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Evidence-Based Information for Hospitalists, Intensivists, and Acute Care Physicians [ALERT]

Risk of Major Bleeding With Concurrent Medications in Atrial Fibrillation Patients Taking New Oral Anticoagulants

By Michael H. Crawford, MD, Editor

SOURCE: Chang SH, Chou IJ, Yeh YH, et al. Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. *JAMA* 2017;318:1250-1259.

Little is known about the risk of bleeding with the new oral anticoagulants (NOACs) in atrial fibrillation (AF) patients on multiple other drugs for various comorbidities. Investigators evaluated the bleeding risk in AF patients on NOACs associated with the concurrent use of 12 commonly prescribed medications that share the metabolism pathways of the NOACs, such as CYP3A4 inhibitors and P-glycoprotein competitors. This was a retrospective analysis of the Taiwan National Health Insurance Administration database, which includes robust clinical information. More than 91,000 patients were identified who demonstrated nonvalvular AF and had received at least one NOAC prescription between 2012 and 2016. The primary outcome was major bleeding, excluding trauma bleeding. The analysis model used a propensity score to adjust for covariates. The mean age of the patients was 75 years. Fifty-six percent were men. Their mean baseline CHA_2DS_2-VASc score was 4, and their HAS-BLED mean score was 3.3. Comorbidities such as heart failure, diabetes, and cerebrovascular disease were common. The NOACs used during the four years were rivaroxaban in 59%, dabigatran in 50%, and apixaban in 14%. There were 4,770 major bleeds per 447,037 person-quarter of years of follow-up. Significant increases in adjusted bleeding rate differences compared to NOAC use alone were seen with amiodarone (14 per 1,000 person-years), fluconazole (138), rifampin (37), and phenytoin (52). Atorvastatin, digoxin, erythromycin and clarithromycin were associated with reduced incidence rates. Other combinations, such as with diltiazem, verapamil, cyclosporine, and other azoles, neither increased nor decreased bleeding rates. There were no differences in bleeding rates on the various combinations between the three NOACs. The authors concluded that in patients taking NOACs, concomitant use of amiodarone, fluconazole, rifampin, and phenytoin is associated with a significant risk of major bleeding compared to NOAC use alone.

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■ COMMENTARY

Many hoped that the NOACs would free clinicians from the concern about drug interactions with warfarin. The authors of this study noted that drug interactions are reduced, but not eliminated, by NOACs. Clearly, there are drugs clinicians should avoid prescribing for patients on NOACs because of a marked increase in the risk of bleeding. These are in the order of risk: fluconazole, phenytoin, rifampin, and amiodarone. The data on amiodarone are different from data presented in the ARISTOTLE study (apixaban vs. warfarin) in which no increase in bleeding risk was found. However, the authors of ARISTOTLE studied far fewer patients and this was the lowest increased risk found in this study. On the other hand, several drugs that are known to increase plasma levels of NOACs in pharmacodynamic studies and were predicted to increase bleeding risk did not in this analysis: diltiazem, verapamil, cyclosporine, and other azoles. Paradoxically, some drugs actually appeared to lower the bleeding risk: atorvastatin, digoxin, and mycin antibiotics. This may be because other positive effects of these drugs lowered bleeding risk or chance, but their use does not seem to be a concern. Of the four drugs that accounted for 20% of the concomitant drug use (digoxin, diltiazem, amiodarone, and atorvastatin), only amiodarone was of concern. The strength of this study is that it was based on a very large and comprehensive nationwide database in a country with a one-payer system. Potential limitations are that this country (Taiwan) represents an Asian population and that the data may not reflect other ethnicities. Also, drug dosages were not considered in the analysis because of the overwhelming complexity this would pose. Additionally, liver and renal function data were not analyzed for the same reason. Finally, there are no data on edoxaban, which was not approved for use in Taiwan during the study period. However, there was no difference between the other three NOACs in the observed interaction patterns, so there is no reason to suspect edoxaban would act differently.

