NEWSLETTER

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AMERICAN SOCIETY OF CRITICAL CARE ANESTHESIOLOGISTS

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President's Message

Professionalism: Disclosure

Todd Dorman, M.D.
ASCCA President

"A day without sunshine is like, you know, night."
- Steve Martin

Disclosure, the revealing to others of normally confidential or private information, is the most ubiquitous response to financial relationships and conflicts of interest in all sectors of society. Rules govern disclosure in many domains that impact the public. For example, in journalism, the Code of Ethics of the Society of Professional Journalists (2005) states that journalists should "disclose unavoidable conflicts" and remain free of associations that may damage their credibility.

Disclosure in health care has become a hot topic. There are many who believe that disclosure is not necessary and others who advocate full disclosure to the point of health care providers having their tax returns made public. Whatever your belief, there is an enormous focus on this topic by accreditation bodies, senate committees, the Office of Inspector General and the media. In keeping with this focus, I have decided to dedicate this article to the concepts surrounding disclosure – including the rationale for disclosure – information regarding its effectiveness, and to providing some opinions on how disclosure will likely be handled in the future.

Before I go any further, let me provide some disclosure to you. I am the Associate Dean and Director for the Office of Continuing Medical Education at The Johns Hopkins University School of Medicine. This office accepts grants for educational activities. Although I presently do not have any other commercial relationships, I have had several in the recent past. Until about a year ago, I held stock in VISICU, Inc. When VISICU was purchased by Phillips, Inc., my stock was paid out. I also served as a consultant to an incubator company, Electrocore, Inc., from 2006 until the summer of 2007. During that time frame, I was paid less than a couple of thousand dollars for advice related to potential development of a new treatment paradigm for a common disease. You may ask why these are relevant and thus disclosed. I have disclosed these because some may wonder if my views are colored by the fact that I have had industry relationships in the past or by the fact that our CME office accepts industry grants. I do not offer these to absolve me of any responsibility, but to be transparent with information that some readers may find useful.

This topic, which is a component of professionalism, is experiencing rapid change. Such change is natural as we develop new filters to view our attitudes and behaviors. Just a decade ago, we viewed safety with the simple filter of "no harm no foul," yet now we not only look at near-misses as important but have begun to ask prospective questions such as "how might the next patient be harmed?" Similarly, our views of conflict are maturing, and we need to re-examine disclosure using these newly developed filters.

Supreme Court Justice Louis Brandeis famously stated, "sunshine is the best disinfectant." Through disclosure, it is believed that the information gap between the informed and the uninformed is reduced. In addition to reducing the information gap, it is generally considered to be a low-cost solution that can be ubiquitously applied.

Disclosure has several potential beneficiaries. In theory, individuals to whom disclosures are made may factor the disclosed information into their judgments about whether to, or to what degree, follow the advice. Institutions can likewise use disclosed information to monitor and attempt to ensure the integrity and impartiality of their members' decisions. Finally, disclosures may help researchers, policymakers, journalists and others investigate the consequences of financial relationships.

So disclosure is easy to do, is associated with minimal costs, and is commonly felt to be beneficial principally through a process akin to "buyer beware." If it is indeed beneficial, then how beneficial is disclosure, and is it sufficient for the management of conflict?

The first concern regarding disclosure is whether or not the disclosure provided is valid. Self-reporting carries the potential for inadequate disclosure related to ignorance or misunderstanding of disclosure policies, lack of effort or deceit. For disclosure to work, the discloseee must always ensure that the information provided is complete and accurate. Unfortunately, there are many examples where, indeed, physicians and researchers have not fully disclosed relevant information. It is highly likely that given the variety of rules and regulations regarding disclosure, including a variety of definitions of the relationships to be disclosed, many of these cases are related to simple misunderstandings. That being said, these instances still raise concerns about the validity of self-reported information. A common response by many is to always disclose all relationships in an attempt to never be caught short. This approach, however, can at times also be misleading as it masks important and critical relationships. We have all experienced this when we sign mortgage or insurance papers where repetitive disclosure forms are signed and important information is simply lost in the sea of trivial information.

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EDITORIAL NOTES

Editorial Policy

The opinions presented are those of the authors only, not of ASCCA. Drug dosages, accuracy and completeness of content are not guaranteed by ASCCA.

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President's Message

Even more fundamentally, it is possible that disclosure may have unintended negative consequences in certain situations. These perverse outcomes of disclosure are important to consider and include:

- The disclosee may overcompensate and downplay the personal benefits and thus not fully recommend an evidence-based approach out of an internal fear of being accused of bias.
- The disclosee may feel freed by disclosure and, through moral licensing, then feel that they can say and recommend anything as it becomes the listener's fault for believing something offered by an individual who has made it clear that they have a conflict. This is the ugly side of the "buyer beware" concept.
- The receiver of the disclosure may discount advice as they may not know if they can trust the disclosee and thus they may not accept evidence-based recommendations.
- The disclosee may be seen as an expert merely on the basis of having these relationships, and thus their recommendations may be followed blindly with less critical consideration.
- The disclosee may be seen as honest and thus blindly followed.

Research has shown that although patients are quite ready to allow for the fact that physicians in general might be biased by conflicts of interest, they are unlikely to believe that their own physician is vulnerable to such bias. Essentially no data exist regarding the impact of these perverse effects on physicians. One would postulate that they may indeed impact some physicians, especially when the information gap is wide, given that the less-informed physician might be a poorer judge of the quality of the evidence provided or just may not recognize inaccurate or incomplete information.

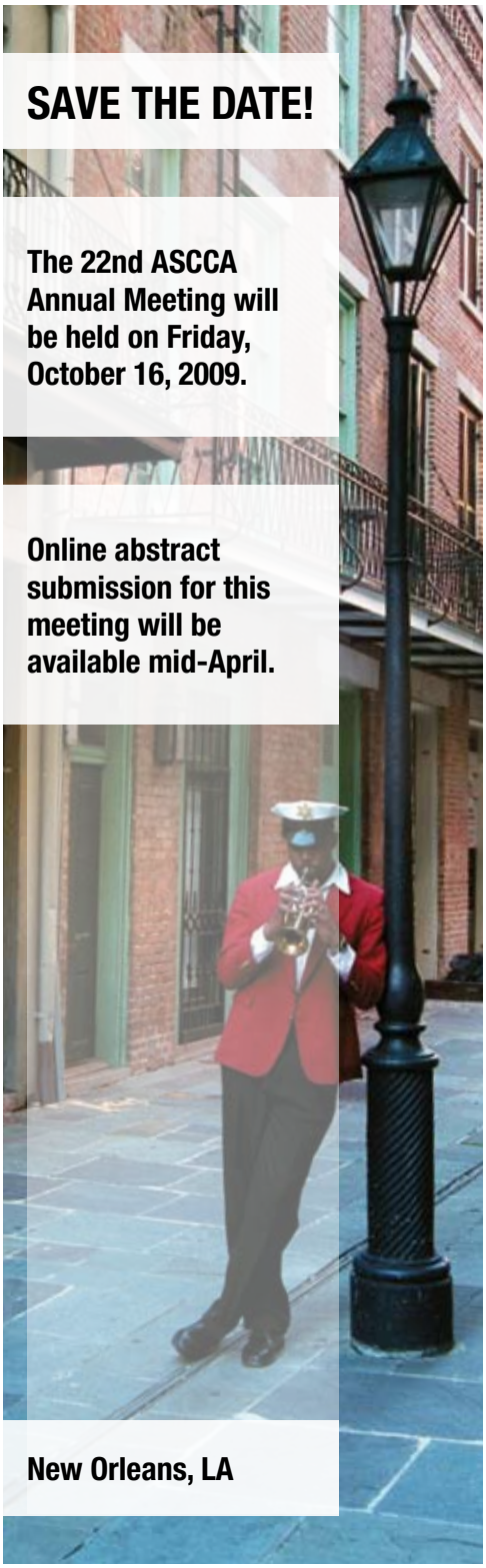
Contrary to common belief, disclosure may actually be more important for the disclosee than for the receiver. This is interesting in that originally it was thought that disclosure benefitted only the receiver (e.g., buyer beware). In fact, when done correctly, disclosure may discourage the acceptance of some relationships and thus through stigma avoidance lead to a self-calibrating effect. When it comes to the proverbial drug company pen and other small inducements, physicians may conclude that accepting these benefits is not worth risking a loss of reputation if they are disclosed. As gifts become larger, however, although the temptation to accept them may increase, so does the likely perception of impropriety and the risk of damage to reputation once disclosed. An important implication of this line of reasoning is that the effectiveness of disclosure as an antidote to biases caused by financial relationships with industry and a deterrent to inappropriate or unnecessary relationships is likely to be increased by policies that set no minimum dollar amount on the gifts or relationships to be disclosed.

So disclosure, like most of what we do, has some benefits and some risks that in the end make disclosure required yet insufficient as a sole means of conflict of interest management. Other strategies are already being added that include advance submission of materials and peer review. All other strategies will be more costly than disclosure, and thus we need to maximize the disclosure process in order to gain the most benefit.

"Research has shown that although patients are quite ready to allow for the fact that physicians in general might be biased by conflicts of interest, they are unlikely to believe that their own physician is vulnerable to such bias."

It is likely that in the near future, full disclosure will be required, even at lectures for students in the classic classroom university setting. Too often during public disclosure at a lecture, the lecturer makes light of disclosure, thus minimizing its "sunshine" potential. When disclosure is done, we need to strive to not make it a joke, but a serious step in providing transparency to the receivers. We will likely be required to disclose financial amounts associated with relationships. Many device manufacturers are already publicly reporting this type of information, and it is highly likely that the trend will not only continue but there will a regulatory requirement to do so. Health care will need to better define each of the types of relationships so that accurate disclosure and interpretation can be made. For instance, consultancy for an incubator company at the infancy of ideas is more akin to research and development, whereas consultancy after phase IV trials are complete is more akin to marketing. Thus merely disclosing a consultancy may not provide adequate "sunshine." Finally, all would benefit from a standardization of the rules regarding disclosure. At present, this variability of rules and requirements belittles the concept and the process and makes any single set of rules seem capricious.

The ASCCA leadership is reviewing our conflict policies and those of ASA that may apply to us. We, like many medical societies, are discussing if we should add disclosure to our Web site, and if so, what should be disclosed and for whom. For example, should only the president disclose, or all executive board members, or the full board? Should committee chairs be included or not? Should our disclosure be for relationships during the past year or for a longer period of time? The Council of Medical Specialty Societies (CMSS) has a task force that is reviewing all member organization policies and will be making recommendations that we will review and take into consideration as we try to navigate this changing landscape.



SAVE THE DATE!

The 22nd ASCCA Annual Meeting will be held on Friday, October 16, 2009.

Online abstract submission for this meeting will be available mid-April.

New Orleans, LA

Pro: Glycemic Control for Critically Ill Patients

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Since a seminal 2001 study[1] by Van de Berghe et al., much attention has been devoted to glycemic control in the critically ill. This study showed that tight control of blood glucose in a surgical ICU population resulted in improvement in numerous outcomes, including a 34-percent reduction of in-hospital mortality. While subsequent studies have not fully confirmed these benefits, there are still many reasons why tight glycemic control in the ICU makes sense. Hyperglycemia is common in ICU patients and has been associated with negative outcomes such as infection, CNS dysfunction and mortality.[2] Similarly, maintenance of normoglycemia via insulin infusion has been shown to decrease rates of nosocomial infections,[3] acute kidney injury,[4] critical illness polyneuromyopathy[5] and neurologic disability.[6] In addition, there are plausible biologic mechanisms by which reducing blood glucose is beneficial, including reduction of oxidative stress and inflammation and improvement of neutrophil function.[2]

While hypoglycemia is four to seven times more common in patients receiving intensive insulin therapy than those on conventional therapy,[7] it is unclear what impact such episodes may have on outcomes. As with any treatment, intensive insulin therapy has risks and benefits that must be managed. There are likely patients who will benefit more from tight glycemic control, as well as patients who are at greater risk for complications. The key to reaping the benefits of tight glycemic control is to better identify these subgroups and learn to reduce adverse events through interventions such as early enteral and parenteral nutrition. More research is necessary to delineate the optimal candidates for tight glycemic control, but this valuable modality should be improved rather than dismissed.

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Con: Glycemic Control for Critically Ill Patients

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Implementation of tight glucose control using intensive insulin therapy in critically ill patients has been embraced in most intensive care units in the nation and worldwide since publication of compelling data showing a 4-percent decrease in absolute mortality.[1] With implementation of standardized protocols to achieve tight glucose control using insulin infusions, it became evident that achievement of target normoglycemia 110 mg/dl is not clinically attainable without complications. Serious questions have been raised about reproducibility and safety of this ICU treatment modality. Subsequent retrospective trials found that glucose level below 140 mg was associated with improved outcomes compared to higher levels, above 180 mg/dl, thus pushing the desired target range to a higher level.[2,3,4] The Gluconotrol trial[5] was initiated to determine target glucose control (79.2-109.8 mg/dl vs 140-180 mg/dl). It was stopped due to a 12-percent incidence of hypoglycemic episodes and increased associated mortality (40 mg/dl or lower). Other groups have reported rates ranging from 5 percent to 30-40 percent in tightly treated patients. Duration of hypoglycemic episodes appears to be an important determinant of outcome.[6] The risk-benefit ratio appears in favor of the group with the higher glucose target (140-180 mg/dl); therefore, it is fair to say that this target has become common practice in most ICU protocols. Risk for hypoglycemia in patients receiving intensive insulin therapy is increased in patients with hepatic, adrenal, renal failure, veno-veno hemofiltration with the use of bicarbonate, female gender, sepsis and in diabetes.[7] In a large retrospective review of critically ill patients, survivors had a lower variability in glucose levels compared with non survivors.[8] In non-ICU patients, fluctuations in blood glucose increased oxidative stress measured by urinary concentration of 8-iso prostaglandin F2 alpha, an index of the peroxidation of eicosanoids. These findings indicate that cell damage was most prominent when the glucose in the culture medium changed rapidly.[9] In the Van den Berghe study from 2006, intensive insulin therapy did not reduce hospital mortality except in patients who stayed in the ICU at least three days.[10] Secondary outcome was also not improved, such as: requirement for dialysis, incidence of bacteremia, hyperbilirubinemia, pronounced inflammation and 28-day mortality.

Rightfully, the former belief of "stress hyperglycemia" as an adaptive physiological response has been challenged. Based on the current evidence, reproducibility of tight glucose control and, possibly more importantly, glucose variability will require safer guidance than current available means. "Generalized management" of critically ill patients does not appear to be the advocated practice based on the evolving literature. Better understanding of the "greater metabolism" will certainly bring more light to the unanswered questions and possibly novel strategies to address metabolic derangements in various states of critical illness.

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Adding Clevidipine to Your Formulary: The Case AGAINST

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The efficacy of clevidipine (ESCAPE-1 and ESCAPE-2) trials compared the drug to intralipid placebo in pre- and post-cardiac surgery patients.[1,2] The studies concluded that clevidipine "could be considered as a first-line IV antihypertensive drug" for CABG patients when compared to placebo. The related ECLIPSE trial showed no significant differences between clevidipine and the three comparator drugs (nitroglycerine, sodium nitroprusside and nicardipine).[3] The exception is a statistical mortality benefit of clevidipine versus nitroprusside.

European researchers compared clevidipine with nitroprusside in a double-blind study of patients undergoing CABG surgery.[4] The results led the study group to conclude that "the efficacy and ease of use of clevidipine and sodium nitroprusside in the control of arterial pressure in post-CABG patients were identical…"

These studies show that clevidipine is equivalent to other agents for acute hemodynamic control. However, it is expensive, and cost is a major factor in adding new, unproven drugs to our formulary. Currently, clevidipine costs approximately 40 percent more than nicardipine.[5]

Other drawbacks remain. Clevidipine must be refrigerated (it is prepared in a white lipid emulsion and is contraindicated with soy or egg allergy or defective lipid metabolism)[6]. Because clevidipine provides a bacterial medium, the vial requires replacement every four hours, further increasing its cost. It also may be confused with propofol.

Clevidipine is no better, more expensive, and probably less safe than proven alternatives. It should be added to a formulary only when a clear benefit can be shown.

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Adding Clevidipine to Your Formulary: The Case FOR

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In the O.R. and ICU environment, hypertension is associated with myocardial ischemia, reperfusion injury and surgical bleeding. The etiology of acute hypertension is the overactivity of the sympathetic nervous system with resulting peripheral vasoconstriction. In this setting, the ideal antihypertensive would be parenteral, have rapid onset and offset, be titratable, have no toxic metabolites, and a favorable side-effect profile. Clevidipine butyrate meets all these criteria. It is a dihydropyridine L-type calcium channel blocker. Clevidipine is arterially selective, reducing peripheral vascular resistance directly, with minimal venous dilatation and has consistent dose-dependent effects. It is > 99.5 percent bound to plasma proteins, metabolized by non-specific blood and tissue esterases, has an initial-phase half-life of one minute and is unaffected by hepatic or renal dysfunction. As it is not metabolized by the cytochrome P450 system, it has low potential to interact with other drugs. In an RCT of cardiac surgical patients, clevidipine was > 90 percent successful in controlling systolic blood pressure. Unlike currently commonly used I.V. anti-hypertensives, clevidipine has no toxic metabolites, no effects on preload, has less potential for overshoot/undershoot hemodynamic parameters and does not need to be protected from light during administration. Concerns for reflex tachycardia can be allayed by the ECLIPSE trials, where there were no significant differences found on the incidence of atrial fibrillation or sinus tachycardia when compared to nitroglycerin, nitroprusside and nicardipine. The ECLIPSE trials also demonstrated no difference in 30-day incidence of death, MI or stroke. These data show that clevidipine should be strongly considered by intensivists and anesthesiologists when starting antihypertensive therapy in the acute setting.

Special thanks to Lisa Weavind, M.D., for facilitating these pro/con articles.

Letter From the Editor

Michael H. Wall, M.D., F.C.C.M.
Editor, ASCCA *Interchange*

In order to make the ASCCA newsletter more interesting to our readership, the editorial board is making several changes to it. The first is that there will be three electronic/PDF editions (March, June and December) and one old-fashioned paper and mailed edition (August). We have also added three new sections to each edition. There will be two to three brief literature reviews of recently published manuscripts, one to two pro/con debates on controversial topics and two to three fellowship program reviews.

Finally, if you have ideas for the newsletter or if you would like to contribute a literature review, pro/con or fellowship review, please let me know.
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Fellowship Review: University of Chicago

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Welcome to the University of Chicago Department of Anesthesia and Critical Care (DACC)! We offer a 12-month fellowship that highlights the scope of critical care medicine at the University of Chicago Medical Center. Our clinical program is designed to accommodate the needs of individual fellows while satisfying the requirements of board eligibility for ABA. Our intention is to allow fellows to design a curriculum that will best prepare them for their subsequent careers. We are proud to recognize our fellowship graduates, who have all taken and passed the critical care board exam – all of whom are finding great successes in their careers as academicians.

Like 6 Fellowships in One

Fellows participate in patient care and supervision of residents and medical students in a variety of ICUs, including cardiothoracic, surgical, medical, neurosciences, pediatrics and the burn center. Three months of electives may be clinical or research. Opportunities are available in clinical or basic science research projects. A second year of combined research or clinical training is available.

Begin With Us, End With Us

A new fellow begins the year with two months in the cardiothoracic ICU and burn center. These ICUs are staffed by faculty from the DACC, and the rotations introduce you to your new life as a fellow, to the hospital culture, and of course, the critical care section of DACC.

The experienced fellow concludes the year with another month in a DACC ICU. You will take an increasingly prominent role in rounds, communications and the educational mission for residents.

The remaining nine months are usually divided as follows: three months of MICU, one or two months of neuroICU, one or two months of PICU, and three months of electives. Rotations last one month and can vary in sequence. As a fellow in each ICU, our expectation is for you to assume the responsibility of respective fellows. That is, in the PICU, you take call as a PICU fellow. In the MICU, you take call as a MICU fellow. While we don't expect you to have immunization schedules memorized, your knowledge and experience as an anesthesiologist will establish your presence in each care team.

Electives. A Time for Choice and Imagination

We appreciate enthusiastic use of your elective time. Besides participation in research projects, fellows have extended their rotations in any ICU. Fellows have also rotated in radiology, nephrology, cardiology, ultrasound and TEE. We welcome creativity!

More Than Just Mattresses and Monitors

More than just counting VADs, vents or ventricular drains, you'll have the opportunity to work with nationally and internationally known faculty.

A partial list can be found at: **anesthesia.uchicago.edu/applicants/fellow_criticalcare.php.**

Feel free to contact our section chief, Professor Michael O'Connor, M.D.,
via our Program Coordinator, Theresa Cumming
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Critical Care Medicine at Stanford

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The critical care medicine (CCM) service at Stanford Hospital has been providing state-of-the-art care for patients with life-threatening conditions for more than 30 years. A comprehensive group of attending physicians from both anesthesia and pulmonary medicine personally directs all care given to patients on the service, teaching programs for residents and students, and a complete fellowship program for those interested in a career in critical care medicine.

The goal of the critical care medicine service is to provide the most effective and immediate care possible to patients who become critically ill in the hope that they will both survive their acute illness and eventually return to their previous state of health.

Critical Care Medicine Fellowship Overview

The Stanford Critical Care Medicine Program is approved by the Accreditation Council for Graduate Medical Education (ACGME) for anesthesia, medicine and surgical CCM. We have also trained fellows with neurology and emergency medicine backgrounds. This mix of backgrounds provides outstanding "cross-fertilization" among the fellows in the program.

The anesthesia CCM fellowship traditionally has been a one-year program involving patient care at Stanford Hospital, the Palo Alto Veterans Affairs Medical Center, and the opportunity for research that may include additional training if desired, but has recently been expanded to an optional two-year program in CCM and cardiac anesthesia. Satisfactory completion of CCM training allows anesthesia CCM fellows to apply for subspecialty certification in CCM by the American Board of Anesthesiology (ABA) if they are certified by the ABA in anesthesiology.

For those anesthesiologists who wish to apply to the two-year program at Stanford in both CCM and cardiac anesthesia, there is great flexibility in constructing a program that meets the individual needs of the applicant. Both services provide outstanding training for the person interested in the perioperative management of patients with cardiothoracic and vascular disease and who would also like to become certified in perioperative transesophageal echocardiography.

With the initiation of accreditation by ACGME in 1987, the Stanford CCM programs in anesthesiology and internal medicine have gained accreditation status each evaluation period; and with the establishment of subspecialty board certification in 1986, the CCM fellows graduating from Stanford have had **100-percent** success in attaining certification.

Clinical Training

The Stanford Hospital intensive care units consist of a 32-bed medical surgical intensive care unit and a 25-bed cardiovascular surgical intensive care unit. The main service for training during the fellowship is the **Medical-Surgical Intensive Care Unit Service**, on which the fellow works and is responsible for the management of 20 to 40 patients. It is important to point out that the MSICU service on which the fellow works is the **primary** team responsible for management of these patients.

Fellows also rotate to the **trauma ICU service** and **cardiothoracic ICU service** at Stanford Hospital and **Medical-Surgical ICU** at the **Palo Alto Veterans Administration Medical Center (PAVAMC)**. The experience at the PAVAMC is similar to that at Stanford, providing additional training in post-operative surgical and cardiac surgical critical care.

Echocardiography

Training in TTE echocardiography is provided each year through a four-week course taught by Stanford cardiologists with an emphasis on basic echocardiographic techniques with helpful case examples. The goal of this course is to allow critical care fellows to use echocardiography to assist in the bedside assessment of critically ill patients in order to quickly identify cardiac pathology such as tamponade, myocardial ischemia and major valve dysfunction as well as to familiarize the fellow with noncardiac applications of ultrasound in the ICU, in addition to ultrasound-guided vascular access techniques.

Research Training

The nonclinical portion of the fellowship is very flexible. However, fellows are expected to participate in some area of research related to critical care. Stanford University has numerous facilities where one can perform clinical and laboratory physiologic and molecular biological studies. A dedicated laboratory with technical, financial and computer support is also available to all fellows. In addition, the varied interests of our faculty can introduce the fellow to a wide variety of investigative skills.

Conclusion

In summary, the Stanford Anesthesia Critical Care Medicine fellowship is the complete package. Whether it is to establish a foundation on which years of investigation can be based, or to develop the clinical acumen required to confidently care for the most critically ill patients in the hospital, the CCM fellowship at Stanford Hospital can provide one with all the needed tools to achieve these goals.

Literature Review: MRC CRASH Trial Collaborators

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Article:

MRC CRASH Trial Collaborators. Predicting outcome after traumatic brain injury: Practical prognostic models based on large cohort of international patients. BRIT MED J. 2008; 336:425-429.

Accompanying Web site and calculator:
www.crash2.lshtm.ac.uk

Prognosticating following a patient's serious head trauma is a difficult part of the practice of many intensivists. The problem is not only one of fathoming ultimate outcomes, including degrees of long-term disability: In many locales, especially developing nations and in populations stricken by armed conflict, prognostication is intimately linked with triage decisions. The essential question being, does the patient's poor prognosis make aggressive intervention unwise, given the resources at hand? To date, there have been very few models that predict neurologic outcomes with any degree of robustness or accuracy and none based on a large population of patients. This model, a product of research at the London School of Hygiene and Tropical Medicine, is a significant advance on all fronts.

In its scope, the model tries to inform decision-making in both the developed and developing world. To do so, it consists of two versions, a basic predictive model (using only clinical signs such as GCS and pupil reactivity at presentation) and a CT model (using clinical signs plus several simple head CT criteria). The model is accessible on the Internet in a very user-friendly form **www.crash2.lshtm.ac.uk** as a Web page calculator so it is universally available.

In its power, it is unexcelled: The model was constructed using a large population of head-injury patients (10,008 patients enrolled in the UK Medical Research Council Corticosteroid Randomisation After Significant Head Injury [CRASH][1,2] study). The population then used for external validation of the model consisted of 8,509 head-injured patients in the IMPACT (International Mission for Prognosis and Clinical Trial meta-analysis) database.[3]

To construct the model, multivariable logistic regression was used to select variables that were independently associated with two patient outcomes: 1) death within 14 days of presentation and 2) degree of disability at six months according to the Glasgow Outcome Scale [Table 1]. The use of an internal (via multiple bootstrap resampling of the cohort) and external validation (by examination of the IMPACT cohort) made the model particularly accurate and highly discriminating.

The basic model input variables (recorded at presentation) were five: a) age, b) Glasgow Coma Scale, c) pupil reactivity and d) the presence of major extracranial injury, plus e) country of location. The CT model input variables were the above four data plus a) the presence of petechial hemorrhages, b) obliteration of the third ventricle or basal cisterns, c) subarachnoid bleeding, d) midline shift and e) unevacuated hematoma.

Table 1. Glasgow Outcome Scale (GOS)

Number	Outcome
1	Good recovery: able to return to work or school
2	Moderate disability: able to live independently; unable to return to work or school
3	Severe disability: able to follow commands/unable to live independently
4	Persistent vegetative state: unable to interact with environment; unresponsive
5	Dead

Consistent with older prognostic models, older age (than 40 years), low Glasgow coma score, absent pupil reactivity and the presence of major extracranial injury predict poor prognosis. This new model also revealed that: 1) obliteration of third ventricle or basilar cisterns was associated with the worst prognosis at 14 days; 2) SAH was an independent predictor of poor outcome; and 3) patients from low-middle income countries had a poorer prognosis than those from high-income countries.

The Web site calculator (also a resource for the paper and other related studies) is supremely easy to use. Input the variables, and the output is immediate: likelihood of death at 14 days (expressed as a percentage) and the likelihood of a favorable (1 or 2 GOS) or unfavorable (3, 4 or 5 GOS) neurologic outcome at six months.

This remarkable article (and Web site) would have been better if example images of the CT variables had been shown. This might decrease ambiguity in making input decisions. The paper's strengths absolutely outweigh this minor criticism.

References:

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CORTICUS for the Rest of Us

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Steroids have enjoyed a renaissance in septic shock, with highlights including Sprung in 1984 and Annane in 2002. Perhaps the pendulum has returned with CORTICUS, a negative study of "Hydrocortisone Therapy for Patients with Septic Shock," (NEW ENG J MED, January 2008).

Summary

- Multicenter, randomized, double-blind, placebo-controlled.
- 52 ICUs, March 2002 to November 2005.
- Sponsors had no role in the design and conduct of the study.
- Inclusion criteria (notable): onset of shock within the previous 72 hours (as defined by a SBP of < 90 mm Hg despite adequate fluid replacement or a need for vasopressors for at least one hour).
- Exclusion criteria (notable): a poor prognosis, life expectancy of < 24 hours.
  - Immunosuppression or previous steroid exposure.
- Randomization.
  - Placebo versus hydrocortisone 50-mg I.V. q6h x 5 d, then q12h x 3d, then q24h x 3 d, then stop.
  - Patients then were evaluated by corticotropin stimulation.
- Absence of a response to corticotropin: an increase in the cortisol < 9 µg/dL.
- Primary end point: rate of death at 28 days.

CORTICUS Reinforcing Sprung '84?

All subgroup analyses of CORTICUS reinforce the dangers of steroid therapy in sepsis. Non-responders had a greater 28-day mortality compared to responders. Non-responders, as defined by corticotropin stimulation test, identify a high-mortality group.

Dividing non-responders into steroid-exposed versus placebo, hypoadrenal patients had a higher 28-day mortality if they received steroids. Despite lower doses compared to Sprung '84, this study suggests that patients with corticotropin-identified hypoadrenalism would avoid mortality if they were able to avoid hydrocortisone.

In all patients randomized to steroids, nonresponders had a higher mortality. Thus, hypoadrenal patients, identified by corticotropin, are especially susceptible to the risks of hydrocortisone therapy. These risks may include superinfection, new sepsis, new septic shock and hyperglycemia.

Comparing the adverse steroid effects in responders and nonresponders, hydrocortisone treatment carried a higher mortality in each group. In responders, this rise in mortality is trivial (0.1 percent). The rise in mortality for nonresponders is an order of magnitude greater (3.1 percent). This reinforces that hypoadrenal patients are especially susceptible to the risks of hydrocortisone therapy, perhaps in a way for which responders are able to compensate.

CORTICUS and Annane '02 Coexistent Truths?

Although none of the subgroup analyses support the use of hydrocortisone in septic shock, this study suffers from a lack of power and a lack of statistical significance. While the uniformity of hydrocortisone's risk is striking, CORTICUS' study design suggests other possibilities when taken in context of Annane '02.

While CORTICUS anticipated a lack of efficacy from fludrocortisone, Annane '02 found statistically significant benefits to the combination of hydrocortisone/fludrocortisone. The benefit of the mineralocorticoid either in isolation or combination may be the prominent benefactor. Similar inferences can be made about time to drug administration, duration of treatment and patterns of steroid taper.

The single consistency between CORTICUS and Annane '02 is the unchanged mortalities of responders whether they received steroid or placebo. This suggests that responders tolerate low-dose hydrocortisone better than non-responders. While this parallels the physiologic metaphor of hypoadrenalism, perhaps the corticotropin test defines only a margin of safety for patients receiving hydrocortisone (despite its non-benefit). Conversely, corticotropin responsiveness may not be useful to guide steroid therapy in septic shock.

Believers and Non-believers

CORTICUS cites a loss of equipoise, which slowed recruitment, followed by study termination. Steroid non-believers may welcome the pendulum of data against hydrocortisone use in septic shock. Believers can point to the design and significance of that data in order to reinforce their clinical use of hydrocortisone. Questions for both include the mechanism of benefit for an oral mineralocorticoid in septic shock, and the clinical relevance of the corticotropin stimulation test.

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