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ABSTRACT & COMMENTARY

Steroids Increase the Risk for Community-acquired *Staphylococcus aureus* Bacteremia

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins reports that he has received research support from Actavis.

SYNOPSIS: A case-control study observed an increased risk for developing community-acquired *Staphylococcus aureus* bacteremia with the use of systemic glucocorticoids. A distinct dose-response relationship was found.

SOURCE: Smit J, Kaasch AJ, Sogaard M, et al. Use of glucocorticoids and risk of community-acquired *Staphylococcus aureus* bacteremia: A population-based case-control study. *Mayo Clin Proc* 2016;91:873-880.

Staphylococcus aureus bacteremia (SAB) continues to cause significant morbidity and mortality. Previous studies produced conflicting results about whether steroids increase the risk of SAB and may have been biased by confounding variables. Therefore, Smit and colleagues sought to more clearly define the risk of SAB associated with the use of steroids.

The investigators used data collected from a population-based registry from northern Denmark. They chose to limit the study to patients with community-acquired SAB (CA-SAB), defined as no previous diagnosis of SAB within five years, because patients with previous SAB are at increased risk for recurrences compared to the general population. Current steroid users were defined as patients whose most recent prescription redemption was within 90 days before the index date. This group was further characterized into new users, defined as those who redeemed their first-ever prescription within 90 days of the index date, and long-term users who redeemed their prescription within 180 days. Former users were defined

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as those patients whose last prescription was 90 to 180 days before the index date, and nonusers were persons who filled no prescriptions for steroids within 180 days of the index date. Prescriptions for inhaled and topical steroids were excluded. Risk for CA-SAB was further assessed among current steroid users according to prednisolone-equivalent cumulative doses, from 150 mg or less up to greater than 1,000 mg. Conditional logistic regression was used to calculate crude and adjusted odds ratios (ORs).

A total of 2,638 patients with CA-SAB were identified, of whom 379 were current users of steroids, along with 26,379 randomly selected controls (1:10 ratio), which included 827 current steroid users. Only 5% of the isolates were methicillin-resistant Staphylococcus aureus (MRSA). Compared to controls, patients with CA-SAB had more co-morbidities, including diabetes (18% vs. 5%), chronic pulmonary diseases (14% vs. 6%), and cancer (25% vs. 7%). The adjusted OR for CA-SAB among new steroid users was 2.73 (95% CI, 2.17-3.45), 2.31 (95% CI, 1.90-2.82) for long-term users, and 1.33 (95% CI, 0.98-1.81) for former users. Also, the risk of CA-SAB increased with escalating doses of steroids. Compared to nonusers, the adjusted OR ranged from 1.32 (95% CI, 1.01-1.72) for those taking a cumulative dose ≤ 150 mg, up to 6.25 (95% CI, 4.74-8.23) for those with a cumulative dose > 1,000 mg. Finally, there were no significant differences in the risk of CA-SAB based on sex or age.

■ COMMENTARY

The results of this study showed there was a considerable risk of developing CA-SAB for patients in the cohort who were taking steroids. Furthermore, the risk increased with higher steroid doses. Smit and colleagues were astute for excluding cases of hospital-acquired SAB, which likely would have introduced confounding variables, such as post-surgical wound infections and SAB caused by intravenous catheters. Although the prevalence of MRSA bacteremia was very low compared to that of the United States, there is no logical reason to suspect that a higher rate of MRSA would have led to any different outcomes.

As the authors mention, there are several pathophysiologic mechanisms by which steroid use might predispose to CA-SAB. For example, steroids inhibit toll-like receptor signaling, a key component in the innate immune response to *S. aureus* infections. Furthermore, steroids reduce phagocytosis, cytokine production, and leukocyte adhesion. Previous studies have demonstrated that the adverse effects of steroids on immunity are dependent on the length of therapy and the dosage used. Wound healing also is impaired by steroids, and this loss of skin barrier protection can allow *S. aureus* to enter deeper tissues and, ultimately, the bloodstream.

Despite the interesting findings of the study, a few words of caution are necessary. First, there were no data on steroid adherence among the patients or on infective foci, such as vascular access devices. Second, patients who use steroids tend to be sicker than the general patient population and, thus, more likely to be susceptible to CA-SAB. Third, the study was conducted in northern Denmark, and the results might not be generalizable to other populations and geographic areas.

What is the take-home message from this study? Clinicians should maintain a high level of suspicion for CA-SAB in patients taking steroids and focus accordingly, i.e., blood cultures and a thorough history and physical examination, with particular attention to joint or back pain and new heart murmurs that might indicate an infected joint, discitis, or endocarditis. ■

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Screening for Coronary Artery Disease Is Underused in Heart Failure

By Van Selby, MD

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

SYNOPSIS: In a large retrospective cohort of patients hospitalized for new-onset heart failure, the majority did not receive testing for ischemic heart disease.

SOURCES: Doshi D, Ben-Yehuda O, Bonafede M, et al. Underutilization of coronary artery disease testing among patients hospitalized with new-onset heart failure. *J Am Coll Cardiol* 2016;68:450-458.

Coronary artery disease (CAD) is the most common cause of heart failure (HF). Current practice guidelines recommend screening for CAD in patients with newly diagnosed HF. However, few studies have evaluated how often clinicians perform diagnostic testing for CAD on patients hospitalized with newly diagnosed HF.

Doshi et al analyzed a large commercial administrative claims database, supplemented by Medicare data. They evaluated the frequency of diagnostic testing for CAD, both during the index hospitalization for new-onset HF and within 90 days of hospitalization. Between 2010 and 2013, the authors identified 67,691 patients.

Overall, 17.5% of patients underwent any testing for ischemic CAD during the index hospitalization, and 27% were evaluated for CAD within 90 days. The most common evaluation method was stress testing, followed by coronary angiography. In a multivariable analysis, predictors of undergoing noninvasive testing for CAD included baseline CAD (odds ratio [OR], 1.25; $P < 0.001$), hypertension, hyperlipidemia, and reduced ejection fraction. Patients who were > 70 years of age and those with prior stroke, peripheral arterial disease, prior arrhythmia, renal disease, or a prior workup for CAD were less likely to receive noninvasive testing for CAD.

Only 2% and 4.3% of patients underwent coronary revascularization during the index hospitalization and at 90 days, respectively. Baseline CAD (OR, 9.27; $P < 0.001$), male sex, diabetes, and smoking all were associated with greater odds of coronary revascularization, and percutaneous coronary intervention was used more commonly than coronary artery bypass grafting (CABG). The authors concluded that diagnostic testing for ischemic CAD is underutilized significantly among patients hospitalized for new-onset HF.

■ COMMENTARY

Not every patient hospitalized for new HF requires evaluation for CAD within 90 days, and the exact percentage of patients who should be evaluated is unknown. However, considering CAD is the most common cause of HF and present in more than half of patients with HF, the rate of CAD testing reported in this study (27% of all patients were evaluated within 90 days) is surprisingly low and suggests, as the authors concluded, that diagnostic testing for CAD is underutilized significantly in this population. Part of the explanation for low use of ischemic evaluation in new HF may be a perceived lack of evidence showing clear benefit of revascularization in patients with HF and CAD. Perhaps because of this lack of data, the most recent HF guidelines from the American College of Cardiology/American Heart Association only make a class IIa recommendation (meaning it is reasonable) to evaluate for CAD in the diagnostic evaluation of new HF. The recent publication of 10-year follow-up from STICHES, showing a mortality benefit associated with coronary artery bypass grafting in patients with CAD and systolic HF, may strengthen the argument for CAD testing. Regardless of the benefits associated with revascularization, identification of CAD also may guide medical therapy of a given patient.

When evaluating findings of large retrospective cohort studies, it is important to acknowledge limitations. Analyses of insurance claims databases depend on accurate coding, and it is possible that diagnostic testing for CAD was not always coded properly. Furthermore, complete clinical information is not available for these patients — some may have had a contraindication to diagnostic testing or other explanation for why testing was not performed. Despite these limitations, given the size of the cohort and the magnitude of the findings, it appears the majority of eligible HF patients are not screened for CAD.

Identifying which HF patients will have underlying CAD is difficult based on clinical history of risk factors alone. Many will not have angina or other clear ischemic symptoms. Once CAD is identified, it may be difficult to determine whether it is the cause of a given patient's HF; however, this should not deter clinicians

from testing. The authors suggested an increasingly cost-conscious medical environment, eager to minimize unnecessary diagnostic testing, is responsible for the low rates of CAD evaluation. By their estimate, clinicians miss 325,000 cases of CAD in patients with congestive HF every year due to underutilization of diagnostic testing. Whatever the reason, the rates of CAD testing reported in this study would strike most cardiologists as inappropriately low, and suggest those of us who evaluate and treat HF should consider screening for CAD more frequently in patients with newly diagnosed HF. ■

The Use of Dexmedetomidine for Sedation May Lead to Earlier Extubation and Decreased Ventilator Adverse Events

By Samuel Nadler, MD, PhD

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

SYNOPSIS: The choice of dexmedetomidine or propofol over midazolam may improve outcomes in patients mechanically ventilated for three or more days.

SOURCE: Klompas M, Li L, Szumita P, et al. Associations between different sedatives and ventilator-associated events, length of stay, and mortality in patients who were mechanically ventilated. *Chest* 2016;149:1373-1379.

It's common to treat critically ill patients on mechanical ventilation with sedative medications. Limited data exist to direct which sedatives are most appropriate to maintain patient comfort yet facilitate timely extubation and minimize adverse events. Previously, benzodiazepine infusions were most common. More recently, propofol and dexmedetomidine have supplanted benzodiazepine, based largely on two studies published in 2009 and 2012.[1,2]

Klompas et al examined how these recommendations generalize into routine practice. This is a retrospective study of 9,603 patients in a single academic center between July 2006 and December 2013. The inclusion criteria specified patients on mechanical ventilation for three or more days. Outcomes studied included time to extubation, time to hospital discharge, ventilator associated events (VAEs), and mortality. Proportional subdistribution hazard models were used to estimate the effect of sedative exposure on these outcomes.

Over the specified time period, researchers identified 86,714 ventilator days. The combination of benzodiazepines and propofol (42%) was the most common sedation method, followed by benzodiazepines alone (21%), propofol alone (12%), and the combination of benzodiazepines, propofol, and dexmedetomidine (10%). Clinicians used dexmedetomidine alone in 0.3% of ventilator days, most commonly in the cardiac surgery ICU. Compared with regimens without benzodiazepines, there was a significantly higher risk of VAEs in patients on midazolam (hazard ratio [HR], 1.4; 95% confidence interval [CI], 1.1-1.7; $P = 0.002$). Compared with regimens without propofol, patients on propofol experienced a higher risk of VAEs (HR, 1.3; 95% CI, 1.1-1.6; $P = 0.003$), infection-related, ventilator-associated complications (IVACs) (HR, 1.6; 95% CI, 1.2-2.2; $P = 0.0009$), and possible or probable pneumonias (HR, 1.5; 95% CI, 1.0-2.2; $P = 0.003$). Direct comparisons of single agents did not reveal statistically significant HRs, although there was a trend toward decreased events in patients on dexmedetomidine. Overall, patients on dexmedetomidine were more likely to be extubated (HR, 2.05; 95% CI, 1.77-2.38; $P < 0.0001$) when compared to patients on regimens without dexmedetomidine and in single-agent comparisons. There were no differences in hospital discharges and mortality among different regimens.

■ COMMENTARY

This study represents a huge, albeit retrospective, cohort study of the effects of various sedative agents on patient outcomes in the ICU. It focuses on patients on prolonged mechanical ventilation, specifically three or more days. The use of proportional sub-distribution hazard models can correct for known confounding variables but cannot eliminate bias in this study.

It is important to note that investigators conducted this study using data on patients admitted between 2006 and 2013. Although efforts were made to correct hazard risks based on year of admission, the bulk of patients were admitted before most practitioners had transitioned away from the use of benzodiazepines. The SEDCOM and MIDEX/PRODEX trials were published in 2009 and 2012, respectively.[1,2]

This is evident by the many patients on propofol and benzodiazepines and benzodiazepine-only regimens. Relatively few patients were on dexmedetomidine only or regimens including dexmedetomidine. Thus, this study may not represent contemporary practice patterns in the ICU.

There were significant differences in the type of ICU using each sedative. The greatest proportion of dexmedetomidine was used in the cardiac surgery (57%) and thoracic surgery (16%) units. While hazard risk adjustments were made for this confounding variable, these patients clearly are different from patients in medical units, which may bias results.

Ultimately, base the decision on which sedatives to use on relative risks and benefits. This study suggested dexmedetomidine-based sedation strategies might facilitate extubation and reduce VAEs and IVACs. However, this did not translate into shorter length of stay or hospital mortality. Greater rates of bradyarrhythmias have been noted with dexmedetomidine. Although Klompas et al did not address depth of sedation in this study, the SEDCOM and MIDEX/PRODEX trials did, and it may lead to improved patient arousability and ability to communicate with dexmedetomidine. This study did not address the cost-effectiveness of these regimens, as dexmedetomidine can be much more expensive than other agents. Thus, while the Klompas et al study hints that dexmedetomidine-based regimens may have benefits, one must consider the many other factors not examined in this study in choosing sedatives for patients on mechanical ventilation in the ICU. ■

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Chocolate Counteracts the Effects of Sleep Deprivation

By George Munoz, MD

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Dr. Munoz reports he is a consultant for UCB, and is on the speakers bureau for Primus and UCB.

SYNOPSIS: An acute administration of a chocolate rich in flavanols (a subclass of flavonoids) was found to mitigate the cardiovascular and cognitive effects of sleep deprivation in a group of young and healthy individuals.

SOURCE: Grassi D, Socci V, Tempesta D, et al. Flavanol-rich chocolate acutely improves arterial function and working memory performance counteracting the effects of sleep deprivation in healthy individuals. *J Hypertens* 2016;34:1298-1308.

Sleep deprivation has become a major health issue in the United States, with more than 50-70 million adults suffering from sleep disorders. It has been found that sleep deprivation can be detrimental for cardiovascular health and cognitive function. Sleep alters the autonomic nervous system; therefore, disorders interrupt the normal regulation of blood pressure (increasing BP) and can lead to increased inflammation, endothelial dysfunction, and increase oxidative stress. Taking it one step further, high BP has been linked to Alzheimer's disease, cognitive impairment, and vascular dementia.

There has been great interest in finding a product that can ameliorate the side effects of sleep deprivation. One food that has caught many people's attention because of its high flavonoid content and potential cardiovascular benefits is cocoa, the (usually) powdered product of chocolate "beans." Flavanols (a subclass of flavonoids, which include catechins, epicatechins, proanthocyanidins, theaflavins, and thearubigins) have been found to improve endothelial function by increasing nitrous oxide availability (aiding in BP regulation). Hence, they might help increase cerebral blood flow and cognitive impairment. To date, many studies have shown an improvement of hippocampal functioning and cognition in general with a flavanol-rich diet, but none have studied whether flavanols in cocoa can diminish the impairments caused by restricting sleep. In a double-blind, randomized, controlled trial, Grassi et al studied whether cocoa could acutely improve cardiovascular and cognitive function after a night of sleep deprivation.

The study recruited 32 healthy participants (16 men and 16 women) with no history of medical, neurological, or psychiatric disorders. Participants all had

a blood pressure of less than 140/90 mmHg and a body mass index (BMI) between 19-30 kg/m2. The researchers excluded smokers, habitual cocoa consumers, and subjects with sleeping disorders, metabolic diseases, or any major cardiovascular risk factor.

Each participant attended four testing sessions: two control sessions in which they were evaluated after undisturbed sleep and two experimental sessions in which they were evaluated after total sleep deprivation. Testing sessions were separated by one week and participants were asked to fast for 12 hours prior to the session. They were given one bar of either a flavanol-rich chocolate (520 mg of flavanols) or a flavanol-poor chocolate (88.5 mg of flavanols). Each chocolate bar weighed 100 g; the flavanol-rich chocolate was 80% cocoa, while the flavanol-poor chocolate was 50% cocoa. Ninety minutes after the chocolate consumption, participants submitted to several cognitive tests and were given a Karolinska sleepiness scale (KSS) to assess their sleepiness. The tests included a psychomotor vigilance task to evaluate response speed and behavioral alertness) and the two-back task (to measure working memory).

Two hours after chocolate consumption, participants were taken into a quiet room where several medical assessments were performed to measure endothelial function, blood pressure, and arterial stiffness. Endothelial function was assessed via the flow mediated dilation (FMD), which tested the brachial artery with the use of ultrasonography. Later, the central and peripheral arterial stiffness was assessed via carotid-femoral pulse wave velocity (PWV), using a probe to record the waveforms and the ECG to calculate wave transit time. Finally, repeated measure analyses of variance (ANOVA) were performed on condition and treatment with different dependent variables. Also, correlations were calculated between the two-back test and changes in FMD and PWV after flavanol-rich chocolate consumption. The level of significance was set at $P < 0.05$.

Results showed that the KSS score (sleepiness) was higher in the sleep deprivation group than the undisturbed sleep group. On the other hand, behavioral measures showed that the average reaction time was slower in the sleep deprivation group ($P = 0.00001$). In other words, sleep deprivation adversely affected alertness and cognitive functions. Also, it showed that the female group's accuracy when sleep-deprived was higher when they consumed the flavanol-rich chocolate vs. the flavanol-poor chocolate ($P = 0.04$). This is significant, since it means that in women, but not men, cocoa was able to improve working memory and cognitive performance altered by lack of sleep.

The cardiovascular measures demonstrated that sleep deprivation does have an effect on cardiovascular health, since it raised the SBP ($P = 0.001$). Also, the effect of treatment (flavanol-rich vs. flavanol-poor) on pulse pressure was significant ($P = 0.004$). The pulse pressure was lower in the flavanol-rich group (mean = 46.44) compared to the flavanol-poor group (mean = 48.47).

When analyzing the FMD, the effect of treatment ($P = 0.00001$) and condition ($P = 0.02$) were significant. Participants showed a higher FMD after consuming the flavanol-rich chocolate (mean = 7.04%) compared to the flavanol-poor chocolate (mean = 5.00%). This supports previous findings stating that administration of flavanol-rich chocolate can increase and improve endothelial function acutely.

The statistical analysis on the PWV showed a non-significant effect of treatment and a significant effect of condition. The interaction of condition and treatment with the PWV was significant ($P = 0.03$), while the PWV was higher on deprivation state when compared to the undisturbed sleep, but only after consuming the flavanol-poor chocolate. This means that the flavanol-rich chocolate was able to maintain the arterial stiffness after a night with no sleep, while the flavanol-poor chocolate increased the arterial stiffness or lack of vascular compliance, which is a predecessor to hypertension and left ventricular dysfunction.

On the other hand, when calculating the ANOVA on the aortic systolic pressure, the gender ($P = 0.001$) and condition ($P = 0.006$) were found to be significant, but the treatment ($P = 0.91$) was found to be non-significant. The same effect was seen on the aortic pulse pressure.

Pearson's r coefficient was used to calculate the relationship between working memory, FMD, and PWV. Researchers found a significant coefficient between FMD and the two-back tests — the higher the FMD, the better the participant performed in the two-back tests ($r = 0.41$; $P = 0.01$). There was no correlation between PWV and the two-back test.

■ COMMENTARY

The Grassi et al study ties into other research, supporting those results and advancing our understanding of the mechanisms behind the effect of cocoa. One of the possible mechanisms that explains the effect of flavanols on BP and arterial function is the ability of flavanols to induce the synthesis and secretion of cortisol, epinephrine, and norepinephrine. Wirtz et al performed a placebo-controlled trial with 64 men to measure cortisol, epinephrine, adrenocorticotropic hormone, and norepinephrine on blood and saliva when subjected to a social stress test after consuming a dark chocolate

with flavonoid and another without flavonoids.[1] The study showed that the flavonoids in the dark chocolate buffered the stress reaction at the peripheral level, specifically the adrenal glands (reducing cortisol and epinephrine), when compared to the flavonoid-poor group. Also, they showed that the high epicatechin level (class of flavan-3-ol, flavanol) in the blood reduced the endocrine stress in the flavonoid group, regardless of the age, BMI, and BP of the participants.

Regarding the effect seen on working memory and cognition, specifically on women, the study suggests that there might be hormonal involvement, as per the mechanism below. Stranges et al found a greater risk of hypertension in women after sleep deprivation and the effect was even greater in premenopausal women.[2] Therefore, it is hypothesized that the greater effect seen in the premenopausal women with the flavanol-rich chocolate may be related to this. More research is needed to determine the mechanism behind the cognitive effects of cocoa flavonoids.

The consumption of one bar of a high-quality dark chocolate (80% cocoa), in contradistinction to milk chocolate containing less cocoa and more sugar, can mitigate the effects of one night of sleep deprivation, especially its cardiovascular repercussions. Hence, it makes sense clinically to encourage patients to consume this type of high-quality chocolate in moderation. Based on these results and previous work, cocoa flavonoids could be a used as a supplement or aid in sleeping disorders. Overall, this study should promote more research on larger and more diverse populations to determine the minimum amount of high-quality chocolate needed to create a positive physiologic effect and at what frequency. Specifically, more research is needed on elderly populations, patients with sleep disorders, and patients with hypertension to investigate if cocoa flavonoids can ameliorate their consequences.

Acknowledgment: Special thanks to Isabela Leoni Garcia, MS Nutrition and Human Performance, Nutrition Intern at The Oasis Institute, for her help and research assistance in this review.

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Triage to a Certified Stroke Center Reduces Early Mortality

By Matthew E. Fink, MD

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Dr. Fink reports he is a retained consultant for Procter & Gamble and Pfizer.

SOURCE: Bekelis K, Marth NJ, Wong K, et al. Primary Stroke Center hospitalization for elderly patients with stroke. Implications for case fatality and travel times. *JAMA Intern* Med doi:10.1001/jamainternalmed.2016.3919.

In a national attempt to improve stroke care, there has been widespread certification of primary stroke centers (PSCs) by The Joint Commission. It has been assumed that outcomes will be better in the PSCs, but there have always been questions regarding how much additional time is acceptable to travel to a PSC, compared to a local hospital, in terms of successful treatment and outcomes. The investigators queried a Medicare database, examining the association of case fatality for patients with stroke when receiving care in a PSC vs. other hospitals, to identify the effects of prolonged travel time. This was a retrospective study of 865,184 elderly patients with stroke, with a mean age of 78.9 years, and 55.5% were female.

The investigators found that 53.9% of the patients were treated in PSCs. In addition, they found that admission to a PSC was associated with a 1.8% lower seven-day mortality and a 1.8% lower 30-day case fatality. Fifty-six patients with stroke needed to be treated in a PSC to save one life at 30 days. In an analysis of the effect of additional travel time, receiving treatment in a PSC was associated with a survival benefit for patients who traveled less than 90 minutes. Traveling more than 90 minutes to reach a PSC offset any benefit of the PSC care. ■

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CME QUESTIONS

1. In the case-control study by Smit, et al., which of the following increased the risk for community-acquired *Staphylococcus aureus* bacteremia?

a. Chronic pulmonary disease

b. Diabetes mellitus

c. Cancer

d. Current use of oral corticosteroids

e. All of the above

2. In the study using a large commercial administrative claims database by Doshi and colleagues, what percentage of patients with heart failure had an evaluation for coronary artery disease within 90 days of their index hospitalization for new-onset heart failure?

a. 14%

b. 27%

c. 52%

d. 88%

3. The retrospective study by Klompas et al. demonstrated which of the following outcomes for patients on mechanical ventilation who received dexmedetomidine for sedation:

a. Decreased duration of mechanical ventilation

b. Decrease hospital length of stay

c. Decreased mortality

d. All of the above

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.

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