The use of amiodarone, fluconazole, rifampin, and phenytoin with NOACs increased the risk of major bleeding, whereas other commonly used drugs in AF patients did not. ■

ORBITA: Learning the Right Lessons From a Sham-controlled Trial of Angioplasty

By Jeffrey Zimmet, MD, PhD

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Dr. Zimmet reports no financial relationships relevant to this field of study.

SOURCE: Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): A double-blind, randomised controlled trial. *Lancet* 2017 Nov 1. pii: S0140-6736(17)32714-9. doi: 10.1016/S0140-6736(17)32714-9. [Epub ahead of print].

While percutaneous coronary intervention (PCI) produces beneficial effects on hard outcomes in acute coronary syndromes, the situation is quite different in chronic stable angina (CSA), where the primary goal of intervention is recognized to be angina reduction. Trials of PCI in CSA have not shown a benefit in terms of mortality or myocardial infarction compared with medical therapy. Also, no one has performed a placebo-controlled trial of PCI in CSA. This, in a nutshell, is what the authors of the ORBITA trial set out to accomplish. Patients were selected carefully. Each patient exhibited angiographically significant disease in a single vessel with "angina or equivalent symptoms." Patients with disease in more than one vessel were excluded, as were patients with left main disease, prior coronary artery bypass grafting, or presentation consistent with acute coronary syndrome. Patients with

severe left ventricular dysfunction also were excluded, and nearly all patients enrolled demonstrated normal ejection fraction.

All patients began with a purely diagnostic coronary angiogram that defined their eligibility. Symptoms were assessed by standard research instruments prior to an intensive six-week medical optimization phase during which medical therapy, including dual antiplatelet therapy, began. Antianginal medications were titrated aggressively in all patients through phone consultations with a cardiologist up to three times per week. Cardiopulmonary exercise testing (CPET) and dobutamine stress echocardiogram (DSE) were performed just prior to the index procedure.

For the research procedure itself, all patients underwent an assessment of fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) before randomization to PCI or placebo, although, interestingly, the operators were blinded to the results of this physiologic testing. Patients were sedated and wore headphones to assure blinding. The primary endpoint was the difference in exercise time increment between groups, assessed six weeks after the procedure. Secondary endpoints included standardized assessments of angina and quality of life, change in peak oxygen uptake, and change in DSE wall motion index.

Two hundred patients underwent randomization: 105 to PCI, and 95 to the sham procedure. Most patients were assessed as exhibiting class II or III angina, and effort tolerance pre-randomization was quite good overall, with patients averaging > 8 minutes on the treadmill. At the index procedure, coronary lesions were assessed to be physiologically severe on average, with a mean FFR value of 0.69. PCI led to improvement to a mean FFR of 0.90. Importantly, approximately 30% of lesions overall were not physiologically significant by FFR and iFR assessment. At the six-week post-procedure assessment, exercise times had increased in both groups. Although the increase was greater in the PCI group, the between-group difference was not statistically significant. The DSE peak stress wall motion score index improved more with PCI than with placebo, demonstrating an objective improvement in ischemia, but no significant differences in symptoms were seen between groups during follow up.

The authors concluded that in patients with medically treated CSA, PCI did not improve exercise time or angina symptoms significantly compared to a sham procedure despite improving hemodynamic and imaging indices of ischemia.

■ COMMENTARY

Predictably, reactions to the ORBITA results, both among cardiologists and in the lay press, have been relatively sensational. Some commentators have used the results to make blanket statements about the utility of PCI in CSA altogether, while others, including the study authors, caution against such overreach. The authors of an accompanying editorial took a particularly black and white view, concluding that there are "no benefits for PCI compared with medical therapy for stable angina, even when angina is refractory to medical therapy." What can cardiologists rightfully believe?

At the base of it, ORBITA was a well-executed and difficult-to-accomplish trial, completing the first-ever study of CSA that included a sham control. The study procedures were meticulous, the blinding was well thought out and effective, and the assessment procedures were comprehensive.

