Message from the Chair
Lance Oyen, PharmD, FCCM

Congress in San Juan was exciting and full of super programming as usual. It was the start of New Year for the section, my role, and the collective thoughts of our section’s many critical care pharmacists. We welcomed the newly elected leaders into Clinical Pharmacy and Pharmacology (CPP) Steering Committee: Ishaq Lat, PharmD, FCCM, joined the Executive Committee as Secretary/Treasurer, and Tyree (Ty) Kiser, PharmD, FCCM, starting his 3-year term as Member at Large. Steve Martin was re-elected to another term on SCCM Council, representing CPP.

Besides myself, the section leaders for 2013-2014 include Immediate Past Chair, Gail Gesin; Chair-Elect Karen McAllen, Secretary/Treasurer Ishaq Lat; Members at Large include Omar Badawi, Amy Dzierba, and Ty Kiser.

New Section Committee Chairs and Vice Chair, respectively, include Xi-Liu DeRyke and Deepali Dixit (Communications); Aimee LeClaire and Jorie Frasiolas (Education); Jenni Morris and Laura Aykroyd (Membership); Eric Mueller and Lisa Harinstein (Patient Safety); Joe Aloi and Moo Sultan (Program); and Seth Bauer and Erin Frazee (Research). Please communicate your interest to the chair of any committee in which you want to participate. The newsletter will highlight activities and initiatives which may be of interest to you. Charges for each committee can be found at the CPP website, under the “Related Links” bar on the right side or within the CPP Section iRoom.

Thanks again to all those who planned, participated in, and attended a successful 2013 SCCM annual Congress. A special thank you goes out to Gail Gesin and all outgoing chairs of committees who did an incredible job all year long in 2012: Kathryn Conner, April Miller, Brian Kopp, Heather Bockheim, Russ Roberts and Pam Smithburger. Lastly, my many thanks go to Jeff Barletta for completing his term on the Steering Committee.

Exciting changes are afoot, including planned renovations of the Society’s web pages and the anticipated opportunity for pharmacists to become board certified in critical care in the near future.
Drug shortage resources will continue to expand for our critical care needs. These are currently located within the LearnICU > Knowledge Areas > Pharmacology content of the sccm.org website.

SCCM committee and task force applications for 2014 appointments are due May 1, 2013. More information can be found in the document **CPP Members with Appointments to SCCM Committees and Task Forces: 2012 Update**, which is located in the CPP Section iRoom. You may also refer to http://www.sccm.org/Membership/CreativeCommunity/Pages/VolunteerOpportunities.aspx.

I would like to hear what CPP and SCCM mean for you and your practice. Input, requests for involvement, and any recognition you would like to see for your fellow member(s) are all encouraged and should be sent to me at oyen.lance@mayo.edu.

### CPP COMMITTEE CORNER

**Communications Committee**

*Xi Liu-Deryke, PharmD (Chair), and Deepali Dixit, PharmD (Chair-Elect)*

The Communications Committee would like to sincerely thank Kathryn Connor (Past Chair) and Amy Dzierba (Member at Large) and last year's committee members for their dedication and service to the CPP Section. The Communications Committee is excited about our new charges this year. We are developing a guideline to help members publish pharmacotherapy articles in AJHP; this will be available in the iRoom in the Communication Committee folder. We are also looking for a new mechanism to enhance CPP Section visibility, access to newsletters, and ways to identify members’ abstracts and posters.

**Congress Reflections**
The CPP Communications Committee again this year will highlight some of the relevant educational sessions at the 2013 SCCM Critical Care Congress in the April newsletter, which will be archived on our website. Many thanks to those members who contributed their time and effort to this service.

If you have any questions regarding membership in the Communications Committee or contributions you would like to make to the CPP Section newsletter, please contact Xi Liu-Deryke at xi.liu@orlandohealth.com or Deepali Dixit at deepali0420@gmail.com.

**Education Committee**

*Aimée LeClaire, PharmD, BCPS (Chair) and Jorie Frasiolas, PharmD, BCPS (Chair-Elect)*

Congratulations to all CPP Section members who presented a poster or platform presentation at the 2013 SCCM Critical Care Congress in San Juan! The CPP Education Committee is collecting these posters or presentations to upload into the CPP Section iRoom. If you presented, please send an electronic (PDF) copy of your poster or slides to Janie Faris at jfaris@dmc.org.

The CPP Education Committee continues to partner with the Society on several key initiatives, including educational modules, a toolkit for protocol implementation and journal club.

SCCM CPP Journal Club continues to be held the third Friday of every month at 2 pm EST; upcoming dates are March 15, April 19, and May 17. If you, your colleague, or a resident would like to present an article during the 2013-2014 residency year or receive the monthly
notification and link to access the Journal Club session, please contact Karen Berger at kberger7@gmail.com or sccmcppjc@gmail.com.

Membership Committee
Jenni Morris, PharmD, BCPS, BCPS (Chair), and Laura Aykroyd, PharmD, BCPS (Chair-elect)

Member Packet
The CPP Section Member Packet has been updated for 2013-2014. The link to this wealth of information is located on the CPP Section home page on the lower right-hand side of the page. The link to the member survey is located on the first page, and all members are encouraged to use this survey to update their demographics, sub-specialties, mentor-mentee participation, speaking interests, and research interests.

Mentor-Mentee Program
The Mentor-Mentee Program provides CPP pharmacist members in critical care, emergency medicine, and pediatrics with guidance in a variety of areas, such as clinical practice, research, teaching, and SCCM/CPP involvement. All CPP Section members are welcome to participate in either a mentor or mentee capacity.

