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ABSTRACT & COMMENTARY

Vancomycin Combined with Piperacillin-Tazobactam Increases the Risk for Acute Kidney Injury

By Richard R. Watkins, MD, MS, FACP, FIDSA

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

SYNOPSIS: A retrospective cohort study found an increased risk of acute kidney injury for patients who received vancomycin in combination with piperacillin-tazobactam compared to those who received vancomycin plus cefepime (hazard ratio = 4.27; 95% confidence interval, 2.73-6.68).

SOURCE: Navalkele B, Pogue JM, Karino S, et al. Risk of acute kidney injury in patients on concomitant vancomycin and piperacillin-tazobactam compared to those on vancomycin and cefepime. *Clin Infect Dis* 2017;64:116-123.

The combination of vancomycin and piperacillin-tazobactam is used frequently in clinical practice. This regimen covers many community and nosocomial pathogens and often is chosen empirically for sepsis. However, recent reports have noted an increased risk for acute kidney injury in patients given concurrent vancomycin and piperacillin-tazobactam. Therefore, Navalkele and colleagues sought to clarify this association and determine if there is a similar risk when vancomycin is paired with cefepime.

The study was a retrospective, matched, cohort study from a single healthcare institution. Inclusion criteria included age ≥ 18 years and having received combination therapy with vancomycin and cefepime or vancomycin and piperacillin-tazobactam for at least 48 hours, with the two antibiotics administered within 24 hours of each other. Patients were

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excluded if their baseline creatinine was > 1.2 mg/dL or if they required dialysis. They were divided into two groups based on the combination received and matched using five variables that are associated with the development of acute kidney injury. These included sepsis severity, ICU status at onset of combination therapy, duration of combination therapy, daily dose of vancomycin received, and number of concomitant nephrotoxic agents received while on combination therapy. Also, to assess the effect of vancomycin on acute kidney injury, the researchers calculated the median trough of vancomycin prior to the onset of acute kidney injury.

There were 279 pairs included in the study population totaling 558 patients. The mean age was 55.9 years and the baseline characteristics were similar between the two groups. Patients who received the vancomycin/piperacillin-tazobactam combination had a higher incidence of septic shock and skin and soft tissue infections. The rate of acute kidney injury was higher in those who received vancomycin/piperacillin-tazobactam vs. vancomycin/cefepime (29.0% vs. 11.1%; hazard ratio [HR] = 4.0; 95% confidence interval [CI], 2.6-6.2; $P < 0.001$). After controlling for differences between the two groups, multivariate analysis found vancomycin/piperacillin-tazobactam was independently associated with the development of acute kidney injury (HR = 4.3; 95% CI, 2.7-6.7; $P < 0.001$). Furthermore, the median time to onset of acute kidney injury was shorter in the vancomycin/piperacillin group (three days) compared to the vancomycin/cefepime group (five days; $P < 0.001$).

While there was no difference in mortality between the two groups, those who received vancomycin/piperacillin-tazobactam had a longer median length of stay (eight days) compared to the vancomycin/cefepime group (six days; $P = 0.01$). The two groups had similar median vancomycin trough levels. However, while no association was found between median trough levels and acute kidney injury in the vancomycin/piperacillin-tazobactam group, a direct relationship was seen for those in the vancomycin/cefepime group. Acute kidney injury occurred in 1% of vancomycin/cefepime patients with mean vancomycin troughs < 15 mg/L, in 5% of those with median troughs between 15 mg/L and 20 mg/L, and in 21% of those with troughs > 20 mg/L.

■ COMMENTARY

The study by Navalkele and colleagues is interesting because it brings to mind the old yet still salient principle of *primum non nocere*. It is notable that the rate of acute kidney injury was three times higher in patients who received vancomycin/piperacillin-tazobactam compared to those who received vancomycin/cefepime. But what is the pathophysiological mechanism that can explain this result?