Although the study benefits from numerous obvious strengths, it also featured some shortcomings that should be highlighted for better understanding of its true message and implications. The study size was relatively small, with only 100 patients in each group, and the patients demonstrated good effort capacity coming into the trial, making it difficult to show an incremental benefit of PCI. In fact, formal CPET showed that peak oxygen uptake at baseline was essentially normal for patients in this age range.

All patients underwent invasive assessment of the index lesions by FFR and iFR, but these results were not used in assessment of lesion significance and were not made available to the operators. As it turned out, although all lesions were judged to be significant angiographically, nearly one-third of patients exhibited FFR values that do not meet current thresholds for interventional treatment and would not be expected to benefit significantly from PCI. At the same time, the change in mean FFR for the entire population was highly important. This suggests a high degree of heterogeneity in lesion severity among patients in this modest-sized trial. However, there is little doubt that these functional assessments are underused in clinical practice.

In performing FFR assessments, four patients in the placebo group underwent unplanned PCI because of lesion disruption by the FFR wire. It is important to recognize that this complication is quite rare with intermediate lesions and is far more likely to occur with truly severe lesions. The end result in this case is that four placebo group patients with the most critical disease were treated by PCI, with obvious potential to skew the data in this small trial.

But the most important lessons are those we should know already, primarily that medical therapy in CSA patients can be effective when performed well, and that both patients and providers should understand that

medical therapy is a viable option for clinical scenarios that fit the trial paradigm. The clinical situation studied in the trial is common in practice, and too often patients come to the cath lab on inadequate medical therapy with a plan to receive a combined diagnostic and therapeutic procedure. Such ad hoc PCI, while extremely common and often in the patient's best interests, can also short-change the discussion of treatment options in favor of interventional therapy. The focus of the trial was more narrow than the editorialists suggested, a point worth emphasizing. The authors of ORBITA studied CSA patients with single-vessel coronary artery disease, normal left ventricular function, and very little functional limitation as defined by formal exercise testing. To extrapolate these results to all CSA patients would be both incorrect and an unfortunate disservice to patients. ■

Deflating Recruitment Maneuvers

By Richard Kallet, MS, RRT, FCCM

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Mr. Kallet reports he is a major stockholder in the Asthma & Allergy Prevention Company, and receives grant/research support from Nihon Kohden.

SOURCE: Cavalcanti AB, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. *JAMA* 2017;318:1335-1345.

The authors of this multinational, prospective, randomized, controlled trial enrolled more than 1,000 subjects with moderate to severe acute respiratory distress syndrome (ARDS) within 72 hours of onset. These patients received either 1) an open lung ventilation (OLV) strategy in which a neuromuscular blockade was administered, followed by a lung recruitment maneuver (RM) with incremental positive end-expiratory pressure (PEEP) levels titrated to the best respiratory-system static compliance, or 2) a conventional low-PEEP lung-protective ventilation (LPV) strategy. Patients had to be hemodynamically stable and without evidence of barotrauma.

At baseline, there was no difference between treatment arms in terms of demographics, illness severity, comorbidities, pulmonary mechanics, gas exchange, or in achieved LPV goals. Sixty-two percent of subjects demonstrated a pulmonary source of ARDS and 67% exhibited septic shock. Of those randomized to OLV, 96% received an initial RM, and 78% received an RM following the PEEP decrement trial. Approximately 63% of subjects required no further RMs vs. 9% who required three or more maneuvers during the trial. On the first two study days, mean PEEP levels were approximately 4 cm H_2O higher in the OLV vs. low-PEEP groups (16.2 vs. 12.0 and 14.2 vs. 10.5 cm H_2O, respectively). Mean plateau and driving pressures were significantly higher in the OLV group, yet both variables were well within accepted LPV boundaries for each group. Mortality in the OLV group was significantly higher at both day 28 and at six months compared to the control low-PEEP group (55.3 vs. 49.3% and 65.3 vs. 59.9%, respectively). The OLV group experienced slightly fewer ventilator-free days than the conventional low-PEEP group; however, both intensive care and hospital lengths of stay were not different.