We are currently seeking individuals willing to serve as mentors, particularly those who would like to mentor PGY2 residents and those that practice in specialty areas, such as pediatrics or emergency medicine. Last year, we had a number of requests for mentors in these areas of practice and only a limited number of mentors with expertise in these fields. To ensure that we are able to find suitable matches for the coming year, we would like to encourage all non-resident section members to volunteer to serve in a mentor capacity. If you or anyone you know is interested, please contact us using the information below or complete the member survey, which can be found on the first page of the Member Packet.

Section members interested in serving in a mentee capacity are encouraged to contact us as early as possible. Although many of our mentees in previous years have been relatively new pharmacists, we would like to emphasize that mentorship is available to pharmacists that may be more experienced but looking to branch into a new area of practice. While there is no absolute deadline for participation as a mentee, the sooner we are contacted, the better the likelihood of facilitating live interaction between mentors and mentees at annual meetings such as ACCP, ASHP, and SCCM. If you would like more information regarding the program or would like to participate, please email either Jenni Morris (jmorris@iuhealth.org) or Laura Aykroyd (laykroyd@iuhealth.org). In an effort to ensure that compatible matches are made, demographic forms are used to gather background information for both mentors and mentees. We look forward to working with everyone and to the continued success of this program.

Patient Safety Committee
Eric W. Mueller, PharmD, FCCM (Chair), and Lisa Harinstein, PharmD, BCPS (Chair-Elect)

The Patient Safety Committee would like to thank our past-chair Pam Smithburger and member at large Omar Badawi for their leadership and guidance over the past year. We also thank all of our dedicated members who continue to work diligently to complete our charges and assure patient safety remains a tenet of the section and SCCM.

In concert with the Education Committee and the SCCM Patient and Family Support Committee, the Patient Safety Committee completed the educational brochure, “Critical Care Medication Information for Families and Caregivers,” which focused on commonly used ICU
medications, pneumonia, and delirium. The brochure can be found at http://www.myicucare.org/SiteCollectionDocuments/PFS12-Medication.pdf. Please let us know if anyone is interested in adding the brochure to their ICU’s educational materials.

The Patient Safety Committee has submitted for consideration a 2014 Congress program titled “Assessing pharmacotherapy-related risk: From the individual clinician to the interdisciplinary team.” We will keep everyone updated on the status of the submission.

A group of Patient Safety Committee members led by Katie Burenheide are finalizing their review on management of alcohol and drug withdrawal in critically ill patients. In addition, a group continues work on a systematic review of adverse drug events occurring in the ICU versus those related to ICU admission or transfer.

The Patient Safety Committee has two main research projects ongoing. The first is a national survey to evaluate standard cardiovascular medication infusion concentrations and rates. We are finalizing revisions to the survey and hope to launch soon. Please look for the survey in the next quarter or so. The second project is a multicenter study evaluating drug-related admissions to the ICU. We also are formalizing additional educational and research opportunities for this year.

Save the date: In July, the Patient Safety Committee will be seeking nominations and submissions for the Excellence in Using Technology to Improve ICU Medication Safety Award and Innovations in ICU Medication Safety Award. Please start thinking of colleagues and groups, including you and yours, who have made relevant contributions to patient safety.

Program Committee
Joseph Alo, PharmD, BCPS (Chair), and Moo Sultan, PharmD, BCPS (Chair-Elect)

The Program Committee would like to thank Heather Bockheim and Amy Dzierba, past chair and member at large, respectively, for their leadership and guidance over the last year. We would also like to thank those members who provided valuable contributions over the past year.

The Visiting Clinical Professor (VCP) Program is now accepting applications for 2014! CPP members interested in advancing the area of critical care practice at their institutions are encouraged to apply. Based on the desired area(s) of focus, the Program Committee will match the awarded applicant with a VCP who is considered to be a well-respected, renowned critical care colleague. This program provides funding to sponsor a 1- to 2-day visit, in which the VCP will provide insight and guidance through interactions with pharmacy and medical practitioners, participate in patient care rounds, and provide a guest lecture. The VCP Program application, as well as an example application, is available in the CPP iRoom on the SCCM website. Please email Joe Alo (joseph.aloi@vtmednet.org) or Moo Sultan (smsultan@unch.unc.edu) for more information or questions regarding the application process.

The Program Committee will also be working to organize the 2014 SCCM Congress Year-in-Review session and Pre-Congress Symposium. More information regarding these programs will be available in future newsletters. If you would like further information and/or to join the Program Committee, please feel free to contact Joe Alo (joseph.aloi@vtmednet.org) or Moo Sultan (smsultan@unch.unc.edu).

Research Committee
Seth Bauer, PharmD, (Chair), and Erin Frazee, PharmD (Vice-chair)
The committee has established and will continue to provide several research-related services available to all CPP members. These services include:

1) Facilitate CPP member-initiated research
   - A procedure document has been developed, which outlines steps for a fully mentored project, a method to affiliate a project with the SCCM-CPP name, and steps for identifying other CPP members to collaborate with on a project. This document also delineates the process for conducting surveys of the CPP membership for the purposes of research.

2) Provide peer pre-review of manuscripts and grants prior to submission

3) Maintain a membership database including practice information, research, and speaking interests

4) Identify and maintain a list of potential funding opportunities/grant agencies for research

5) Provide monthly reviews of literature pertinent to critical care pharmacotherapy (literature updates)

Please see the Research Committee folder in the CPP iRoom for policy and procedure documents for these services. The iRoom also contains the membership database, monthly literature updates, and research resources document.

A new and exciting charge this year is to explore options for a research consult support service in response to requests looking for other researchers with specific experience.

If you would like further information and/or to join this committee, please feel free to contact Seth Bauer (bauers@ccf.org) or Erin Frazee (frazee.erin@mayo.edu).