It does not appear to be directly related to vancomycin toxicity, since there were no differences in the median vancomycin troughs between the two groups. Indeed, both cefepime and piperacillin/tazobactam are β-lactam antibiotics primarily metabolized through the kidneys and similarly require dosage adjustment with impaired renal function. The investigators did not attempt to further characterize the type of acute kidney injury or speculate about their findings. However, β-lactams are known to cause acute interstitial nephritis, and perhaps vancomycin somehow magnifies this risk. Ideally, a prospective, randomized clinical trial should be conducted to clarify the risk of acute kidney injury and elucidate the underlying etiology. Whether such a trial could be funded remains to be seen.

Like previous retrospective studies that also showed an increased risk of acute kidney injury with vancomycin and piperacillin-tazobactam, the study by Navalkele and colleagues may have been influenced by unmeasured confounding variables, limiting the generalizability of the findings. Despite this, clinicians should be aware of the potential for acute kidney injury and carefully weigh the risks and benefits. Given that the median onset of acute kidney injury was three days, one reasonable approach would be to de-escalate therapy based on culture data, which often are available by 48-72 hours. Indeed, this is a circumstance in which rapid diagnostic testing would be valuable. ■

ABSTRACT & COMMENTARY

Do Antipsychotics Help with Delirium?

By Martin Lipsky, MD

Chancellor, South Jordan Campus, Roseman University of Health Sciences, South Jordan, UT

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

SYNOPSIS: In palliative care patients suffering from delirium, managing delirium precipitants and individualized supportive strategies alone work better than adding risperidone or haloperidol.

SOURCE: Agar MR, Lawlor PG, Quinn S, et al. Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: A randomized clinical trial. *JAMA Intern Med* 2017;177:34-42.

Patients in palliative care commonly experience delirium. Symptom relief is important for these patients. Crafting evidence-based strategies to address delirium optimally is crucial. Management strategies include both pharmacologic and non-pharmacologic methods. Antipsychotics remain one of the most commonly used pharmacologic treatments, yet the risks associated with their use[1] make it essential to evaluate their benefits. Agar et al[2] set out to determine if risperidone or haloperidol, administered in addition to non-pharmacologic care, provided additional benefit in reducing symptoms of delirium when compared to placebo.

The study was a double-blind, parallel-arm, dose-titrated, randomized, clinical trial conducted at 11 Australian inpatient hospice or hospital palliative care services. The study consisted of 247 participants with a mean age of 74.9 years who exhibited a life-limiting illness, delirium, and a delirium score (sum of Nursing Delirium Screen Scale behavioral, communication, and perceptual items) of 1 or more. Among the study group, 85 were women and 218 patients had cancer, making it the most common diagnosis. In the intention-to-treat analysis, 82 received risperidone, 81 received haloperidol, and 84 received placebo. Participants in the risperidone arm demonstrated significantly higher delirium scores compared to placebo (on average 0.24 units higher, 95% confidence interval [CI], 0.06-0.42; P = 0.009). The authors discovered similarly significant differences in the haloperidol arm. Both treatment arms experienced significantly more extrapyramidal effect, and dropout rates for the risperidone group (31 of 82 patients) were about twice the rates of haloperidol (18 of 81 patients) and placebo (15 of 84 patients). Overall survival rate in the placebo group was better than for both the risperidone and haloperidol groups, but only the difference for those receiving haloperidol (hazard ratio, 1.73; 95% CI, 1.20-2.50; P = 0.03) achieved statistical significance, (placebo vs. risperidone arm hazard ratio, 1.29; 95% CI, 0.91-1.84; P = 0.14).

The authors concluded that for palliative care patients presenting with delirium, management of delirium precipitants and supportive strategies alone result in lower delirium scores and shorter duration of symptoms than when adding either risperidone or haloperidol.