■ COMMENTARY

ARDS presenting with severe hypoxemia refractory to high PEEP levels often reflects the contribution of enormous compressive forces emanating from reduced chest wall compliance. Over several decades, mounting evidence suggests that inspiratory pressures between 40-60 cm H_2O are necessary to fully recruit dorsal-caudal regions and reverse intractable hypoxemia. While the mechanical foundation for a recruitment maneuver is sound, its application in ARDS has remained uncertain given both the heterogeneous nature of lung injury and the inability to ascertain the amount of potentially recruitable lung vs. consolidated lung. Moreover, the degree to which atelectrauma contributes to lung injury and mortality risk in ARDS has (up to this point) remained unanswered.

Clearly, the Cavalcanti et al study indicates that an open lung ventilation strategy with recruitment maneuvers and higher PEEP should not be used routinely in the management of ARDS. Nonetheless, more in-depth analysis of the study results is needed to determine how OLV should be used going forward. At this juncture, it would be unwise to reject the use of RM in ARDS categorically. First, 63% of subjects received only two RMs, the duration of which was a total of eight minutes at plateau pressures of 40-60 cm H_2O at a safe driving pressure. Given what is known about ventilator-induced lung injury, it's implausible that such brief exposure could affect mortality that profoundly.

What is plausible is that the 46 patients who received three or more RMs may have been harmed. Subjects requiring repeated RMs may have been less recruitable and more susceptible to aggravating a proinflammatory state in a study sample characterized by pulmonary ARDS and septic shock. This would include regional

lung overdistension, the possibility of bacterial translocation, and repeated gastrointestinal ischemia/reperfusion injury.[1,2] The higher mean PEEP levels in the OLV group would not explain the increased mortality, as it was only 3-4 cm H_2O above the conventional low-PEEP group. In contrast, differences in mean PEEP in three previous major LPV studies (ALVEOLI, EXPRESS, LOVS) was 6-8 cm H_2O. A similar relationship existed for higher mean plateau and driving pressures in those studies compared to the ART study.

What can we reasonably conclude at this juncture? The OLV strategy is not necessary for managing the vast majority of ARDS cases, and atelectrauma is unlikely to be a mortality driver when LPV incorporates reasonable levels of PEEP early in the acute phase (e.g., ~12-16 cm H_2O). However, there exists a small subset of ARDS where these levels of PEEP and other ancillary therapies are insufficient. These situations are likely restricted to cases of severe lung injury complicated by markedly reduced chest wall compliance that necessitate the OLV strategy as a temporizing measure to stabilize oxygenation and reduce long-term exposure to hyperoxia. Unfortunately, given that these cases represent such a small minority of ARDS, we will never see an adequately powered study to provide conclusive evidence in a timely manner. ■

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Physician Burnout: A Multi-specialty Perspective

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

SOURCES: Holoshitz N, Wann S. Burnout — There's an app for that. Helping physicians deal with job-related stress. *JAMA Cardiol* 2017; Jun. 14. doi: 10.1001/jamacardio.2017.1758. [Epub ahead of print].
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Z73.0 Burnout: a state of physical or mental exhaustion

In 2015, the International Classification of Diseases, 10th revision (ICD-10) "elevated" burnout to a billable diagnosis.[1] Burnout — a syndrome developed in response to workplace stressors and often characterized by emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment — is not unique to the medical profession.[2] Yet, well before ICD-10, the medical world recognized a growing need for studies of physician burnout; the effect of this insidious condition on the individual provider, family members, patients, the healthcare team, and the healthcare system has too many implications to ignore.

A Brief Historical Perspective

Drug addicts in treatment who stared at a cigarette until it "burned out" prompted psychologist Herbert Freudenberger, working with this population in the mid-1970s, to coin the term "burnout." In his research and writings, he applied the term to a phenomenon he observed among his colleagues and staff members who exhibited a slow but steady decline in energy, motivation, and commitment to the job, as well as emotional depletion over time.[3]

Maslach and Johnson extended the work of Freudenberger and, in the 1980s, developed a scale to measure degree and effect of burnout. Notably, the Maslach Burnout Inventory (MBI) remains in use today as one of the few validated tools to measure this state. The team was the first to describe burnout as an all-encompassing phenomenon involving emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment stemming from the weight of professional stressors and responsibilities.[4]