**Congress Reflections: 42th Annual Critical Care Congress**

**Liver Failure in the ICU**
(By Katie Gannon, PharmD, BCPS)

**Metabolic Considerations in Critically Ill Patients with Hepatic Insufficiencies**

*Speaker: Lewis J. Kaplan*

- Patients with liver failure often present with metabolic acidosis due to increased incidence of hypoperfusion and a reduced clearance of lactate. Acidosis can be exacerbated by the addition of Cl⁻ and albumin molecules, as this may cause an imbalance to electrical neutrality. Therefore, the choice of fluids in this patient population may have a larger impact than originally thought.
- Hepatic encephalopathy is a result of activation of the inflammatory cascade, increased ammonia and glutamate trapping within the neuron.
- Hepatorenal syndrome is a result of renal vasoconstriction and impaired blood flow. Consider utilization of a sodium bicarbonate to manage hyperchloremia and renal dysfunction, as hemodialysis may be poorly tolerated in these patients.
- Starvation occurs early, within 12 hours vs. 3 days, in ICU patients with liver failure. Consider the use of continuous tube feeding to improve cognitive function. Avoid use of tryptophan, as aromatic amino acids can result in toxic oxygen metabolites. Enteral nutrition is preferred over parenteral nutrition. Liver failure patients have a normal protein requirement. The addition of probiotics is unlikely to have an effect.

**Drug Dosing Considerations in Liver Failure**

*Speaker: Tyree H. Kiser, PharmD, BCPS*
Considerations regarding drugs and liver failure include: 1) how a drug enters into a hepatocyte (passive diffusion vs. active transport), and 2) if a drug undergoes biliary excretion.

Most medications undergo passive diffusion, oxidative metabolism via cytochrome P450 enzymes, and are cleared via the kidney. The Child-Pugh Score is used for drug dosing recommendations in liver impairment. Child-Pugh Class A usually requires little dose adjustment; Class B requires 25% to 50% dose reduction, and Class C often requires >50% dose reduction.

However, medication dosing considerations are not always simple, as different metabolic functions are impaired at different rates in the progression of liver disease. For example, CYP2C19 enzyme is affected early, while CYP2E1 maintains function throughout the late stages of liver disease. In addition, many cytochrome enzymes have genetic polymorphisms that may also influence drug metabolism. Phase I metabolism (oxidation, reduction, and hydrolysis) is affected early. Phase II metabolism (glucuronidation) is affected later in disease.

Drugs with a high extraction ratio are dependent on hepatic blood flow. The bioavailability is one way to determine if a medication has a high or low extraction ratio. Increased bioavailability suggests a low extraction ratio, while a decreased bioavailability is characteristic of a high extraction ratio. Drugs with high extraction ratios will have a significant increase in bioavailability, and will require a dose reduction in patients with liver failure. Drugs with high protein binding tend to have increased free concentration of active medication in liver disease, and will need dose adjustment.

As bilirubin levels are increased in liver disease, drug clearance is impaired. Drugs undergoing biliary elimination, such as argatroban and ceftriaxone, require dose reduction. Clear recommendations are lacking. Overall, loading dose of medications is unlikely to change (no need to adjust first dose), while maintenance doses may require adjustment.

Consider the drug’s safety profile vs. efficacy profile to determine if adjustment is needed (i.e., ceftriaxone less likely to produce toxic effect vs. phenytoin has a high risk for toxicity). Utilize therapeutic monitoring when available, and choose the most efficacious medication that is not impacted by hepatic function. For acute hepatic dysfunction, medication adjustments should be based on the patient’s chronic disease state, as it is hard to predict how fast hepatic function will recover.

When to Treat and When to Ignore Tachycardia in ICU Patients
(By Olabisi Falana, PharmD, BCPS)

Dysrhythmias in the ICU
Speakers: Steven M. Hollenberg and Ricardo Martinez-Ruiz, MD
During this session, Dr. Hollenberg discussed sinus tachycardia in ICU patients and Dr. Martinez-Ruiz discussed atrioventricular blockade and bradycardia.

Appropriate sinus tachycardia
- Physiologic response: exercise, fever, stress/anxiety/fever, hypotension, hypovolemia, anemia, ischemia, congestive heart failure, pulmonary embolism, and sepsis
- Drugs: atropine, catecholamine, thyroid hormone, alcohol, amphetamine, nicotine, and caffeine

Inappropriate sinus tachycardia
- No apparent heart disease or provoking cause; precise cause is unknown, but thought to be related to autonomic imbalance.
- Patients are usually young and often female; occurs after viral infections in some cases.
- May occur after electrophysiology procedures, usually atrioventricular (AV) node ablation.
- May produce symptoms such as palpitations, shortness of breath, and dizziness.
Treatment approach

- Determine whether sinus tachycardia is appropriate or not, and address any underlying causes.
  - Only treat sinus tachycardia when necessary, such as in setting of myocardial infarction and compromised cardiac filling.
- In the setting of rate-related hypotension (i.e., when tachycardia compromises cardiac filling), short-acting beta blockers, such as metoprolol, esmolol, or calcium channel blockers, may be used. Digoxin may be used if hypotension (due to vasodilatory properties) limits the use of these agents.
- Ivabradine
  - Selectively inhibits the hyperpolarization-activated cyclic nucleotide gate (funny channel)
  - Decreases heart rate, especially in patients who cannot tolerate beta blockers
  - More effective in patient with baseline heart rate greater than 77 beats/minute
  - No effect on contractility or blood pressure
  - In patients with heart failure, ivabradine decreased hospitalization but did not show mortality benefit
  - Extrapolation to ICU patients without trials is contentious
  - Not currently available in the U.S. (approved in Europe)
- Other options: maneuvers to increase intravascular volume (salt intake, mineralocorticoid, etc.), sympathetic excess respond to beta blockers; decreasing vagal tone is usually not helpful.