■ COMMENTARY

Antipsychotics are used commonly to alleviate the troubling behavioral symptoms associated with delirium. Despite the wide use of antipsychotics to help control behavioral symptoms, Agar et al found that not only may antipsychotics provide no benefit, risperidone and haloperidol seem to increase the intensity and duration of symptoms. Less surprising was that haloperidol use decreased overall survival. Other studies also demonstrated the dangers of antipsychotic drugs in the elderly and indicated that older patients presenting with dementia treated with atypical antipsychotics experienced about twice the mortality rate of those taking placebo.[3]

Although the first-line treatment for delirium is avoiding precipitating factors and instituting non-pharmacologic measures, antipsychotics are used commonly for uncontrolled symptoms because of their perceived effectiveness. These findings, demonstrating that those taking either risperidol or haloperidol experience less symptom relief and worsened survival, suggest that these agents should not be used to treat elderly patients suffering from delirium. The authors noted one study limitation was that few participants were younger than 65 years of age, and perhaps these drugs might demonstrate less risk and greater utility in younger patients. It is also possible that other drugs in this class may be more effective. However, even though the authors highlighted the need for further study, at this point this study suggests that antipsychotics exhibit little or no treatment role for patients in palliative care with symptoms of delirium. ■

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ABSTRACT & COMMENTARY

Hemoconcentration Associated with Lower Mortality in Acute Heart Failure

By Van Selby, MD

Assistant Professor of Medicine, University of California, San Francisco, Cardiology Division, Advanced Heart Failure Section

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

SYNOPSIS: Among patients hospitalized for acute heart failure, hemoconcentration was associated with reduced 90-day mortality and may be a useful marker for guiding therapy.

SOURCE: Breidthardt T, Weidmann ZM, Twerenbold R, et al. Impact of haemoconcentration during acute heart failure therapy on mortality and its relationship with worsening renal function. *Eur J Heart Fail* 2017;19:226-236.

Decongestion is a primary goal in the management of acute heart failure (AHF), and hemoconcentration has been identified as a potential marker of decongestion. Breidthardt et al sought to evaluate the association between hemoconcentration, worsening renal function (WRF), and mortality in patients hospitalized for AHF. In a prospective cohort of 1,019 patients hospitalized for AHF at a single academic center in Switzerland, serial measurements of hematocrit, hemoglobin, total protein, creatinine, and albumin levels were made. Hemoconcentration was defined as a simultaneous increase in at least three of the four markers above admission values at any point during hospitalization. Patients with hemoconcentration were further subdivided into those achieving early (day 1-4) vs. late (day 5 or beyond) hemoconcentration. Worsening renal function (WRF) was defined as any increase of at least 0.3 mg/dL in serum creatinine at any time during hospitalization. The primary outcome was 90-day mortality.

Overall, 38.5% of patients met criteria for hemoconcentration during their hospitalization, and the median time until the occurrence of hemoconcentration was 6.3 days. There were no significant baseline clinical or demographic differences between those with and without hemoconcentration. Patients with hemoconcentration had greater evidence of successful decongestion during their hospitalization as measured by change in B-type natiuretic peptide level and weight loss. After adjusting for other predictors of death, hemoconcentration was associated with reduced 90-day mortality (hazard ratio [HR], 0.59; $P = 0.01$). However, the mortality reduction was only observed in patients with late hemoconcentration (late vs. early hemoconcentration HR, 0.41; $P = 0.03$). Patients with hemoconcentration were more likely to develop WRF (37.1 vs. 30.8%; $P = 0.04$). However, patients with hemoconcentration and WRF still had lower 90-day mortality than patients without hemoconcentration. The authors concluded that hemoconcentration is an inexpensive and easily accessible measure of adequate decongestion in AHF and is associated with lower mortality.