Although the scientific literature did not identify burnout

until the 1970s, there is evidence that the syndrome existed well before that time. For example, when viewed through the lens of 2017, a 1953 published case study of a psychiatric nurse diagnosed with "exhaustion reaction" would qualify for a burnout diagnosis.[5] Popular literature also hints that burnout existed as far back as the turn of the 19th century, with progressive mental exhaustion, disillusionment, and loss of drive plaguing a protagonist in Thomas Mann's 1901 *Buddenbrooks* (revived as a 2008 movie).[3]

The bulk of empirical studies in this field began in the 1980s with the development of research-validated tools. By the turn of the 20th century, articles describing "doctor discontent" and low morale pointed to a growth of burnout in the medical profession, with measurements of physician satisfaction declining from 1986 to 1997.[6] In response to this problem, in 2001, The Joint Commission mandated that all hospitals establish a policy to address the well-being of physicians (distinct from disciplinary processes).[7]

In 2015, Shanafelt et al published data regarding burnout collected in 2014 from 6,880 U.S. physicians and compared the results to a similar survey from 2011. There was a significant increase in reports of burnout among U.S. physicians — 45.4% in 2011 to 54.4% in 2014 ($P < 0.001$); this trend was consistent across 24 specialties.[8]

In a 2017 survey looking at a national sample of family physicians, Rassolian et al noted workplace factors frequently associated with physicians self-identifying as "burnt out" included the time burden of electronic medical record documentation (especially time spent at home), a hectic pace, and a chaotic work environment.[9]

Where Are We Now?

Last year saw an uptick in articles and studies regarding burnout in physicians. In recent months, multiple articles have been published on the topic in both academic and clinical journals. The three selected for review here represent different perspectives across the broad field of medicine.

In "Burnout — There's an App for That," an opinion piece in *JAMA Cardiology*, Holoshitz et al emphasized the consequences of burnout, such as higher rates of drug and alcohol abuse in physicians with burnout and the association with depression and suicide. These authors urged readers to consider mindful meditation or, acknowledging the difficulty of finding time during a busy day, to download a mindfulness app for both instruction and practice of this technique. They cited a Cochrane database study associating mindfulness with improvement in burnout scores among hospital practitioners as well as primary care providers.

Holoshitz et al noted, "Empathy, membership in a caring community of peers, and a balanced lifestyle are central to countering burnout." Furthermore, they recommended a change in the relationship between healthcare providers and healthcare institutions. They believe such a change should move in a direction to encourage institutions to support individuals in efforts to adjust work schedules, work intensity, and achieve a true work-life equilibrium.

In "Physician Burnout: The Hidden Health Care Crisis," gastroenterologists Lacy et al presented a case study of a young gastroenterologist with burnout and reviewed the relevant literature discussing risk factors, causes, and treatment. They applied the characteristics of burnout — emotional exhaustion, depersonalization, and a reduced sense of personal accomplishment — to physicians specifically. They noted that a physician with emotional exhaustion may be depleted of compassion, that depersonalization may lead to detachment, and that a decreased sense of personal accomplishment leaves many feeling less able to complete tasks and less satisfied with patient care.

This team also emphasized prevention, noting that being self-aware of the potential for burnout is the first step in prevention. They encouraged physicians to practice self-care, sleep, exercise, and learn to "say no." When discussing prevention and treatment, they emphasized literature support for organizational interventions, including leadership efforts to create a positive work environment that allows physicians some autonomy and encourages balance, rather than simply filling schedules with more tasks and/or patient time.

In an article in *JAMA Internal Medicine*, Panagioti et al presented a meta-analysis of studies regarding interventions to address burnout in physicians. They included 19 studies incorporating 1,550 physicians. They identified three main objectives in their study: 1) assess the effectiveness of interventions to reduce the development of physician burnout; 2) assess which type of intervention — organizational or individual — is more effective; and 3) assess if the experience of the physician or type of healthcare setting affects the effectiveness of the intervention.