AV blockade and bradycardia

- AV dissociation occurs when the atrium and ventricles are functioning independently.
- Two major mechanism can explain this:
  - Slowing of the dominant pacemaker (sinus node), thereby permitting escape of other pacemakers
  - Acceleration of latent pacemakers where junctional rhythms or ventricular tachycardia overtake the atrial mechanism
- Incomplete AV dissociation occurs when beats from the atrium go into the ventricle to produce capture or fusion beats.
- Atrial electrocardiography (EKG) helps in determining what kind of AV dissociation a patient has.
- When atrial EKG does not allow for accurate assessment of atrial activity, epicardial EKG should be performed.

Strategies for Preventing and Treating Pain, Agitation & Delirium in Clinical Practice
(by Mindy Joseph, PharmD, BCPS)

New Strategies for Preventing and Treating Pain, Agitation, and Delirium in ICU Patients
Speaker: Aaron M. Joffe, DO
The pain, agitation, and delirium (PAD) care bundle, introduced as a guide to providing adequate control in the ICU setting, involved looking at each component and evaluating the severity, treating and subsequently preventing recurrence.
- Pain was evaluated with the following:
  - Critical care pain observation tool
  - Behavioral pain scale (BPS)
- Sedation was evaluated with the following:
  - Ramsay Scale
  - Sedation-Agitation Scale
  - Richmond Agitation Sedation Scale
- Delirium was evaluated using the Confusion-Assessment Method for ICU (CAM-ICU)
Dr. Joffe focused on using adequate tools to evaluate patients and using those tools to guide treatment.

An Integrated Approach to Implementing the Pain, Agitation, and Delirium Clinical Practice Guidelines
Speaker: Juliana Barr, MD, FCCM
Focusing on an integrated approach to managing pain, agitation, and delirium (PAD) in the ICU will allow the opportunity for a patient to have fewer days on mechanical ventilations as well as decrease ICU and hospital lengths of stay. The basis of an integrated approach requires the involvement of physicians, nurses, respiratory therapists, pharmacists, physical therapy, administration, family, and the patient.

- There are four key steps to a successful integrated approach to managing PAD
  - Step one: Implement pain, agitation, and delirium assessment tools in the ICU
  - Step two: Incorporate PAD assessments into daily ICU care plan
  - Step three: Apply ICU specific pain, agitation, and delirium management protocols
  - Step four: Link to other strategies to reduce the need for medications, improve outcomes

Pain, Agitation, and Delirium Guidelines Implementation Strategies to Minimize Post-Intensive Care Syndrome (PICS)
When implementing the ICU PAD bundle, it is important to look at the metrics to assure effectiveness. This involves reviewing process measures, such as hours at target sedation level, use of benzodiazepines, and early mobility. Outcome measures need to be assessed, as well as measures of quality of life, functional status, length of stay, ventilation-free days, and delirium-free days. For the ICU PAD bundle to be effective, it is important to educate the staff and work together as a team to ensure the goals are being met.

- Need to focus on the “ABCDEFGH”
  - Awakening
  - Breathing
  - Coordination
  - Delirium assessment
  - Early mobility
  - Family involvement, follow-up referrals
  - Good hand-off communication
  - Handing family written information about consequences of critical illness and potential referrals
- Following the above procedures can aid in preventing post-intensive care syndrome and a better overall quality of life post-ICU stay:
  - Mental health – posttraumatic distress syndrome, depression, anxiety
  - Cognition – function, memory, attention
  - Physical capacity – neuromuscular, pulmonary

The Effect of New Guidelines on ICU Care
(by Julie Kalabalik, PharmD, BCPS)

Sedation, Analgesia, Delirium Guidelines: Key Changes from 2002
Speaker: Juliana Barr, MD, FCCM
- Dr. Barr provided a summary of the clinical practice guidelines for the management of pain, agitation, and delirium (PAD) in the intensive care unit. In comparison to 2002 guidelines, the latest clinical practice guidelines are more integrated, interdisciplinary, and patient-centered.
Both nonpharmacologic and pharmacologic interventions are included in new ICU PAD guidelines. Amongst many recommendations, guidelines now emphasize appropriate pain management prior to initiation of sedatives, moving away from the routine use of benzodiazepines, and preference for light sedation over deep sedation. Dr. Barr recommended avoiding benzodiazepines in patients who are delirious due to reasons other than alcohol and benzodiazepine withdrawal, and to use antipsychotics judiciously and incorporate early mobility into bundles.

Implementation is encouraged through the use of an ICU PAD care bundle. Dr. Barr explained that the expected benefits of implementing an ICU PAD bundle may include decreased duration of mechanical ventilation, decreased ICU length of stay, increased bed availability, decreased healthcare costs per patient, increased long-term cognitive function, increased number of patients discharged to home, and increased saved lives.

Insulin Infusion Guidelines: Maximizing Safety and Consistency
Speaker: Judith Jacobi, PharmD, FCCM
- Published in December 2012, insulin infusion guidelines focus on safe use of insulin. The task force evaluated randomized, controlled trials and cohort studies.
- Insulin infusion guidelines suggest a blood glucose reading ≥150 mg/dL as a trigger for the initiation of insulin therapy with titration to maintain blood glucose <150 mg/dL for most adult ICU patients. Guidelines also suggest maintenance of blood glucose values <180 mg/dL using a protocol that achieves a low rate of hypoglycemia (blood glucose ≤70 mg/dL). Some patient populations may benefit from tighter control (100–150 mg/dL).
- Dr. Jacobi emphasized the importance of a safe and reliable insulin infusion protocol and the evaluation of the safety of protocols that may already be in place. Hypoglycemia prevention should include evaluation of insulin infusion protocols and system level activities that may affect blood glucose control, assuring accurate monitoring, adequate training of nurses on how to use the protocol, and recognizing risk factors and clinical changes that may impact blood glucose.
- Monitoring blood glucose every 1–2 hours is appropriate and suggested. Guidelines suggest that most point-of-care glucose meters are acceptable but not optimal for routine blood glucose testing; potential limitations in accuracy of glucose meters include patients with anemia, hypoxia, and interfering drugs.
- Dr. Jacobi encouraged multidisciplinary communication regarding patients on insulin infusion therapy, with specific goals and evaluating changes in clinical status, nutritional support, and medications.

Year in Review: Pharmacy
(By Elizabeth Short, PharmD, BCPS)

Infection: Year-End Review
Speaker: Simon W. Lam, PharmD
Methicillin-resistant Staphylococcus aureus (MRSA) pneumonia treatment
- Linezolid in MRSA nosocomial pneumonia study (PMID: 22247123) showed linezolid was noninferior and superior to vancomycin in end-of-therapy clinical response. However, clinical response was evaluated by investigators and adjudicated by the company sponsors. Without that adjudication, the superiority criteria would not have been met with linezolid. There was no difference in 60-day mortality rates.

Beta-lactam dosing strategies
- Clinical and microbiological efficacy of continuous versus intermittent application of meropenem in critically ill patients (PMID: 22742765) showed a numerically higher rate of microbiologic and clinical cure, but did not achieve statistical significance. The median...
Minimum inhibitory concentration (MIC) for meropenem was 0.125; therefore, the pharmacodynamic advantages may be more pronounced with higher MICs.

- **Continuous infusion of beta-lactam antibiotics in severe sepsis** (PMID: 23074313) much more readily reached the pharmacokinetic goal for the serum level above MIC. There was a statistically significant increase in rate of clinical cure associated with continuous infusion.

- **Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam** (PMID: 23074314) was a meta-analysis of 14 studies that analyzed carbapenems and piperacillin-tazobactam. While mortality was lower, there was no difference in clinical cure (50% of studies did not report a clinical cure rate).

**Treatment of Klebsiella pneumoniae carbapenemase-producing (KPC)-producing organisms**

- Previous studies and a 2010 Food and Drug Administration warning have suggested increased mortality with tigecycline monotherapy.

- **Excess deaths associated with tigecycline after approval based on noninferiority trials** (PMID: 22467668) showed a 0.7% absolute increase in overall mortality with tigecycline monotherapy, which translates to 1 death with every 143 patients who were treated. There was a 2.9% absolute increase in noncure rate, which translates to 1 noncure with every 34 patients treated. Both published and unpublished data as well as approved and non-approved indications were included. No significant heterogeneity was associated with these studies. The mortality distribution risk was primarily in the more severe infections, including hospital-acquired pneumonia (HAP), MRSA, and vancomycin-resistant Enterococcus (VRE) infections.

- **Treatment outcome of bacteremia due to KPC-producing Klebsiella pneumoniae: superiority of combination antimicrobial regimens** (PMID: 22252816) was a case-control retrospective study in 41 patients with KPC bacteremia that evaluated for risk factors associated with survival and mortality. The combination regimen group was associated with a significant reduction in mortality. In the multivariate analysis, combination therapy was an independent predictor of survival. The most common combination therapy was a carbapenem plus either colistin or tigecycline.

- **Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae: importance of combination therapy** (PMID: 22752516) evaluated 125 patients with KPC bacteremia. Combination therapy was associated with a decreased risk of mortality and improved clinical success. Septic shock, inadequate initial therapy, and high baseline severity scores were associated with increased mortality.

- **Association between colistin dose and microbiologic outcomes in patients with multidrug-resistant gram-negative bacteremia** (PMID: 23090926) concluded that patients who achieved microbiologic success had a statistically significant higher colistin dose; however, there was no difference in 28-day survival.

- **High-dose, extended-interval colistin administration in critically ill patients** (PMID: 22423120) reported a 82% clinical cure rate in patients with sepsis with a gram-negative bacilli infection. Colistin was administered as a 300-mg load followed by 150 mg every 12 hours. Acute kidney injury (AKI) occurred in 17.8% but recovered within 10 days of stopping colistin.

**Invasive candidiasis**

- **Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis** (PMID: 22412055) suggested echinocandins provide improved survival and greater clinical success in invasive candidiasis.
• Fluconazole versus an echinocandin for *Candida glabrata* fungaemia (PMID: 23212115) showed no difference in 14-day global response (microbiologic and clinical response) between a 5-day treatment with fluconazole or echinocandin. However, the echinocandin group had a higher baseline severity of illness. After adjusting for this, the echinocandin group was independently associated with a global response.

• European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients (PMID: 23137135) strongly recommended targeted treatment of candidemia with echinocandins (A1); whereas, fluconazole is recommended with marginal strength (CIII).

**Updates in Nutrition**

*Speaker: Scott W. Mueller, PharmD, BCPS*

• **Optimal Protein and Energy Nutrition Decreases Mortality in Mechanically Ventilated, Critically Ill Patients** (PMID: 22167076) evaluated the impact of a nutrition-targeted approach using an algorithm to get patients to goal. A decrease in 28-day mortality was observed in patients who achieved both protein and energy targets, but was not significant in patients only achieving energy targets.

• **EDEN trial** (PMID: 22307571) compared trophic and full enteral feeding during the first 6 days of mechanical ventilation in acute lung injury patients. No difference was observed in the primary outcome of ventilator-free days. Early hypocaloric feeding did not increase ventilator-free days. It could be concluded that enteral nutrition of 25% caloric delivery is not better than 80% caloric delivery.

• **Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients** (PMID: 23218813) showed in patients receiving <60% of target caloric delivery by enteral nutrition on day 3 may have a lower probability of nosocomial infection.

**Anticoagulation: What have we learned in 2012?**

*Speaker: Todd A. Miano, PharmD, BCPS*

• The 2012 *Chest* guidelines recommend a 4-factor prothrombin complex concentrate (PCC) over fresh frozen plasma (FFP) for patients with warfarin-associated major bleeding for rapid reversal of anticoagulation. The international normalized ratio (INR) is a surrogate measure, and the optimal INR target may differ based on the patient’s clinical status. What is of most interest is achieving hemostasis.

• The benefit versus risk of bleeding with triple therapy of warfarin, clopidogrel, and aspirin is not well evaluated. Indications for each component of triple therapy need to be critically evaluated to minimize the risk of bleeding.

**Optimizing Fluid Management in Sepsis**

*(by Ryan Van Engel, Pharm D)*

**Fluid Selection to Modulate the Sepsis Response and Prevent Organ Dysfunction**

*Speaker: Ronald G. Pearl*

• Discussion focused on the choice of fluid resuscitation to prevent organ dysfunction in patients who present in severe sepsis.

• The data demonstrating that crystalloids are superior to hetastarches were reviewed and data showed that balanced and unbalanced crystalloids are equal. Hetastarches have been shown to increase the incidence of renal replacement therapy and to increase the risk of mortality at 90 days.

• Saline, although one of the popular crystalloid choices, can cause a hyperchloric metabolic acidosis, especially when used over long periods in patients with renal failure.
• There is strong evidence that the use of albumin reduces the incidence of poor outcomes. Comparing albumin vs saline for replacement fluid, evidence showed an 8.4% reduction in negative outcomes but was not statistically significant.

• If SVO2 is less than 70%, blood should be considered for replacement fluid with a goal hematocrit of above 30%. The goal is to improve microcirculation in these patients.

• The presenter’s choice of fluid replacement would be a combination of balanced crystalloids and albumin, and transfusion to a hemoglobin of 9% and an SVO2 greater than 70%. Crystalloids should be used for the maintenance phase.

When to Transition from the Flow to the Ebb Phase of Sepsis Fluid Resuscitation

*Speaker: Greg S. Martin*

• Using central venous pressure (CVP) goals of 8-12 mm Hg (12-15 mm Hg if mechanically vented) to determine when to stop fluids are just arbitrary numbers.

• Transition from flow to ebb phase needs to be individualized. Late phase fluid restriction and diuresis have been proven to be beneficial in acute respiratory distress syndrome (ARDS) patients.

The presenter’s recommendation for transitioning from flow to ebb phase fluid resuscitation is that it should be done when the patient moves from unstable to stable.

Review of Medications Commonly Used in Pregnancy and Critical Illness

*(By Joanna Stollings, PharmD, BCPS)*

*Speaker: Lisa Burry, PharmD*

• <1% of drugs result in fetal malformation

• Drug metabolism
  o Increased CYP2C19 activity
    ▪ Decreased phenytoin activity
  o Increased CYP3A4 activity
  o Decreased CYP1A2 activity
    ▪ Increased sensitivity to caffeine

• The fetus is most vulnerable at 3-8 weeks

• Rapid sequence intubation
  o Propofol, rocuronium, and narcotics are safe to use
  o Avoid etomidate

• Preeclampsia
  o Esmolol: avoid, can result in fetal bradycardia
  o Hydralazine: can result in hypotension, tachycardia, and decreased Apgar scores
  o Nitroprusside: can cause cyanide toxicity in fetus

• Antiarrhythmics
  o Avoid phenytoin and amiodarone

• Vaspressors
  o Vasopressin can result in uterine contractions

• Antimicrobials
  o Beta-lactams: safe
  o Clindamycin: safe
  o Tetracyclines: not safe
  o Ciprofloxacin: safe
  o Trimethoprim: avoid in the first trimester
Vitamin D Deficiency in Adult Critically Ill Patients
Mona K. Patel, PharmD

Vitamin D deficiency or insufficiency affects nearly one billion people worldwide. Between 40% and 100% of the population living in the United States and Europe are affected. Insufficient levels have been documented in 57% of medical inpatients and 50% to 97% of critically ill patients.

Vitamin D has traditionally been associated with regulation of calcium, phosphate, and bone homeostasis. Recognition of pleiotropic effects in recent years, however, has highlighted its importance to numerous other disease states. Vitamin D has demonstrated effects on immune modulation, cancer, osteoarthritis, diabetes, and cardiovascular disease. Deficiency has also been associated with higher morbidity and mortality in the general, elderly, and cardiac transplant populations.

The two forms of vitamin D, vitamin D2 (ergocalciferol) and D3 (cholecalciferol), come from multiple sources including sunlight, diet, and supplements. Vitamin D3 accounts for the majority of stores and is cutaneously synthesized when ultraviolet light acts upon 7-dehydrocholesterol found in keratinocytes. Fortified diets contain both vitamin D2 and D3, but account for less than 10% of total body vitamin D stores. Both forms can be found in supplements. The liver hydroxylates vitamin D2 and D3 to 25-hydroxyvitamin D [25(OH)D], which in turn is hydroxylated by the kidney to the biologically active form, 1,25-dihydroxyvitamin D [1,25(OH)2D]. Typically, 25(OH)D is measured to determine vitamin D stores.

Diagnostic criteria of vitamin D deficiency, insufficiency, and sufficiency can vary between studies and expert organizations. The United States Endocrine Society guidelines define deficiency as a 25(OH)D level less than 20 ng/mL, insufficiency between 21-29 ng/mL, and sufficiency as 30 to 100 ng/mL. However, the Institute of Medicine, deficiency is less than 12 ng/mL, insufficiency is 12 to 19 ng/mL, and sufficiency is 20 to 50 ng/mL. Numerous factors can affect vitamin D levels, including calcium intake, age, body fat, mobility, season, sun exposure, race, renal failure, and genetic factors. Hemodilution and acute fluid shifts may also change levels. A recent observational trial identified hospital admission during spring months, low serum albumin levels, and high Simplified Acute Physiology Score (SAPS) II as independent predictors of deficiency at ICU admission. Although existing data identify optimal levels associated with bone health in the general population, appropriate levels in critically ill patients remain undetermined.

The increased morbidity and mortality rates seen with deficiency and the vitamin’s pleiotropic effects on immunity, glucose and calcium regulation, and endothelial function have raised questions regarding the impact on critically ill patients. Numerous observational trials have attempted to address these effects. Several studies have evaluated the relationship between vitamin D deficiency and mortality in critically ill patients. Braun and colleagues conducted the largest evaluation with their multicenter observational study of 2399 medical and surgical intensive care unit (ICU) patients. This study included patients in whom a 25(OH)D level was drawn between 7 and 365 days before admission. Deficiency, insufficiency, and sufficiency was defined as 25(OH)D levels less than or equal to 15 ng/mL, 16 to 29 ng/mL, and greater than or equal to 30 ng/mL, respectively. Risk of 30-day mortality after ICU admission was 1.7 and 1.3 times statistically significantly higher in those who were deficient and insufficient, respectively, compared to those who were sufficient. The relationship remained after adjustments for covariates such as age, race, gender, comorbidities, season, sepsis, and type (medical versus surgical). Statistically significant increases in mortality were also seen with 90-day, 365-day,
and in-hospital mortality with both groups.\textsuperscript{17} Investigators from the group conducted a similar trial in 2012 evaluating the same outcomes. The later trial included 1325 patients in whom a 25(OH)D level was drawn 7 days before or after ICU admission. Approximately 80\% of patients had levels drawn up to 7 days after ICU admission. Risk of 30-day mortality after ICU admission was 1.9 and 1.3 times statistically significantly higher in those who were deficient and insufficient, respectively, compared to individuals who were sufficient, with the same relationship remaining after adjustments for significant covariates. Statistically significant increases in 90-day, 365-day, and in-hospital mortality were also seen with the deficient group, but not the insufficient group.\textsuperscript{18} Conversely, Arnson and colleagues did not see a difference in 60-day mortality in their observational trial of 130 patients, but they did observe a shorter survival time in the deficient group (15.3±12.4 vs 24.2±16.5 days, \( P<0.05 \)).\textsuperscript{19}

Recent evidence also shows that vitamin D deficiency may be associated with an increased length of ICU stay. One observational trial of 66 surgical ICU patients, in whom 25(OH)D levels were drawn on ICU admission, found that deficiency was associated with longer hospital length of stay than sufficiency (29±27 vs 17±14 days, \( P=0.03 \)). Compared to sufficient patients with Acute Physiology and Chronic Health Evaluation (APACHE) II scores \( \geq 18 \), deficient patients with APACHE II scores \( \geq 18 \) had longer length of hospital stay (49±36 vs 13±13 days, \( P<0.0001 \)) and ICU stay (34±32 days vs 7±11 days, \( P<0.0001 \)).\textsuperscript{20} Higgins and colleagues observed that patients with vitamin D sufficiency had a shorter time to ICU discharge alive than those with deficient levels (hazard ratio 2.11; 95\% confidence interval [CI], 1.27-3.51) in their prospective trial involving 196 patients.\textsuperscript{21} Low vitamin D levels obtained within 24 hours of surgical ICU admission were also associated with longer length of ICU stay and increased ICU cost in another recent observational trial evaluating 258 patients.\textsuperscript{22}

The impact of vitamin D deficiency on infections in the critically ill has also been evaluated. Flynn and colleagues found higher rates of infection, defined as bacteremia, pneumonia, urinary tract infection, intra-abdominal infection, or skin-soft tissue infection, in the deficient group compared to the sufficient group.\textsuperscript{20} The incidence of pneumonia was higher in the deficient group than sufficient group in another observational trial.\textsuperscript{21} The results, however, were not statistically significant in either trial, unlike the study of Braun and colleagues who did find a statistically significant relationship: deficient patients who had blood cultures drawn 48 hours before or after ICU admission had a 1.6 times greater risk of bacteremia compared to sufficient patients.\textsuperscript{17} Cecchi and colleagues examined the relationship of vitamin D deficiency and sepsis by obtaining a 25(OH)D level within 24 hours of ICU admission in 68 trauma and 92 severe sepsis/septic shock patients. The investigators found that, although there was no difference in mortality between the two groups, levels were lower in sepsis/septic shock versus trauma patients (10.1 ng/mL vs 18.4 ng/mL, \( P<0.0001 \)).\textsuperscript{23}

In addition to effects on mortality, length of stay, and infection, vitamin D deficiency may also negatively impact renal function in ICU patients. An observational, multicenter study of 2075 critically ill patients in whom a 25(OH)D level was drawn 7 days before or after ICU admission showed that deficiency (odds ratio [OR] 1.73; 95\%CI, 1.30-2.30; \( P<0.001 \)) and insufficiency (OR 1.49; 95\%CI, 1.15-1.94; \( P=0.003 \)) were associated with a higher risk for acute kidney injury than sufficiency. Both deficiency and sufficiency remained predictors of acute injury after adjustment for significant covariates, such as age, race, gender, comorbidities, season, sepsis, and type (surgical versus medical).\textsuperscript{24}

Despite growing evidence illustrating the relationship between vitamin D deficiency and negative outcomes, the body of literature on vitamin D supplementation in critically ill patients remains small. The recommended daily vitamin D allowance is 600 IU/day, but doses as high as 1500 to 2000 IU/day may be needed to maintain levels above 30 ng/mL in the general
population.\textsuperscript{1,7} Dosing in critically ill patients remains unknown. A few small studies including 22 to 33 patients have evaluated the impact of various intravenous and oral cholecalciferol regimens, which ranged from a one-time dose to daily administration, on measured 25(OH)D levels. These studies have reported mixed results on normalization of vitamin D levels.\textsuperscript{6,25-27} The clinical impact of supplementation also remains unclear.

Once thought to be a chronic condition, vitamin D deficiency may have acute detrimental effects. Numerous observational studies show a relationship between low vitamin D levels and adverse outcomes in critically ill patients, but it is unclear if this association is a causative relationship or merely a reflection of disease severity. It is unknown if enhancement of levels leads to improved outcomes. Evaluation of safety, efficacy, and dosing of supplementation also remains unidentified in this patient population. Studies that address these questions are needed before routine administration of vitamin D can be recommended in critically ill patients.

References

**Member Spotlight**

*By Stacey Folse, PharmD, MPH, BCPS*

**Christopher Paciullo, PharmD, BCPS**
*(Specialist in the Cardiothoracic Surgery ICU)*

Dr. Christopher Paciullo became interested in critical care during his Advanced Pharmacy Practice Experiences (APPEs) as a Doctor of Pharmacy student at the University of Rhode Island College of Pharmacy. Following graduation he completed a PGY1 pharmacy residency at Saint Joseph Healthcare in Lexington, Kentucky in 2008 and PGY2 critical care residency at the University of Kentucky in 2009. After completing his residency training, Dr. Paciullo joined the department of pharmaceutical services at Emory University Hospital in Atlanta, Georgia, as a Cardiothoracic Surgery ICU Clinical Pharmacy Specialist.

Emory University Hospital is a 587-bed academic medical center which focuses on patient care, education of healthcare professionals, research addressing health and illness, and health policies for the prevention and treatment of disease. It was named in 11 of 16 specialties ranked by *U.S. News and World Report* in 2012 and ranked second on the 2012 United Health Consortium (UHC) quality rankings. The institution’s cardiothoracic surgery ICU is an open 18-bed unit serving a wide array of cardiac surgery patients.
Dr. Paciullo is an excellent example of someone who embodies the focus of Emory. His day consists of a variety of clinical, administrative, research, and teaching activities. His areas of interest include mechanical circulatory support, advanced hemodynamics, shock, and renal replacement therapy, which are the foci of much of his research. He is typically involved with a couple of projects at a time and enjoys the challenging and diverse nature of this area of clinical practice. Some of his previous research endeavors include multidrug-resistant infections in left ventricular assist devices, adverse effects associated with tranexamic acid, and management of acute hypertension in the cardiac surgery population. Currently, Dr. Paciullo’s research is related to the use of methylene blue and its adverse effects in cardiac surgery patients.

While his clinical responsibilities and research endeavors keep him busy, Dr. Paciullo still maintains a dedication to scholarship and involvement in professional organizations. He has written book chapters and published several peer-reviewed articles on topics such as the use of chromogenic factor X, heparin-induced thrombocytopenia, and methylene blue use in septic shock. Most recently he co-authored the article, “Vancomycin Clearance in High-Volume Venovenous Hemofiltration,” published in *Annals of Pharmacotherapy* this year. In addition, Dr. Paciullo is actively involved in several professional organizations, such as the American College of Clinical Pharmacy (ACCP), Society of Critical Care Medicine (SCCM), and the Georgia Society of Health-Systems Pharmacists (GSHP). He was recently elected to serve as Secretary/Treasurer for ACCP’s Critical Care PRN and appointed to ACCP’s Programming Committee and SCCM’s Post-Graduate Education Committee.

Of Dr. Paciullo’s daily activities, he is most fond of teaching. He serves as a preceptor to pharmacy students and PGY1 and PGY2 residents, and enjoys presenting information they were unexposed to in school. He finds a satisfaction in describing a foreign concept and witnessing the student’s or resident’s moment of clarity. In addition, he has an appointment at Mercer University College of Pharmacy and Health Sciences, where he serves as an adjunct clinical assistant professor and provides lectures in cardiovascular pharmacology. He also teaches at Emory University School of Medicine, providing lectures in clinical pharmacology for the physician assistant program. At the start of the 2012 residency year, he transitioned from his position as PGY1 Pharmacy Residency Clinical Coordinator to Residency Program Director. In his short time in this position, he has been instrumental in expanding the number of PGY1 residents and advancing the residency curriculum to include a resident on-call program.

In his spare time, Dr. Paciullo enjoys playing golf, scuba diving, and working out. In the next 5 years he envisions he will still practice as cardiothoracic surgery clinical specialist, but will continue to expand on his research in the area of cardiothoracic surgery and remain committed to active participation in professional organizations. When asked his advice for critical care residents and new practitioners, he encourages them to stay, or become, involved with SCCM’s CPP Section and ACCP’s Critical Care PRN, both of which provide excellent networking opportunities with wonderful practitioners.
Communications Committee members are charged with publishing the newsletter. Thanks to the following members:

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**Upcoming SCCM Congress Meetings – Save the Date!**

<table>
<thead>
<tr>
<th>Year</th>
<th>Date</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>January 9-13</td>
<td>San Francisco, California</td>
</tr>
<tr>
<td>2015</td>
<td>January 17-21</td>
<td>Phoenix, Arizona</td>
</tr>
<tr>
<td>2016</td>
<td>February 20-24</td>
<td>Orlando, Florida</td>
</tr>
</tbody>
</table>