



INTERCHANGE

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President's Column: Perioperative Surgical Home: An Opportunity for Critical Care Anesthesiologists



Brenda G. Fahy, M.D., F.C.C.M.

Currently, there is a re-animation process surrounding the role of anesthesiologists and perioperative surgical care with the concept of a perioperative surgical home (PSH). This re-animation process has already begun in Europe, and there are some lessons to be learned from the European model, including the use of Enhanced Recovery After Surgery (ERAS). Following the Society of Critical Care Anesthesiologists Annual Meeting in Montréal on Friday, May 16th, the International Anesthesia Research Society (IARS) is having an afternoon symposium titled, "Enhanced Surgical Recovery Program: The Role of the Anesthesiologist" on Sunday, May 18th, 2014 from 1:30 to 4:30 pm during the IARS 2014 Annual Meeting.

The development of the PSH represents additional opportunities for anesthesiologists for perioperative care participation and, specifically, anesthesiologists with critical care subspecialty expertise. Critical care anesthesiologists are uniquely poised for this opportunity because of their knowledge and expertise in the

perioperative continuum, including the use of their primary expertise as anesthesiologists. Within the scope of critical care, providers have the expertise to prepare and optimize critically ill patients preoperatively for elective and emergent surgical procedures. The practice of critical care by its very nature interacts within the larger health care system and often includes the transfer of patients between hospitals for their optimal care and discharge planning. The

numerous yet-to-be answered questions, and opportunities abound for contributions to the development of this model. Improving patient care throughout the perioperative continuum with the PSH model represents a goal for the Society of Critical Care Anesthesiologists to work toward, and our members can seek potential opportunities to contribute their expertise to the various aspects of the PSH model. This may require critical care anesthesiologists

Within the scope of critical care, providers have the expertise to prepare and optimize critically ill patients preoperatively for elective and emergent surgical procedures.

latter involves transitions of care, including early mobility during the postoperative period to enable earlier discharge and planning for skilled facility placement at a rehabilitation clinic or nursing home. Transitions of care are one aspect of the PSH that can allow for more coordinated care, including improved communication with those providing care after discharge to better optimize patient follow-up and quality of care.

With the advent of the PSH, there remain

outside Europe to begin to think differently about how their unique background of critical care experience affords opportunity. Hopefully there will be ongoing dialogue about areas for potential contributions to the PSH within the Society of Critical Care Anesthesiologists. I am looking forward to seeing all of you on May 16th for the SOCCA Annual Meeting in Montréal, Canada. Additional meeting details are available at www.socca.org.

This is my last newsletter as President of SOCCA. I have had the opportunity to work with a group of talented, terrific individuals – from the Board of Directors and executive directors to those who have volunteered their expertise and efforts to advance SOCCA this year and in the past. It's been my honor to serve as the President of this organization and I appreciate all the efforts that have been put forth by many individuals collectively to benefit SOCCA. The continued partnership with IARS should continue to propel SOCCA's future goals and I look forward to continued contributions on behalf of SOCCA.

Brenda G. Fahy MD
Brenda Fahy

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www.SOCCA.org

Membership

Membership in SOCCA is open to all anesthesiologists and residents in approved anesthesiology programs. Visit **www.socca.org/membership.php** for complete information on SOCCA membership.

SOCCA Dues

Dues are \$160 for active members; \$110 for affiliate members and \$25 for educational members. Medical Student Membership, individuals in full-time training in an accredited school of medicine, is free. Dues may be paid online at **www.SOCCA.org/membership.php**.

EDITORIAL NOTES

Editorial Policy

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

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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 **jmcrath@iars.org**.

ECMO – The Extreme Panacea Machine

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*“All men make mistakes,
 but a good man yields when
 he knows his course is
 wrong, and repairs the evil.
 The only crime is pride.”
 —Sophocles, Antigone*

In the early 1970s researchers got the idea that the “heart-lung” machine used for cardiac surgery might have applications outside the operating room.¹ During that time case reports appeared in the literature describing the use of the extra-corporeal membrane oxygenator (ECMO) to treat severe pre-transplant cardiac or pulmonary disease in children, many times with success. In 1989, the Extracorporeal Life Support Organization (ELSO) was formed as a “consortium of health care professionals and scientists who are dedicated to the development and evaluation of novel therapies for support of failing organ systems”² and the organization keeps statistics and publishes guidelines for both institution of ECMO and when it should be either 1) not considered or 2) when it should be discontinued if it is started emergently and there are contraindicating patient factors. It is important to remember that ECMO was and still is a therapy primarily considered for use in children and neonates with refractory respiratory or cardiac failure. However, as would be expected, it has found its way into the adult patient population, and there is a body of largely non-prospective evidence to suggest that it may increase survival in acute

respiratory distress syndrome (ARDS) patients, those with other forms of pulmonary failure, and cardiac arrest.³⁻⁵