Notably, the number of eligible studies increased from one in 2005 to six in 2015. Although most studies were performed in the United States, many countries, including Canada, Israel, Australia, and several western European countries, were represented.

Selected Results

Results were interpreted using standardized mean difference (SMD) — a useful measure when comparing multiple studies with a variety of interventions.

Sometimes used interchangeably with "treatment effect," a negative SMD in this case indicates the degree to which treatment is more effective than control. The following guidelines help to interpret the magnitude of effect: SMD = 0.2 small; SMD = 0.5 medium; SMD = 0.8 large.[9]

Based on these results and their analysis, Panagioti et al concluded that interventions for burnout in physicians showed evidence of efficacy ("small significant" reduction in burnout).

More specifically, this group noted that organizational-directed interventions have higher treatment effects than physician-directed interventions, and that the most impact has been shown when experienced physicians are involved and when interventions are performed in primary care settings.

These articles demonstrate different approaches to physician burnout: an opinion article promoting self-care; a literature review promoting prevention; and a meta-analysis suggesting that organizational interventions are most effective in combating burnout, but that individual physician effort at self-regulation and mind-body techniques can be effective.

Although these articles limited subjects to physicians, the evidence is mounting that advanced practice practitioners are at risk for burnout as well.[10]

There is little doubt that rigorous, large-scale studies are necessary to further illuminate the path of burnout prevention and recovery. In the interim, perhaps the most significant takeaway message for all practitioners includes the following:

- Be aware of the potential hazards of burnout; think about preventive efforts early in your career.
- Consider "practicing what you preach" in terms of self-care — make time for exercise, eat well, socialize, and practice mindfulness or self-awareness.
- Actively intervene to remind health organizations that initiatives to encourage a healthy work-life balance among all providers will provide benefit to many — not only the individual provider, but also patients and the healthcare system as a whole. Remind administrators of the financial implications associated with burnt-out providers (resulting from potential increases in poor patient satisfaction ratings, high provider turnover, and early retirement, for example). Work together with practitioners in your own organization to "speak with one voice" to emphasize the importance of preventing and fighting burnout.
- Speak for implementing practical and concrete interventions, such as decreased workloads, reduction of repetitive non-technical tasks, and adjusting work hours to allow time for personal growth and development.

Few of us imagined our lives as physicians would involve struggling with issues of burnout; most entering the profession expect a fulfilling professional career in concert with a satisfying family and social life. Yet the staggering reality of burnout growth in physicians tells us another story. Learning to guard against burnout can help all providers accept the importance of shaping a professional lifestyle that involves elements of moderation, self-reflection, and self-awareness. Just as the simple act of hand-washing has critical importance in the complex issue of infection control, developing a basic habit of self-care, including an expectation that provider self-care will be supported actively by healthcare organizations, can become key in stemming the growth of burnout in our profession. ■

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CME QUESTIONS

1. According to the retrospective study by Chang and colleagues, of patients taking new oral anticoagulants (NOACs), concomitant use of which of the following drugs was associated with a significant risk of major bleeding compared to NOAC use alone?

a. Amiodarone

b. Fluconazole

c. Rifampin

d. Phenytoin

e. All of the above

2. In the double-blind, randomized, sham-controlled trial of angioplasty in patients with single vessel coronary artery disease and chronic stable angina, what outcomes were observed in patients undergoing percutaneous coronary intervention compared to medical management alone?

a. No difference in exercise time or angina symptoms

b. Decreased incidence of subsequent myocardial infarction

c. Improved one-year mortality

d. Improvement in left ventricular ejection fraction

e. All of the above

3. In the prospective, randomized, controlled clinical trial by Cavalcanti and co-investigators, use of an open-lung ventilation strategy in patients with moderate-to-severe ARDS was associated with what outcomes compared to standard lung-protective ventilation?

a. A decreased ICU length of stay

b. A decreased hospital length of stay

c. Decreased mortality at 28 days and at six months

d. Increased mortality at 28 days and at six months

e. Decreased readmission rates to the ICU

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and;
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems.