are responsible for all patient care and teaching rounds during their rotation.

The Medical-Surgical Intensive Care Unit at Stanford University Medical Center is the main training ICU for fellows. The anesthesiology fellows will spend approximately five months in this unit, where they are responsible for the primary management of 20-45 patients. Fellows are exposed to a broad scope of pathology in the fields of medicine, neuroscience, orthopedics, OB/GYN, ENT and bone marrow transplant. The service is composed of faculty from Anesthesiology, Pulmonology, and Emergency Medicine and the resident team populates from Anesthesiology, Internal Medicine and Emergency Medicine.

While on the Medical-Surgical ICU service, fellows provide many vital services within the hospital. Fellows are directly involved in resident and medical student supervision and teaching. Our fellows also serve as the leaders of the rapid response teams (RRT), code blue teams, and work closely with crisis nurses to triage critically ill patients throughout the hospital and the emergency room. Fellows are the first-line physicians to work with our active transfer center and also work closely with the hospital nursing supervisor regarding bed control throughout the hospital. Fellows have an active dialog with the CCM attending regarding all new admissions and difficult situations, and the on-call CCM attending returns to the hospital for backup as needed. This interactive, in-house approach offers our fellows the opportunity to learn the nature of providing critical care services in a large tertiary hospital.

Making the Rounds

While the home base unit provides a multidisciplinary approach in itself, our fellows also rotate through the Cardiothoracic ICU and the Trauma Surgical ICU at Stanford University Medical Center, the Medical-Surgical ICU at the Palo Alto VA Hospital, and the Medical ICU at Santa Clara Valley Medical Center. The cardiothoracic ICU provides management experience for postoperative complex cardiovascular, thoracic and heart/lung transplant patients. Fellows also gain exposure to heart failure patients requiring mechanical left ventricular assist devices.

The Stanford Trauma Surgical ICU rotation offers a broad experience in the care of critically ill patients with surgical diseases and processes (trauma, general surgery, vascular surgery and liver transplant). Our fellows function as a junior attending on this rotation and provide supervision to Surgery, Emergency Medicine and Anesthesiology residents. During this rotation, the fellows serve on the trauma team and gain experience with tracheostomy, bronchoscopy and bedside surgical procedures.

The experience at Palo Alto VA Medical-Surgical ICU is similar to that at Stanford, providing additional training with medically ill patients as well as postoperative general surgical and cardiac surgical patients. The rotation at Santa Clara Valley Medical Center provides additional training in a medical ICU in a county hospital environment.

Each fellow spends one month on an elective of their choice. Many fellows have designed their own electives to fit their specific interests or future career goals. Some examples of the elective rotations available at Stanford include

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the neurology critical care consult service, advanced training in echocardiography (both transthoracic and transesophageal), inpatient nephrology, critical care infectious disease and palliative care.

Several of our CCM faculty have a long-term interest in overseas anesthesia missions, and there are opportunities for fellows to participate. Fellows this year are travelling to Venezuela and Liberia.

The combination of all of these services and rotations provides an outstanding training environment for our fellows and prepares them for their future in critical care medicine.

Bedside-Focused Echocardiography: Pioneers of a Developing Field

Bedside-focused echocardiography has become an increasingly important diagnostic tool for critical care practitioners. Training in echocardiography is provided early during the fellowship with a full day workshop at the start of the fellowship and a one-week one-on-one course taught by Dr. Anne-Sophie Beraud, a cardiologist dedicated to ICU echocardiography education. Through this course, fellows learn how to use echocardiography to assist in the bedside assessment of critically ill patients, including evaluating volume status, identifying cardiac tamponade, assessing cardiac function and diagnosing major valve dysfunction. After completing this training, fellows are able to use bedside TTE in their daily assessment of patients and to review and dictate the TTE readings with Dr. Beraud throughout the year.

Research: A Wide Variety of Academic Curiosity

Stanford ICU fellows spend three months per year on a research rotation. Fellows are encouraged to become involved in projects early in their training in order to maximize their productivity and learning experience. Dr. Andrew Patterson, the chair of Society of Critical Care Medicine Congress 2012, is the faculty director for research and serves as a mentor to all fellows. There are a variety of projects and trials being conducted at Stanford and there truly is something for everyone. Our current fellows are conducting projects in the following arenas: medical education and simulation in critical care, echocardiography use in critical care, lung ultrasound use in the ICU, platelet function alterations with dexmedetomidine in cardiac surgery patients, quality improvement in rapid airway response teams, and quality improvement measures with bundled ICU order sets. Research time can also be spent developing academic pursuits such as speaking at national conferences, teaching medical student courses, advancing resident ICU curriculum, providing nurse education in the ICU and writing book chapters. These are only a few examples of the wide array of research opportunities and academic projects available to our fellows.

Education: Fellows as Learners and Teachers Every Day of the Week

Daily rounds on all critical care services are teaching rounds (CCM attendings round 365 days per year) and include patient-based bedside teaching to improve patient care and medical knowledge. Daily radiographic and imaging interpretation is taught with CCM attendings and radiologists. The fellowship provides daily, structured formal didactics in a variety of ways. The core curriculum for the critical care medicine fellowship is taught by attending faculty every Thursday at noon, and a trauma lunch lecture occurs every Friday and is highly reviewed by all fellows. All divisions of critical care medicine meet the second Wednesday of every month for the Multidisciplinary ICU Conference. For the first six months of the year, formal echocardiography/ultrasound lectures take place at noon on Tuesdays and complements the bedside TTE training. Fellows are encouraged to attend the pulmonary critical care case conference on Wednesdays. There is a monthly ER/ICU conference to highlight our interaction with the emergency department.

Critical care multidisciplinary meetings occur every Monday in which all care providers meet to discuss patient outcomes. Practice-based learning and systems-based learning occur in the critical care quality improvement committee and in implementation of our protocols, which meets every other Tuesday and allows fellows to have the opportunity to learn about initiatives taking place within the hospital.

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Fellowship Review: Stanford University Medical Center Critical Care Fellowship

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Fellows also have the opportunity to be teachers and provide a variety of lectures and presentations throughout the year. Journal club takes place at an upscale Palo Alto restaurant the first Thursday of every month and is highly attended by residents, fellows and faculty. Fellows also present at monthly M&M lectures, teach at the daily resident conferences, prepare board review study guides for all core lectures, direct the anesthesia simulation course for medical students on critical care rotations, assist at the anesthesia resident central line workshop and participate in code blue simulation training. Anesthesia fellows actively participate in the airway training of our non-anesthesia fellows with state-of-the-art videolaryngoscopy and fiberoptic equipment.

Applications and Interest

Options for graduating residents in anesthesiology include a one-year critical care fellowship or a two-year critical care/cardiac anesthesiology fellowship. For graduating medical students who are interested in a Critical Care Anesthesiology career, there is a newly formed combined anesthesia residency/critical care medicine fellowship program beginning with the 2012 match. You can find more information in the following website **http://med.stanford.edu/criticalcare/education/fellowship.html**. Please feel free to contact Dr. Fred Mihm, Anesthesia Critical Care Fellowship Program Director (**fmihm@stanford.edu**), or the fellowship program assistant Bernadett Mahanay (**bromo@stanford.edu**) with any questions. You can also contact us (**hbma@stanford.edu, erinkh@stanford.edu**) if you have any questions. We wish you the best in the pursuit of critical care medicine training!

Society of Critical Care Anesthesiologists SOCCA

25TH ANNUAL MEETING AND CRITICAL CARE UPDATE

Plan now to attend the Society of Critical Care Anesthesiologists 25th Annual Meeting and Critical Care Update to be held Friday, October 12, 2012 in Washington, DC

CALL FOR ABSTRACTS

Online Submission Available: April 23, 2012
Deadline for Submission: June 4, 2012

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YOUNG INVESTIGATOR AWARD

This award is presented annually to the resident or fellow whose research exemplifies the Society's mission to educate anesthesiologists in the care of critically ill patients and to foster the knowledge and practice of critical care medicine by anesthesiologists. The recipient of the Young Investigator Award will be asked to make an oral presentation of his or her work at the SOCCA Annual Meeting. Please indicate your interest to be considered for this award by checking the respective box on the online submission form at www.socca.org.

Literature Review: Fluid Resuscitation Study Complicated by a Background of Scientific Misconduct

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Article reviewed: Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S. The CHEST Management Committee. Fluid Resuscitation with 6% Hydroxyethyl Starch (130/0.4) in Acutely Ill Patients: An Updated Systematic Review and Meta-Analysis. *Anesth Analg*. 2012; 114(1):159-169.

You have received a patient to the ICU after a 7-hour surgery during which the patient received 6 liters of crystalloid solution and continues to require fluid resuscitation for a borderline hypotension. Concerned about crystalloids-induced tissue edema, a member of the ICU team asks if there is a benefit of giving a liter of the colloid 6% hydroxyl-ethyl starch 130/0.4 (HES) in order to minimize the total volume of administered I.V. fluids? What would be your response?

According to a recent systematic review and meta-analysis published in *Anesthesia & Analgesia*, the answer would be "we don't know." The authors concluded that current evidence does not allow reliable estimation of either the benefits or the risks of administering HES to critically ill patients. The outcomes that authors examined in the analyzed studies (n=16) were:

1. Death (n=104 in 1,184 participant)
2. Need for renal replacement therapy (RRT)
3. Urinary output
4. Transfusion of packed red blood cells (PRBCs)
5. Estimated or measured blood loss.

> "In addition to addressing the clinically important issue of the role of colloids in fluid management in critical ill patients, the article addressed the impact of scientific misconduct on clinical practice and on the conduct of subsequent studies."

The only outcome that was amenable to meta-analysis was death, which showed no difference between HES and control groups (relative risk 0.95). However, the confidence intervals (CI) were wide enough to make it possible that HES use could be associated with either benefit or harm (95% CI 0.64-1.42, p=0.73). The other four outcomes were not amenable to meta-analysis because of insufficient quality and quantity of data.

The importance of this systematic review and meta-analysis stems from several aspects:

1. The fundamental importance of fluid management in critical care with continued examination and re-examination of the roles of crystalloids, colloids, hypertonic solutions, blood products and blood substitutes, as well as hemopoeitic and hemostatic agents.
2. Common use of HES (most frequent colloid used worldwide) despite insufficient evidence.
3. Recent retraction of 11 reports about HES that were authored by Boldt et al., with some of these reports having been used as evidence of safety and efficacy in manufacturer product information sheet and in submission to regulatory agencies.
4. The performance of meta-analyses both with and without the retracted study showed no difference in mortality in either case. Including the 11 retracted studies added 14 more deaths and resulted in a relative risk of death of 0.92 with a 95% CI of 0.63-1.34, and p= 0.95.

In addition to addressing the clinically important issue of the role of colloids in fluid management in critical ill patients, the article addressed the impact of scientific misconduct on clinical practice and on the conduct of subsequent studies. The authors of this meta-analysis were the CHEST investigator group, and the CHEST Management Committee, with CHEST standing for Crystalloid versus HydroxyEthyl Starch Trial. This is the same group of investigators that performed the SAFE (Saline versus Albumin Fluid Evaluation) study, which included about 7,000 patients

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Literature Review: Fluid Resuscitation Study Complicated by a Background of Scientific Misconduct

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and showed no difference in outcome between the two groups. Similar to the SAFE study, the CHEST trial is going to include 7,000 patients, with a similar protocol, a primary outcome of 90-day mortality, secondary outcomes as those examined in this meta-analysis, and expected publication in 2012.

During the conduct of the CHEST trial, the retraction of the 11 articles by Boldt et al. took place, with four of these articles having been cited in the background section of the CHEST protocol. In response to this retraction, the CHEST Management Committee initiated a number of measures, including conducting this meta-analysis with and without the retracted studies.

The authors of this meta-analysis provided meticulous description of their methodology. The study selection process examined four electronic databases (Ovid MEDLINE, EMBASE, CENTRAL and controlled-trials.com) plus hand-search of reference lists of other published systematic reviews. Out of 3,504 studies that the initial search yielded, only 16 were finally included in the meta-analysis with an additional 11 that met inclusion criteria but were in the retracted group.

This article indicates that 1) high-quality trials are needed to provide high-quality evidence for practice questions, and 2) high-quality trials and proper data analysis can overcome rare events of scientific misconduct.

Question:

According to a recent meta-analysis, administration of 6% hydroxyl-ethyl starch 130/0.4 to critically ill patient is associated with which one of the following:

A. Increased mortality
B. Worsening renal function
C. Coagulopathy
D. Increased blood transfusion requirements
E. None of the above

Answer: E

Literature Review: Impact of a National Propofol Shortage on Duration of Mechanical Ventilation at an Academic Medical Center

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Roberts R, Ruthazer R, Chi A, Grover A, Newman M, Bhat S, Benotti S, Garpestad E, Nasraway SA, Howard W, Devlin JW. Impact of a national propofol shortage on duration of mechanical ventilation at an academic medical center. *Crit Care Med.* 2012; 40(2):406-11.

Numerous medication shortages have impacted the specialty of critical care medicine over the past few years, including antibiotics, vasoactive drugs, neuromuscular blocking drugs and analgesic/sedation agents. Of these, the delivery of propofol to most health care systems was, perhaps, the most significantly impacted. Shortages of propofol began in late 2009 for many hospitals and continued through the middle of 2010. The consequence of this severe shortage of propofol for patients is largely unknown. Dr. Roberts and colleagues, therefore, conducted an evaluation of the effect of this shortage in patients requiring mechanical ventilation in their intensive care unit.

In their single-center, retrospective, before/after study of the effect of the national shortage of propofol on the duration of mechanical ventilation (MV) in a single academic medical center, the authors evaluated patient outcomes from October 2009 through May 2010 (the "after" period) compared to patient outcomes from October 2008 through May 2009 (the "before" period). During this interval, these investigators found a significant reduction in the percentage of patients who received at least 24 hours of propofol infusion (Table 1) and an increase in the percentage of patients who received a non-propofol sedative (Table 1). Despite the groups having similar baseline characteristics, the investigators found a significantly longer duration of MV during the period after the shortage compared to the period before the shortage (9.6 days vs. 6.7 days [p=0.02]).

This article is the first publication that has demonstrated a potentially significant negative consequence of a national drug shortage to patients in the intensive care unit. Although the authors determined that patients required approximately two more days of mechanical ventilation during the shortage, multivariate linear regression modeling performed by these investigators determined that admission to the medical service, higher APACHE II score, and the use of pressure-controlled ventilation were all significantly associated with an increased duration of mechanical ventilation in these patient cohorts. Interestingly, when all of these risk factors were included in a subsequent risk model, the duration of ventilation was found to be similar (not statistically different) between the before-and-after propofol shortage groups. In this regard, the authors of this article demonstrate one of the most important lessons when evaluating critical care literature. Namely, that many factors affect the outcomes of our patients – the selection of sedative agent, while important, appears to interact with a host of other variables and apparently has only a small part to play in the overall length of mechanical ventilation.

Undoubtedly, more drug shortages will occur in the future. To fully evaluate the effect of these shortages in our patients, we will have to carefully analyze the confounding effect of the many interrelated factors. At that point, we will have to find a way to mitigate the effect of these shortages or decide that care can be provided safely in many different ways.

Table 1: Use of Sedative Agents Before and After Propofol Shortages

	Before Shortage (%)	After Shortage (%)	p-value
Propofol	94	15	< 0.001
Midazolam	36	73	< 0.001
Lorazepam	7	14	0.04
Dexmedetomidine	9	27	<0.001

Modified from: Roberts R, Ruthazer R, Chi A, et al. Impact of a national propofol shortage on duration of mechanical ventilation at an academic medical center. *Crit Care Med.* 2012; 40(2):406-11.

Literature Review: Delaying Total Parenteral Nutrition: Better Late and Maybe, Even Better, Never

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Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med.* 2011; 365:506-517.

The term *hyperalimentation* was first used in the American medical literature around 1887 when advanced tuberculosis was still endemic.[2,4] The practice of caring for tubercular patients with "phthisis" (i.e., cachexia, wasting, or emaciation from disease) consisted of, in part, hyperalimentation, or augmenting caloric intake with slurries of ground food with milk or water, by way of an orogastric or nasogastric tube.[4]

The term *parenteral feeding* came from a different lineage. It was coined around 1912,[5] though it referred to experiments on animals, not human clinical applications, in which either serum proteins or nutrients were given subcutaneously or intravenously.

When the actual clinical practice as we know it debuted in the late 1960s,[8] the term "hyperalimentation" was co-opted, even though it then referred to the administration of sterile intravenous nutrient solutions to critically ill patients through centrally placed intravenous catheters. Because the alimentary canal was now circumvented, 'hyperalimentation' was evidently perceived as a misnomer.

The terms *parenteral nutrition or total parenteral nutrition* (TPN, i.e., if all nutrients are supplied intravenously) have since gradually replaced "hyperalimentation." When the complications (mostly increased incidence of sepsis, especially fungal)[10] of parenteral nutrition became better known in the early 1970s, then tube feeding had a resurgence in interest. The gut again became the first choice for ICU nutrition of NPO patients. Soon the metalepsis *enteral nutrition*, though coined in 1948, reappeared colloquially some 30 years later. The "enteral nutrition" of 1980 to the present time, ironically, actually refers to the 19th century practice of "hyperalimentation."

The long struggle to establish parenteral nutrition (PN or TPN) as a mainstay of therapy began a half-century ago. Stanley Dudrick, an academic surgeon from Yale, is one of the fathers of parenteral nutrition. He and his colleagues were the first to document successful positive nitrogen balance and good health in animals and humans supported entirely by parenteral nutrition.[7,8,9]

Dudrick summarized in a recent historical review the Herculean difficulties surmounted, over half a century, in establishing TPN as a state-of-the-art nutritional therapy:[8]

> "[They] included: (1) formulate complete parenteral nutrient solutions (did not exist), (2) concentrate substrate components to 5–6 times isotonicity without precipitation (not easily done), (3) demonstrate utility and safety of long-term central venous catheterization (not looked upon with favor by the medical hierarchy), (4) demonstrate efficacy and safety of long-term infusion of hypertonic nutrient solutions (contrary to clinical practices at the time), (5) maintain asepsis and antisepsis throughout solution preparation and delivery (required a major culture change), and (6) anticipate, avoid, and correct metabolic imbalances or derangements (a monumental challenge and undertaking)."[8]

Since its advent, TPN has been followed by continuous controversy, always centered on the question of risk plus cost versus benefit. Risk has almost always presented from sepsis or complications of catheter placement in the central circulation. Cost was and remains high in comparison to enteral feeding. Benefit often was hard to document, especially in cases where return of gut function was not predictable, and the course of PN delayed in onset and brief in duration.

Suffice it to say that the experts of TPN, Dudrick included, have been adamant since the beginning about its use only in cases where the gut is surgically absent or absolutely nonfunctional. Nevertheless practice patterns were such that the new therapy was overwhelmingly popular in the years 1969 to 1971, and TPN was used in cases outside the subset of patients whom the experts had considered fitting candidates.

Reports about serious infections, fungal septicemia especially (c. 30-50 percent mortality) surfaced. Not so obvious or well remembered, though, were the inevitable problems related to central line placement in the pre-ultrasonography, pre-patient safety, see-one-do-one-teach-one era. Overall, concern about the safety of parenteral nutrition peaked with Curry and Quie's 1971 article, prompting this jeremiad in an accompanying editorial by Duma:[3]

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Literature Review: Delaying Total Parenteral Nutrition: Better Late and Maybe, Even Better, Never

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"In this era of increasing nosocomial and iatrogenic diseases, the study by Curry and Quie in this issue of the Journal is of considerable import, for the authors' observations of frequent fungemia (in retrospective studies 67 per cent) or septicemia (in prospective studies 27 per cent) associated with or resulting from intravenous hyperalimentation disturbs everyone and must procreate misgivings about the "blessings" of "progress" and "modern medicine." Although the mortality directly attributable to such fungemia could not be ascertained with certainty, the authors judged it as considerable, perhaps greater than 50 per cent…"

"…Should the consumer (the patient) have a voice in its administration? After all, we demand a signed permit before appendectomy, the mortality of which in uncomplicated cases is less than 1 per cent. Can hyperalimentation be made safe, or at least safer than it is?"[3]

"…Should the consumer (the patient) have a voice in its administration? After all, we demand a signed permit before appendectomy, the mortality of which in uncomplicated cases is less than 1 per cent. Can hyperalimentation be made safe, or at least safer than it is?"

The controversy rages on. The paper by Casaer et al,[1] featured in this review is a report of a large (4,640 patients) randomized, multicenter trial comparing the risks and benefits of early initiation of parenteral nutrition (European guidelines)[12] versus late initiation (Canadian[14] and American[13] guidelines) in adult ICU patients.

Methods:

In the European-guideline (early initiation) limb (2,312 patients), parenteral nutrition was initiated within 48 hours after ICU admission. In the Canadian and American-guideline (late initiation) limb (2,328) patients, parenteral nutrition was begun day eight or later. Also, early enteral nutrition (identical protocol for both limbs) was applied. Insulin infusions were used for all patients to control hyperglycemia.

Patients who were assigned to the **early-initiation group** first received intravenous 20 percent glucose solution: 400 kcal per day on ICU day 1 and 800 kcal per day on day two. On day three, PN (OliClinomel or Clinimix, Baxter, Deerfield, IL, USA) was initiated, with the dose targeted to 100 percent of the caloric goal through combined enteral and parenteral nutrition (except when clinicians predicted that the patient would tolerate sufficient enteral nutrition or oral feeding on day three). The amount of parenteral nutrition was calculated daily as the difference between the total energy intake (protein energy included) that was effectively delivered by enteral nutrition and the calculated caloric goal. The maximum caloric goal for all patients was 2,880 kcal per day. When enteral nutrition met 80 percent of the calculated caloric goal or when the patient was able to resume oral nutrition, parenteral nutrition stopped. Parenteral nutrition was restarted whenever enteral or oral intake fell below 50 percent of the calculated caloric needs.

Patients who were assigned to the **late-initiation group** first received 5 percent glucose solution in an equal volume to that of the parenteral nutrition administered in the early-initiation group in order to provide adequate hydration, with the delivered volume of enteral nutrition taken into account. If enteral nutrition was inadequate after seven days in the ICU, parenteral nutrition was initiated on day eight to reach the caloric goal.

All patients who were unable to eat by day two received enteral nutrition via duodenal tubes Twice-daily increases in the infusion rates for enteral nutrition and prokinetic agents were also used. Patients in both study groups received parenteral trace elements, minerals (potassium, phosphate, and magnesium), and vitamins early in their ICU stay.

Results:

The baseline characteristics of the patients were remarkably similar, except for their mean weights (the early initiation group weighed one kg more, ($p </= 0.05$) a statistically though probably not a clinically significant difference.

More patients in the late-initiation group were discharged alive from the ICU ($p </= 0.007$). More patients in the late initiation group had hypoglycemia during the study intervention ($p </= 0.001$). The late-initiation patients spent a median one day less in the ICU ($p </= 0.02$), had significantly fewer patients in the lengthy-ICU stay (three day) category ($p</= 0.02$), and had a 1.06 hazard ratio (1.00 – 1.13) for live discharge from the ICU ($p</= 0.04$) compared with the early-initiation group.)

With regard to days spent on mechanical ventilation, those in the late initiation group had a shorter mean duration of mechanical ventilation ($p </= 0.02$), fewer patients in the long (greater than two days') mechanical ventilation group ($p </= 0.006$) with a hazard ratio of 1.06 (0.99 – 1.12) for briefer time

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to weaning from mechanical ventilation (p </= 0.07).

Patients in the late-initiation group were also likely to require fewer days of renal replacement therapy (p </= 0.008), spend two fewer days in hospital (p </= 0.04) and be much less likely to have lengthy (> 15 day) hospitalizations (p</= 0.001).

The distinction between the limbs became more pronounced when looking at complications, especially infectious ones (Table 1)

Discussion:

Criticism of the Casaer et al. paper in the journal's correspondence dealt with a number of issues.[11] Blinding was not entirely possible because of the nature of the methods, but, again, the authors pointed out that the data was analyzed by persons outside of the ICU who were unfamiliar with the patients.

One set of correspondents, Felbinger et al,[11] pointed out that more than half of the patients were *status post* cardiac surgery. Most ICU practitioners do not routinely support CV surgery patients with parenteral nutrition, yet they were a large fraction of study patients. The authors replied that nevertheless, these cardiac patients met criteria for nutritional support. Could this be a statement about the generally poor nutrition in the surgical population?

The incidence of infectious complications in the TPN-1970s era of Duma[3] and Curry and Quie[10] was considerable, with sepsis occurring in 67 percent of patients receiving TPN in a retrospective analysis, and if measured prospectively, in 27 percent of TPN patients.[10] Things have improved considerably since then, with Casaer et al. in 2011 identifying prospectively only 6.1 percent sepsis (late-initiation group) and 7.5 percent sepsis (early-initiation group) in such patients.[1] (Table 1.) But sepsis is still a tremendous risk-burden among those receiving TPN, given that mortality from sepsis, especially from fungal septicemia, remains very high today.

Hyperglycemia is a well-known risk factor for infectious complications. Here the unindicted co-conspirator in cases of sepsis was presumed to be the 20 percent glucose solution used as first nutritional therapy in the early-initiation group.[11] One correspondent pointed this out, referring to the NICE-SUGAR study,[11,15] which showed that hyperglycemia, as well as the use of insulin necessitated by it, were associated with increased infection rates, longer ICU stays, and worse outcomes overall.[11,15] Curiously, Casaer et al did not quantitate episodes of hyperglycemia,[1] of which there must have been many, probably as many as the recorded episodes of hypoglycemia.

In sum, it appears that late initiation is superior to early initiation of PN (as defined by the study protocol). Specifically late initiation of PN may be associated with faster recovery, fewer days supported by mechanical ventilation or renal replacement therapy and a savings of $1,600 per patient, faster discharge from the ICU and hospital, fewer ICU infections, and a higher (for whatever it is worth) C-reactive protein level.

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Table 1: Infectious Outcomes in Casaer, et al,[1] (N = 4,640)

Variable	Late-initiation (n = 2,328)	Early-initiation (n = 2,312)	P value
New infection – no. (%)			
Any	531 (22.8)	605 (26.2)	0.008
Airway or lung	381 (16.4)	447 (19.3)	0.009
Bloodstream *	142 (6.1)	174 (7.5)	0.05
Wound	64 (2.7)	98 (4.2)	0.006
Urinary tract	60 (2.6)	72 (3.1)	0.28
**cf. Curry and Quie: PN-associated sepsis rates 67% (retrospective), 27% (prospective).[10] See also the accompanying editorial of Duma.[3]*			
Inflammation Outcome			
Median peak C-reactive protein level during ICU stay (interquartile range) - mg/l			
Med peak CRP	190.6 (100.8 – 263.2)	159.7 (84.3 – 243.5)	<0.001

Lastly, the costs incurred in the late-initiation group were less by about €1,100 ($1,600), (p </= 0.04).

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If less PN is better, then, what if we consider calorie-underfeeding (advocated by Bistrian in his correspondence[11] or the use of even less PN (advocated by the authors in their reply to the correspondence[11] or no PN as comparison limbs in future studies? There appears so far to be no proven floor beneath which PN is absolutely beneficial, except, of course, when there is no alternative due to absent gut.

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Question:

Which one of the following was NOT found to be an outcome of patients receiving late-TPN initiation among 4,640 hospitalized intensive care unit patients in a recent New England of Medicine study of parenteral nutrition by Casaer et al?[10] (Choose one of the following):

A. Significantly lower incidence of bloodstream infections (p </= 0.05).
B. Significantly lower levels of C-reactive protein.
C. Shorter mean duration of mechanical ventilation (p </= 0.02).
D. Fewer days of renal-replacement therapy (p </= 0.008).
E. More likely to be discharged alive from the ICU (p </= 0.007).

Answer: B

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