All hail CESAR

The signature (and only) prospective, randomized ECMO study in an adult population was undertaken in 2009, when Peek and colleagues conducted the CESAR (Conventional ventilatory support versus Extracorporeal membrane oxygenation for Severe Adult Respiratory failure) trial in the United Kingdom.⁶ The study meant to answer the following questions: 1) is ECMO safe; and 2) is it cost-effective, using that country’s quality-adjusted life year (QALY) method? The investigators concluded that ECMO was relatively safe and cost-effective by U.K. standards, yet it was met with considerable criticism on methodological grounds and its (in)applicability to other health systems, notably the “resource infinite” U.S. model.⁷⁻⁹ One commentator noted that, “survival without severe disability was achieved but at approximately twice the cost and twice the length of stay.”¹⁰ The authors also touched upon what will be an increasingly greater problem – “reasonableness of access.”

Once such reasonableness problem concerns patients awaiting lung transplantation. Since ECMO emerged as a therapy for those with respiratory or cardiac failure refractory to other treatments, the medical literature is sprinkled with case reports of patients who have survived despite the odds. In 2013, Hoopes and colleagues concluded that using “artificial lung technology” is both technically feasible and logistically viable.¹¹ Interestingly, the ELSO guidelines counsel against routinely using ECMO for patients awaiting transplants.² The guidelines point out that ECMO therapy is expensive and hazardous, not to mention the fact that transplantable organs, particularly lungs, are increasingly scarce. Furthermore, ECMO is extremely resource intensive. The

ELSO’s “Guidelines for ECMO Centers” is quite exhaustive in scope and detail, and also states that a center should have at least six patients cannulated per year.

Who may live and who may die?

Much like the time when ventilators were novel and few hospitals had them, the advent of ECMO will pose many ethical dilemmas; however the following discussion will be confined to the scarcity of ECMO centers and circuits. Per ELSO guidelines, a phalanx of clinicians of various levels is required to initiate, maintain, and coordinate ECMO care, which centers on each program’s medical director. The toll on families is high and multi-factorial, and thus requires specially trained counseling personnel.¹² However, the ELSO guidelines do not discuss the potential need to triage patients who may fall within the criteria for inclusion. Consider the following scenario: a facility has six ECMO circuits, staff and resources to safely maintain five, and four patients receiving treatment, none of whom are projected for decannulation criteria in the next several days. The community has seen an unusually large number of H1N1 patients and the medical intensive care unit (MICU) has 2 such patients who meet ECMO criteria: both are young and relatively healthy, with refractory ARDS and no secondary organ failure. However, only one can be safely cannulated due to institutional resource limitations. Which patient will it be and who decides? The ELSO charges each institution with answering such dilemmas but gives a dearth of actual guidance.

Such an approach seems to be fraught with peril, leaving families grieving and hospitals grasping at ethical straws. Furthermore, there seems to be no standardized triage process among recognized ECMO centers. However, one may consider the United Network for Organ Sharing (UNOS) as a template for the

Continued on page 4

ECMO – The Extreme Panacea Machine, continued

Continued from page 3

stewardship of ECMO as an increasingly used but scarce resource.¹³ UNOS is centralized nationally, with a board of directors to ensure both quality and equality. Of course, there have been news accounts of patients who circumvented this system to obtain a transplant, but they are few. UNOS appears to function well. One could consider the “ECMO unit” (machine + staff) akin to a solid organ: much in demand and very scarce. A “United Network for ECMO Sharing” would function in much the same way as UNOS. One benefit would be that approval for ECMO cannulation in clinically and ethically challenging cases could be made by an impartial committee to ensure justice for candidates (in the above example, what if one of the patients was a close relative of a prominent donor or a relative of the program director?). Obviously, there would be barriers to such an organizational scheme. For example, some families may not have the means to pay for safe critical care transport to the nearest center with an available circuit, particularly if the patient lacks health insurance, let alone the cost of weeks or more of lodging. What is clear is that at some point society must determine when and if ECMO is a treatment for which the financial burden is worth sharing.

Our center alone has generated a good deal of local publicity on ECMO, one news outlet dubbing it the “extreme flu machine,”^{15,16} and so it is simply a matter of time before there must be a public debate about fair use. Only more independent, prospective or well done observational research on ECMO in the U.S. can help answer emerging ethical and clinical questions unique to our healthcare culture. The sooner the better.

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Fellowship Review: Beth Israel Deaconess Medical Center



*Shahzad Shaefi, M.D.
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Trauma ICU, the Surgical ICU and the Cardiovascular ICU.

The ten-bed Trauma Intensive Care Unit (ICU) houses the patients of the busy Acute Care Surgery and Trauma Surgery teams with ample trauma volume. The Surgical ICU is a fifteen-bed unit admitting a wide variety of general surgical, neuroscience (active open and endovascular service) transplant (liver, pancreas, kidney), and thoracic surgery (tracheal and parenchymal work) patients needing advanced care. The sixteen-bed Cardiovascular ICU cares for a wide variety of operative cardiac and vascular surgery patients including those patients needing

ventricular assist devices and extracorporeal membrane oxygenation (ECMO), thoracic aortic surgical cases as well as other complex vascular surgery. Alongside the ICU rotations, fellows receive advanced ECMO training on a two-week rotation at Boston Children's Hospital. These rotations comprise nine training months, leaving three months of elective time. Popular choices include transthoracic echocardiography with the Cardiology Department, advanced operating room transesophageal echocardiography, radiology, blood banking, and other medicine subspecialties.

The program's emphasis on education begins with weekly comprehensive journal club sessions. Three to four major articles are covered on topics spanning the entire spectrum of critical care medicine. Additionally, subspecialists in cardiology, nephrology, radiology, perfusion, transfusion medicine, pharmacy and other divisions form the backbone of our fellow-level weekly didactic lecture series. A weekly echocardiography conference also covers major topics and teaching cases in both TTE and TEE.

Furthering their education, all fellows partake in an intense, ten-session transthoracic echocardiography class in the innovative Cardiac Anesthesia Simulation Center. These sessions form the foundation upon which fellows build their skills in focused transthoracic echocardiography (FTTE). Use of FTTE in an acutely ill patient is emphasized at BIDMC as a way to gather useful information quickly and rule out life-threatening diagnoses. At the end of the year, fellows are comfortable with using surface and transesophageal echocardiography in their practice and take the Examination of Special Competence in Adult Echocardiography offered by the National Board of Echocardiography. Many have gone on to start critical care ultrasound programs at other institutions.

As a teaching hospital of Harvard Medical School, BIDMC has the opportunity to collaborate with the other major academic institutions in the city. Fellows are encouraged to join any of the ongoing, accessible, grant-funded and world-class research projects in the division. Projects range from early mobility initiatives in the ICU to cutting-edge ideas using three-dimensional transthoracic echocardiography or clinical research in aspects of acute respiratory distress syndrome. Most recently, the division received a 5.3 million dollar grant from the Gordon and Betty Moore Foundation to advance the use of systems engineering and information technology in enabling patient and family-centered care. Fellows are active participants in this project.

Interested candidates should send enquiries by email to:
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(Karen Granquist, J.D.)
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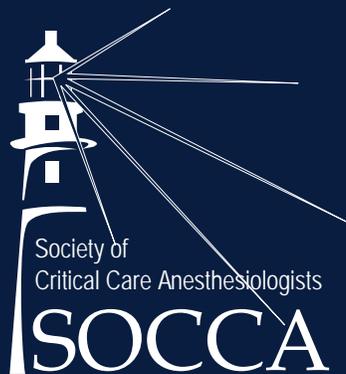
Final Program

SOCCA

Presented prior to the IARS 2014 Annual Meeting and International Science Symposium

27th Annual Meeting and Critical Care Update

May 16, 2014 | Fairmont The Queen Elizabeth Hotel | Montréal, Canada



Plan to attend this meeting if you are a(n)...

- Critical Care Specialists
- Perioperative Physicians
- Clinical and Research Scientists
- Intensivists
- Other Healthcare Professionals Interested in Critical Care Medicine

Online Registration is available at www.SOCCA.org



Welcome Letter

Welcome to the SOCCA 27th Annual Meeting and Critical Care Update in Montréal, Canada! For the first time this year, the Society of Critical Care Anesthesiologists (SOCCA) Annual Meeting will be held in conjunction with the International Anesthesia Research Society (IARS) 2014 Annual Meeting and International Science Symposium. SOCCA registrants will be able to take advantage of even more valuable education sessions, beginning with the SOCCA 27th Annual Meeting on May 16 and continuing with a full day focused on critical care at the IARS 2014 Annual Meeting on May 17.

The Annual Meeting Program Committee, comprised of Dr. Carlee Clark, Dr. Patricia Murphy and Dr. Daryl Kor, has constructed a stimulating program with sessions on the latest updates in the practice of critical care, original research presented by your colleagues in the poster room, and many opportunities for networking including a reception to conclude the meeting.

Sessions Include:

Session I

The SOCCA 27th Annual Meeting will kick off with a session focused on *RV: The Forgotten Ventricle in the ICU*. Topics will include management of acute pulmonary hypertension, the role of right mechanical heart assist and bedside point of care ultrasound assessment.

Session II

Celebrating Science, the second session of the Annual Meeting, will introduce the important publications that are valuable to critical care medicine now while highlighting abstracts presented by your peers.

Session III

Biomedical and Health Informatics in the ICU, will discuss ways to improve healthcare and new methods for achieving this goal.

Session IV

Session IV will evaluate best practices for *Interactive Case Management*.

Critical-Care Focused Day – May 17

The Saturday IARS education program offers a special focus on critical care, including two SOCCA Workshops, a Panel and a Problem-Based Learning Discussion session:

- SOCCA: *Critical Care Ultrasound Workshop*
- SOCCA: *Perioperative ACLS Simulation Workshop*
- SOCCA: *From the ICU to the OR: Critical Illness Intraoperative Decisions in the OR*
- SOCCA: *A Complex Challenge: Spinal Instrumentation Requiring Aggressive Resuscitation Techniques and Multimodal Analgesia*

We are confident that you will find this combined meeting a rewarding experience! Enjoy the beautiful city of Montréal and all it has to offer!

Sincerely,

Brenda G. Fahy, M.D., M.C.C.M.
SOCCA President

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Continuing Medical Education (CME) Activity Information

Activity Overview

The Society of Critical Care Anesthesiologists 27th Annual Meeting seeks to optimize outcomes for critically ill patients and their families by providing updates and expert discussion on topics of interest to anesthesiologists practicing critical care and perioperative medicine through advancing knowledge, improving competence and enhancing performance of intensive care teams.

Target Audience

The SOCCA 27th Annual Meeting and Critical Care Update is designed for anesthesiologists in the clinical and laboratory setting who desire to improve development of anesthesiology teaching methods by engaging in an interchange of ideas as represented in this meeting.

Accreditation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the International Anesthesia Research Society (IARS) and the Society of Critical Care Anesthesiologists (SOCCA). The IARS is accredited by the ACCME to provide continuing medical education for physicians.

American Medical Association (AMA)

Credit Designation Statement

The International Anesthesia Research Society designates this live activity for a maximum of 7 *AMA PRA Category 1 Credits*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Educational Objectives

As a result of participation in this CME activity, learners should be able to:

- Recognize the current state of emerging knowledge and practice patterns and assess the relevance for their professional practice;
- Incorporate new knowledge from advances in anesthesiology practice into their professional practice areas; and
- Recognize gaps in their knowledge, behavior, and patient outcomes that may result in a need for additional education and training.

Disclosure

The IARS complies with ACCME Essential Areas, Standards and Policies regarding industry support of CME Activities. The IARS has implemented policies and practices with respect to the planning, implementation and presentation of this activity to identify and resolve potential conflicts of interest for all persons in a position to control content.

Session Learner Objectives

What's New in Management of Acute Pulmonary Hypertension in the ICU

- Recognize the different mechanism of acute pulmonary hypertension and its consequence on RV function.
- Develop an approach in the treatment of acute pulmonary hypertension in the ICU.

Role of Right Mechanical Heart Assist

- Recognize the risk factors for RV failure following LVAD implant.
- Review the management of RV failure.
- Evaluate the role of mechanical RV support.

Bedside Point of Care Ultrasound in Assessment of RV Function

- Recognize the pathophysiology of right ventricular failure.
- Recognize the common transthoracic views of the Right Ventricle.
- Integrate a comprehensive bedside Point of care US assessment.

Important Publications You Might Have Missed

- Identify key articles that influence medical care in critically ill patients.
- Describe the population, intervention, control group, and outcome for each study discussed.

Innovative Informatics Approaches to Improve Healthcare Delivery in the ICU

- Identify opportunities for improvement in current clinical workflows and their outcomes.
- Illustrate how to improve situational awareness and decision support with innovative informatics to impact ICU patient outcomes.
- Elucidate barriers to the use of technology to drive patient care.
- Address security concerns in the ICU with medical technology.

Tele-ICU: Optimizing Care Delivery in Under-Resourced ICUs

- Recognize the need for Tele-ICU services in the US.
- Discuss the outcome data related to Tele-ICU utilization.
- Identify what the future of Tele-ICU might look like.

The Future of Clinical Informatics in the ICU

- Recognize the existing and future electronic medical record infrastructure in critical care environments.
- Discuss lost data and the value that may exist in this data.
- Use these data systems to improve quality and conduct research.

Interactive Case Management

- List considerations for induction of anesthesia in unstable patients.
- Discuss current controversies in perioperative fluid management.
- Characterize risks in emergent blood product transfusion.



Program Schedule

Friday, May 16, 2014

- 6:30 a.m. – 5:00 p.m. Registration
- 7:30 – 8:00 a.m. Continental Breakfast – Exhibits Open
- 8:00 – 8:05 a.m. Welcome and Introduction
Carlee Clark, M.D.; Daryl Kor, M.D.
- 8:05 – 8:15 a.m. IARS Leadership Opening Remarks
Denise J. Wedel, M.D. – Board Chair

Session I - RV: The Forgotten Ventricle in the ICU

- 8:20 – 8:50 a.m. What's New in Management of Acute Pulmonary Hypertension in the ICU
Andre A. Denault, M.D.
- 8:55 – 9:25 a.m. Role of Right Mechanical Heart Assist
Vivek Rao, M.D., Ph.D., FRCPS
- 9:30 – 10:00 a.m. Bedside Point of Care Ultrasound in Assessment of RV Function
Massimiliano Meineri, M.D.
- 10:00 – 10:15 a.m. Break and Visit with Vendors

Session II - Celebrating Science

- 10:20 – 11:10 a.m. Important Publications You Might Have Missed
Vivek Moitra, M.D. – Moderator
Panelists:
Steven B. Greenberg, M.D.
Erin K. Hennessey, M.D.
Brian Wessman, M.D.
- 11:15 – 11:30 a.m. **Young Investigator Award and Abstract Presentation**
"Focused Echocardiography During Glucagon Administration To Diagnose Beta Blocker-induced Cardiomyopathy"
Andrew Young, M.D.
- 11:35 – 11:40 a.m. Introduction of ASA Representative
Aryeh Shander, M.D., FCCM
- 11:45 – 11:55 a.m. ASA Address
John P. Abenstein, M.D. – ASA President-Elect

- 12:00 – 1:00 p.m. Lunch and Burchardi Award
Burchardi Award Recipient
Michael F. Heine, M.D.

Session III – Biomedical and Health Informatics in the ICU

- 1:00 – 1:20 p.m. Innovative Informatics Approaches to Improve Healthcare Delivery in the ICU
Lisa Weavind, M.D.
- 1:25 – 1:45 p.m. Tele-ICU: Optimizing Care Delivery in Under-Resourced ICUs
Ruben Azocar, M.D.
- 1:50 – 2:10 p.m. The Future of Clinical Informatics in the ICU
James Blum, M.D.
- 2:15 – 2:50 p.m. Moderated Poster Session
- 2:15 – 2:50 p.m. Break and Vendor Visits
- 2:55 – 3:25 p.m. **Lifetime Achievement Award Presentation**
"Laws and Axioms to Live By – or – Some Stuff I've Learned Along The Way"
Clifford S. Deutschman, M.S., M.D., MCCM

Session IV – Interactive Case Management

- 3:30 – 3:35 p.m. Introduction
Daniel R. Brown, M.D., Ph.D., FCCM - Moderator
- 3:35 – 4:55 p.m. **Panelists:**
Brenda G. Fahy, M.D., MCCM
Michael F. O'Connor, M.D., FCCM
Avery Tung, M.D., FCCM
- 4:55 – 5:00 pm. Closing Remarks
- 5:00 – 5:45 p.m. SOCCA Annual Business Meeting
- 5:00 – 6:00 p.m. Resident/Fellow Program
- 5:45 – 7:00 p.m. Welcome Reception

Nominating Committee Candidate Announcement

The SOCCA Nominating Committee will present the following slate of candidates to the SOCCA membership at the Society's Annual Membership Business Meeting on Friday, May 16, 2014 at the SOCCA 27th Annual Meeting and Critical Care Update at the Fairmont The Queen Elizabeth Hotel in Montréal, Canada.

Voting will be done electronically in 2014 and will open on Friday, May 16. Information regarding the electronic voting will be provided to members prior to the Annual Meeting.

SOCCA members will vote to elect a President-Elect (2-year term), a Secretary (2-year term), a Treasurer (2-year term), and three (3) Board of Directors (3-year term). The terms will begin May 2014.

President-Elect: Avery Tung, M.D.

Secretary: Miguel A. Cobas, M.D.

Treasurer: Daniel R. Brown, M.D., Ph.D., FCCM

Board of Directors: Benjamin A. Kohl, M.D., FCCM
Stephen D. Surgenor, M.D.
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Daniel R. Brown, MD,
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The SOCCA Membership Team:
Bonnie Akimoto and Erik Rosales may be reached at SOCCA@iars.org

The SOCCA Staff Liaison:
Julie McGrath may be reached at [SOCCAm eetings@iars.org](mailto:SOCCAm meetings@iars.org)

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IARS

International Anesthesia Research Society

A Review of Current and Novel Antiplatelet Agents



*Jonathan Shoopman, M.D.
Milwaukee, Wisconsin
Anesthesiologist who specializes in
anesthesiology and critical care medicine.*

Antiplatelet agents are widely used in the prevention and treatment of thrombotic diseases. There are multiple antiplatelet agents in current clinical usage and development, and knowledge of each one's indications and potential side effects are necessary for intensivists caring for the patients on these medications.

Antiplatelet drugs are classified primarily according to the molecular mechanism through which they have their pharmacologic effect, and this article will address the indications, pharmacology, and potential limitations of the agents within each category.

COX-1 INHIBITORS:

Drugs in this class:

Aspirin

Indication:

The secondary prevention of atherothrombotic disease¹

Mechanism of Action:

Aspirin works by inhibiting the prostaglandin-producing enzyme cyclooxygenase, which can affect inflammation, fever, protection of gastric mucosa, regulation of renal function and platelet aggregation.⁴ The platelet

prostaglandin thromboxane A₂ increases expression of fibrinogen receptors on platelet membranes and facilitates fibrin cross-links between platelets to form a platelet plug. COX-1 inhibition by aspirin is irreversible and regular low doses lead to more than 95% suppression of thromboxane A₂ production.^{6,8}

Limitations of COX-1 Inhibitors:

1. Gastrointestinal bleeding or intolerance.
2. There are patients who seem to have resistance to aspirin, and recurrent vascular events are not infrequent in patients on chronic aspirin therapy, at a rate of 6-8% per year.⁵ Whereas "aspirin resistance" is thought to be affected by compliance, cigarette smoking, hyperlipidemia, and diabetes, the exact mechanism is a focus of ongoing research, especially with respect to the need for dual or multiple antiplatelet therapy.⁶

ADP RECEPTOR ANTAGONISTS:

Drugs in this class:

Ticlopidine (Ticlid), clopidogrel (Plavix) and prasugrel (Effient) are the current agents used in this class.

Indication:

MI, stroke/TIA or symptomatic peripheral arterial disease, usually used in conjunction with aspirin

Mechanism of Action:

Thienopyridines inhibit adenosine diphosphate (ADP)-dependent platelet function by irreversible modification of the platelet P_{2Y}₁₂ receptor. Drug effects persist for the life of the platelet. Short-lived active metabolites are generated from the orally administered prodrug via cytochrome P450.⁷ Due to the unfavorable side effect profile of ticlopidine (diarrhea, neutropenia and aplastic anemia), clopidogrel has become the preferred thienopyridine.⁸ Important differences in metabolism and efficacy exist between clopidogrel and prasugrel.

Clopidogrel, a second-generation thienopy-

ridine, is metabolized by cytochrome P450 from prodrug to active form in a two-step process.⁹ Genetic variability in metabolism exists, with poor metabolizers exhibiting higher rates of cardiovascular events. Genetic testing for cytochrome P450 2C19 (CYP2C19) polymorphisms can identify patients at increased risk for treatment failure and should be considered prior to initiating therapy in patients at high risk for poor outcomes.

Prasugrel, a third-generation Thienopyridine, requires a single-step cytochrome-dependent metabolism from prodrug to active form. Unlike clopidogrel, common P450 genetic variants do not significantly affect active drug levels. Onset of action is faster than clopidogrel

Prasugrel has been shown to generate an active metabolite more efficiently than clopidogrel, leading to higher levels of platelet inhibition.¹⁹ The PRINCIPLE-TIMI 44 trial²⁰ demonstrated that prasugrel achieved superior platelet inhibition when compared to high-dose clopidogrel. In the TRITON-TIMI 38 trial²¹ prasugrel reduced the composite endpoint of death, nonfatal MI and nonfatal stroke by 20% in comparison to clopidogrel. However, rates of major hemorrhage were higher by 32% in the prasugrel group compared to the clopidogrel group. Due to the higher bleeding risk, prasugrel is recommended for those patients who are poor metabolizers of clopidogrel and in those patients at lower risk for bleeding complications.

Limitations of Thienopyridines:

1. The metabolism of clopidogrel, which is a prodrug requiring two-step activation involving several hepatic cytochrome P isoenzymes for conversion to the active metabolite.²² This results in a delayed onset of action (6-8 hours after a 300mg loading dose) and potentially increases the risk of ischemic events.
2. Irreversible binding to P_{2Y}₁₂ receptors, leading to a gradual recovery of platelet function after drug withdrawal. In the

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CURE study, among patients undergoing coronary artery bypass graft, bleeding tended to be more common if CABG was performed within five days of clopidogrel administration, as evidenced by chest tube output and blood product administration.¹²

3. The broad interindividual variability in levels of platelet inhibition achieved with clopidogrel with reports showing that about 30% of patients experience clopidogrel "nonresponsiveness" despite appropriate dosing.²⁴

REVERSIBLE ADP-RECEPTOR ANTAGONISTS: Drugs in this class:

Ticagrelor (Brilinta, oral agent), cangrelor (intravenous agent) and elinogrel (both intravenous and oral) are associated with rapid onset and offset of platelet inhibition. Of these, only ticagrelor is approved for clinical use.²⁵

Indication:

Stable coronary artery disease for prevention of ischemic events or prevention of stroke or death from vascular causes

Mechanism of Action:

Ticagrelor belongs to the class of drugs termed cyclopentyl-triazolo-pyrimidines. Like the thienopyridines, ticagrelor blocks the platelet P2Y₁₂ receptor to inhibit the prothrombotic effects of ADP.²⁵ Ticagrelor binds reversibly to P2Y₁₂ and does not require metabolic activation. It needs only 1.5-3.0 hours to reach peak plasma levels, allowing a rapid antiplatelet effect.^{26,27} Ticagrelor's half-life is approximately 12 hours and its antiplatelet effect is low at 48 hours after the last dose.²⁸ It has a faster onset than clopidogrel and does not require conversion from a prodrug, which means there is less variability in patient responsiveness.

Limitations of Reversible

ADP-receptor antagonists:

1. Ticagrelor requires twice-daily dosing, raising concerns with compliance
2. Higher incidence of hemorrhagic stroke and GI bleeding with ticagrelor compared with clopidogrel is also concerning and is a definite limitation of its use.³⁵

THROMBIN RECEPTOR ANTAGONISTS:

Thrombin interacts with two platelet receptors called PAR-1 and PAR-4. Protease-activated receptor 1 is the predominant receptor in humans and has a higher affinity for thrombin compared with PAR-4.³⁶ Two agents against PAR-1 are currently under investigation. Vorapaxar is a potent oral thrombin receptor antagonist with a half-life of 126-269 hours that inhibits platelet function for up to 4 weeks after discontinuation.^{37,38} Two ongoing phase 3 trials are underway with vorapaxar^{38,39,40} and a second oral agent, atopaxar, has recently completed phase 2 evaluation.⁴¹

GLYCOPROTEIN IIb/IIIa INHIBITORS:

Drugs in this class:

Abciximab (Reopro), eptifibatide (Integrilin) and tirofiban (Aggrastat).

Indication:

Randomized clinical trials have demonstrated that adjunctive therapy with GP IIb/IIIa antagonists decrease the combined endpoint of death, myocardial infarction and target vessel revascularization after PCI.^{50,51}

This class of antiplatelet agents is associated with greatest clinical benefit in the following scenarios:

1. Conditions associated with a high likelihood of intracoronary thrombosis, such as ST-elevation and non-ST-elevation MI where an invasive strategy is planned.
2. When the anticoagulant is heparin rather than a direct-thrombin inhibitor.

3. When the patient has not been treated before PCI with a P2Y₁₂ antagonist.
4. In unstable ACS patients who require transfer to a PCI center.
5. To reduce the risk of stent thrombosis in a patient with ST-elevation MI (especially when there is not adequate pretreatment with a P2Y₁₂ antagonist).

Mechanism of Action:

Abciximab is a monoclonal antibody that displays a rapid on-rate, binding to platelets in less than 1 min.⁴⁶ The dissociation (off-rate) of abciximab is measured in hours.⁴⁷ Abciximab has the greatest affinity for GP IIb/IIIa among the drugs in this class.⁴⁷ Eptifibatide and tirofiban are small molecules that exhibit a longer half-life compared with abciximab, 2.5 h and 2h, respectively.⁴⁸ Another key difference is the off-rate of eptifibatide and tirofiban which is 10-15 seconds compared with hours for abciximab.⁴⁹

Limitations of Glycoprotein IIb/IIIa inhibitors:

Oral GP IIb/IIIa inhibitors have been studied but the results have been disappointing. Because of an increased risk of death in those treated with oral agents, further development was abandoned.⁵⁷

PHOSPHODIESTERASE INHIBITORS:

Drugs in this class:

Cilostazol (Pletal) and dipyridamole (Persantine) are two commonly used agents in this class.^{58,59} The combination drug of dipyridamole and aspirin is sold under the trade name of Aggrenox.

Indication:

Intermittent claudication is a frequent consequence of peripheral arterial disease with a prevalence of 2-9% in individuals greater than 50 years.⁵⁹ Treatment options for this disease

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are limited, with surgical intervention reserved for severe or progressive cases.⁶⁰

Pharmacotherapy is reserved for patients resistant to risk factor modification, exercise and diet changes.⁶⁰

Mechanism of Action:

The phosphodiesterase inhibitors function as both vasodilators and antiplatelet drugs. Cilostazol is a reversible type III phosphodiesterase inhibitor with vasodilator and antiplatelet effects. The inhibition of PDE-III by cilostazol results in a rise in intracellular cyclic adenosine monophosphate (cAMP) levels in PDE-III-rich cells such as platelets, vascular smooth muscle cells, endothelial cells and cardiocytes.⁶¹ Cilostazol also inhibits adenosine uptake into cells, leading to an elevation of interstitial and circulating adenosine levels. By elevating cAMP levels and blocking calcium ion release, cilostazol inhibits contraction of smooth muscle cells and produces non-homogenous vasodilation, especially in the femoral arteries.⁶² Disease progression might be slowed through its antiproliferative effect on vascular smooth muscle.⁶³ *Up to 12 weeks of therapy may be required before symptoms improve.*

The phosphodiesterase inhibitor dipyridamole had previously been used as a coronary vasodilator and was later developed as a platelet inhibitor acting via the ADP mechanism, showing improved efficacy in conjunction with aspirin in cerebrovascular disease.^{65,66}

Limitations of Phosphodiesterase inhibitors:

1. Cilostazol is contraindicated in patients with heart failure of any severity due to theoretical concerns related to its mechanism of action and classification as a phosphodiesterase inhibitor.⁵⁹
2. Cilostazol is metabolized extensively by the cytochrome isoenzymes CYP3A4 and CYP2C19. When known inhibitors of these isoenzymes (erythromycin, diltiazem,

fluconazole, etc.) are coadministered with cilostazol, supratherapeutic levels have been observed.⁶⁴

Summary:

In summary, a multitude of clinical conditions are currently treated with antiplatelet therapy. Novel drug classes that target unique aspects of platelet aggregation are introduced here as well as newer generation drugs in familiar classes. For the peri- and operative clinician, an understanding of the pharmacology and indications for each agent is crucial.

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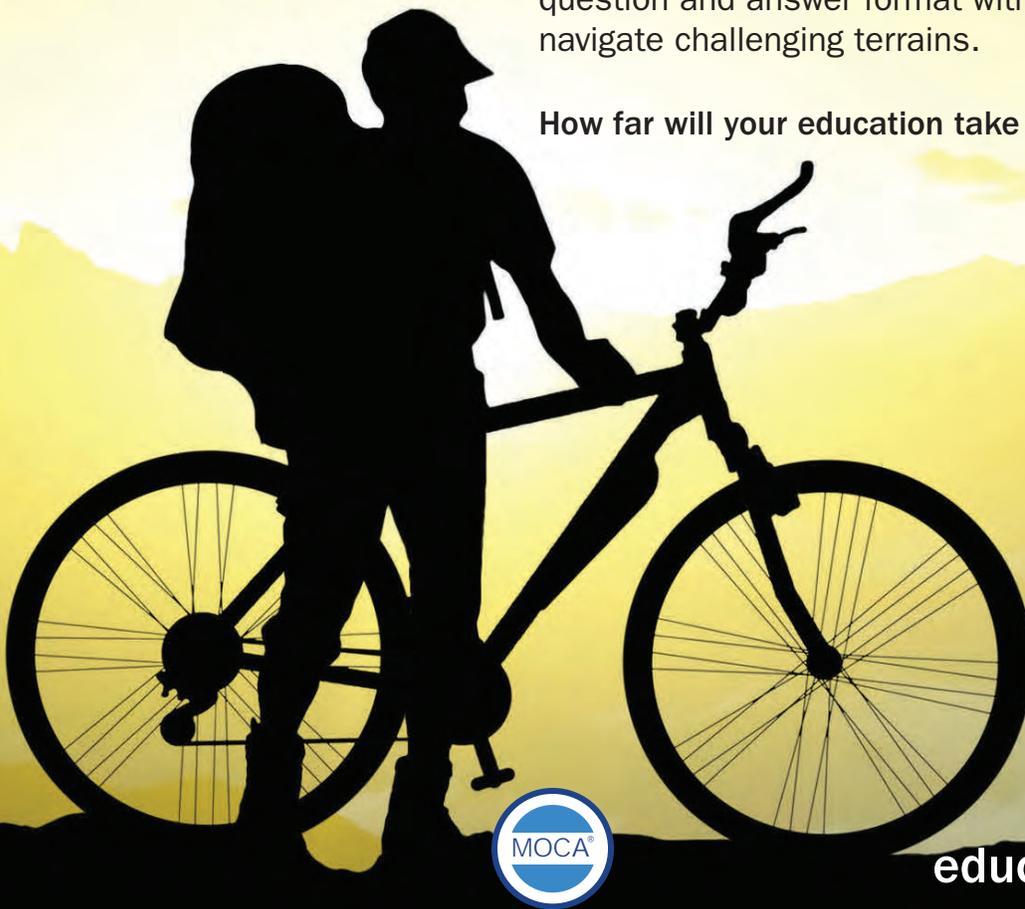
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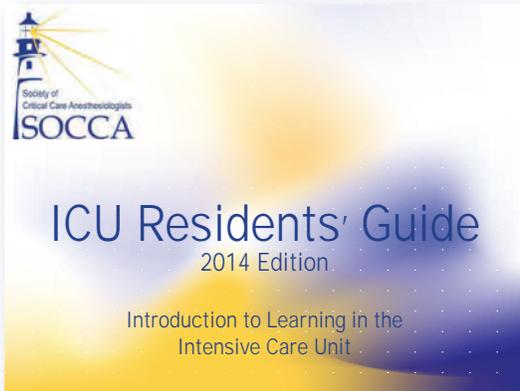
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SOCCA'S Updated ICU Residents' Guide

The updated Residents' Guide will now be available in two versions: **iBook for iOS devices** and **PDF** for other platforms. Look for the updated Guide at the SOCCA 27th Annual Meeting and Critical Care Update, May 16, in Montréal.

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