■ COMMENTARY

Correction of hypervolemia is a mainstay of treatment for AHF. However, accurate assessment of volume status can be challenging, and often is made based on a combination of physical exam, symptoms, imaging studies, and laboratory results. Studies have found that many AHF patients ultimately leave the hospital without adequate fluid removal, contributing to high observed rates of readmission and adverse outcomes after hospital discharge. Accurate, reliable assessment of congestion has been referred to as the Holy Grail of heart failure management, and additional tools to guide treatment of AHF are needed. The concept of hemoconcentration as a clinical marker is based on the idea that successfully reducing intravascular volume must lead to an increased concentration of large intravascular molecules such as hemoglobin and albumin. Several prior studies have identified a correlation between hemoconcentration and improved outcomes

after hospitalization for AHF. However, these studies often were performed in highly selected populations, without rigorous definitions for hemoconcentration. This study is among the largest to date, evaluating hemoconcentration prospectively in a real-world AHF cohort. The findings strengthen the association between hemoconcentration and reduced mortality following hospitalization for AHF. In this study, there was a clear distinction between patients who achieved early vs. late hemoconcentration. Survival among patients who achieved hemoconcentration within the first four days of hospitalization was no better than among those who did not achieve hemoconcentration. The authors suggested that patients achieving later hemoconcentration may be more likely to experience persistent hemoconcentration, and, therefore, a slow and steady approach to diuretics may be preferable.

The finding that patients with hemoconcentration are more likely to develop worsening renal failure during hospitalization has been reported previously. WRF often prompts clinicians to de-escalate diuretic therapy, and may explain why many of the "early hemoconcentrators" in this study regressed to "no hemoconcentration" by the time of discharge, and, therefore, had higher mortality compared to those with a late, sustained hemoconcentration. The authors showed the benefits of decongestion (and hemoconcentration) outweigh the risks associated with WRF, suggesting clinicians should not let a small rise in creatinine prevent them from achieving adequate diuresis in patients admitted for AHF.

The primary limitation of this study is its observational design. Although there is a clear association between hemoconcentration and improved outcomes, we cannot conclude that incorporating hemoconcentration as a therapeutic target in AHF management protocols will improve mortality. Hopefully, future studies will address this. This study adds to a growing body of literature demonstrating the prognostic value of hemoconcentration in AHF. No measurement of volume status is perfect, and hemoconcentration cannot replace other measures completely. Rather, it should be viewed as another tool to complement the current options for assessing congestion. It is a low-cost, practical, noninvasive test, and given the clear association with outcomes, clinicians should strongly consider incorporating hemoconcentration into the management of AHF. ■

ABSTRACT & COMMENTARY

Hyperoxia in ICU Patients May Cause Harm

By Samuel Nadler, MD, PhD

Critical Care, Pulmonary Medicine, The Polyclinic, Madison Center, Seattle; Clinical Instructor, University of Washington, Seattle

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

SYNOPSIS: Patients randomized to maintain oxygen saturation between 94-98% experienced better outcomes than patients allowed to receive partial pressure of oxygen > 150 mmHg.

SOURCE: Girardis M, et al. Effect of conservative vs. conventional oxygen therapy on mortality among patients in an intensive care unit. *JAMA* 2016;316:1583-1589.

Supplemental oxygen is a ubiquitous therapy in the ICU, although precise targets for oxygen saturation (SpO_2) and arterial partial pressure of oxygen (PaO_2) are unclear. Although it is clear that hypoxia can lead to harm, data showing that hyperoxia produces harmful effects are more limited. The OXYGEN-ICU trial was a single-center, randomized, clinical study that examined the effects of oxygen delivery on mortality in patients in the ICU. Adult patients with an expected stay in the ICU of > 72 hours were randomized to either conservative or conventional oxygen therapy. Patients in the conservative group received supplemental oxygen titrated to maintain SpO_2 between 94-98% or PaO_2 between 70-100 mmHg. Patients in the conventional control group received supplemental oxygen according to standard ICU protocols targeting SpO_2 97-100% and allowing PaO_2 values up to 150 mmHg. Patients who were pregnant, immunosuppressed, or transitioned to comfort measures only were excluded. This study was meant to enroll 660 patients for adequate power to detect a 6% mortality difference but was terminated early due to an earthquake, limiting further enrollment and an unscheduled interim analysis demonstrating significant benefit with the conservative protocol. Overall, this study enrolled 480 patients, with 236 randomized to conservative oxygen therapy and 244 to conventional therapy. Although the two groups were randomized, some important differences in each group are notable. Fewer patients in the

conservative arm presented with COPD, chronic liver disease, respiratory failure, mechanical ventilation, shock, liver failure, renal failure, and documented infections overall, leading to a lower Simplified Acute Physiology Score II (SAPS II) in the conservative group compared to the conventional arm (37 vs. 39, respectively). Trial conductors used a modified intention-to-treat model was used that censored patients enrolled in the trial who left the ICU within 72 hours. Thus, 216 patients were included in the conservative analysis and 218 in the conventional group. With these caveats, conservative therapy led to an absolute risk reduction in ICU mortality of 8.6% (11.6% vs. 20.3% in the conservative vs. conventional groups, respectively; $P = 0.01$). With conservative oxygen therapy, there also were improvements in many secondary outcomes, including hospital mortality, shock, bacteremia, and mechanical ventilation-free hours. A subgroup post-hoc analysis of only patients on mechanical ventilation also demonstrated mortality benefit (absolute risk reduction 5%; 95% confidence interval, 0-9%).

■ COMMENTARY

At first, this study seems to indicate that targeting more modest SpO_2 goals of 94-98% may be beneficial to ICU patients. However, several caveats deserve mention. First, this study was terminated early due to factors beyond the control of the investigators, but early termination predisposes to overestimation of effect size. The study was not terminated due to pre-specified futility criteria as might affect other trials terminated due to safety concerns. While randomized, the conservative therapy arm clearly contained lower-acuity patients, and this could certainly influence the outcomes. Overall, there were few events in each arm, which also can affect the reliability of these data. However, this study shows trends similar to other studies of conservative vs. conventional oxygen delivery. The AVOID investigators demonstrated that supplemental oxygen administered to patients with acute ST-segment elevation myocardial infarction without oxygen desaturation led to larger infarct size and may increase early myocardial injury.[1] The PROXI trial demonstrated that higher FiO_2 during anesthesia for abdominal surgery led to an increased likelihood of infection.[2] In contrast, a smaller pilot study from the CLOSE and ANZIC investigators failed to show significant effects on mortality in mechanically ventilated patients.[3]

This study adds to the body of evidence that supplemental oxygen delivery without regard to need can be harmful. More importantly, this study seems to indicate that there is no strong indication to supplement SpO_2 levels close to 100%, and that patients with SpO_2 of 94% may not need supplemental oxygen in the ICU. Targeting more modest SpO_2 and PaO_2 goals clearly is not harmful and may lead to certain benefits. ■

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ABSTRACT & COMMENTARY

High-sensitivity Cardiac Troponin

By Michael H. Crawford, MD

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

SYNOPSIS: In patients with new-onset chest pain without ECG evidence of an ST-elevation myocardial infarcition, conversion to the use of a high-sensitivity troponin T assay with three-hour retesting in three hospitals was compared to maintaining the fourth-generation troponin T assay with six-hour retesting in three other hospitals. The use of high-sensitivity troponin T resulted in lower ED length of stay and costs, without increasing the use of coronary angiography or stress testing.

SOURCES: Twerenbold R, Jaeger C, Rubini Gimenez M, et al. Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction. *Eur Heart J* 2016;37:3324-3332.

Crea F, Jaffe AS, Collinson PO, et al. Should the 1h algorithm for rule in and rule out of acute myocardial infarction be used universally? *Eur Hear J* 2016;37:3316-3323.

Januzzi JL. Troponins in equipoise. *Eur Heart J* 2016;37:3333-3334.

Although the introduction of high-sensitivity troponin assays in some health systems has decreased the time necessary to accurately diagnose an acute myocardial infarction (MI), there has been

concern that its use would lead to an increase in inappropriate coronary angiography. Investigators from the Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) study assessed the effect of switching from fourth-generation troponin T assays to high-sensitivity troponin T(hsTnT) on use of coronary angiography, cardiac stress testing, and time to ED discharge in three hospitals in Europe. Three hospitals in APACE who did not switch were used as controls. Patients in the ED with chest pain for less than 12 hours that was suggestive of acute MI were recruited. Those with ECG ST elevation MI or end-stage renal disease on dialysis were excluded. The troponin T protocol required repeat testing at six hours and the hsTnT protocol after three hours. Of the 2,544 patients entered over about six years, 57% were enrolled before and 43% after the switch. There were baseline characteristic differences in the patients between the two study periods, and there was an increase in the diagnosis of acute MI in the second period (14% vs. 10%; $P < 0.001$). Also, there was a corresponding decrease in the diagnosis of unstable angina from 14% to 9%, but the overall acute coronary syndrome (ACS) rate was unchanged (24% vs. 23%; P = NS). In addition, the discharge diagnosis of chest pain of unknown origin decreased from 48% to 38% ($P < 0.001$). The rate of coronary angiography was identical between the two phases (23%), and the rate of stress testing was similar (12% vs. 10%). Finally, ED length of stay was reduced in the hsTnT group by 79 minutes ($P < 0.001$), and costs were reduced 20% ($P = 0.002$). There were no significant changes in these parameters in the control group over the same two time periods. The authors concluded that the use of hsTnT did not increase the use of coronary angiography or stress testing, but did reduce ED length of stay and costs.

■ COMMENTARY

Current troponin assays used in the United States are imprecise at low values where the risk of missing an early non-ST segment myocardial infarction is highest. In addition to the usual clinical and ECG data, the six-hour troponin retest has been advanced to overcome this problem. The advent of high-sensitivity troponin tests has allowed for a three-hour retest protocol to perform similarly to the six-hour protocol. However, there has been resistance to adopting the three-hour test protocol because of concerns that it would generate considerable false positives and would increase costs and inappropriate coronary angiography. The adoption of the hsTnT with a three-hour protocol in three hospitals in the APACE research consortium allowed the investigators to compare their experience to experiences of the hospitals still using the standard troponin T six-hour protocol. Although not a randomized trial, the results are compelling. Coronary angiography and stress testing rates remained constant, and ED length of stay decreased significantly. There were no changes in these parameters over the same time frame in the control hospitals. The authors argued that adoption of the three-hour retest in the hsTnT protocol improved the precision of allocating patients for further testing or discharge home.

There are limitations to the study. There were baseline differences between the patients before and after the switch in the test hospitals, which the investigators adjusted for, but a propensity analysis was not performed. Also, only troponin T was studied, so the results may not be applicable to troponin I. In addition, patients with end-stage renal disease on hemodialysis were excluded. It is well known that troponin T levels are higher in such patients, which adds complexity to the use of the three-hour protocol, were it to be used more widely. Finally, there are no outcome data, so we don't know if the three-hour protocol resulted in better care.

The most recent European Society of Cardiology guidelines recommend a one-hour retest protocol with high-sensitivity troponin, which wasn't tested in this study, but there are other data supporting its use. The expected changes in high-sensitivity troponin over one hour usually will be less than that seen with three- or six-hour retest protocols, raising the concern that specificity will be less due to the difficulty in interpreting small rises in troponin. If this is the case, the one-hour protocol could increase angiography and other costs. Clearly, the barriers to high-sensitivity troponin testing are falling, and I would anticipate adoption of these tests in the United States in the near future. In appropriate patients where non-ST elevation acute MI is highly likely clinically, these tests could increase the rapidity of diagnosis and appropriate treatment. However, we know from our experience with fourth-generation troponin testing that the test will be applied widely to largely inappropriate patients, worsening the current troponimania we are dealing with now. ■

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CME QUESTIONS

1. The retrospective matched cohort study by Navalkele comparing vancomycin and piperacillin-tazobactam to vancomycin and cefepime demonstrated that vancomycin + pipercillin-tazobactam was associated with which of the following?

a. A significantly higher rate of acute kidney injury

b. A higher mortality

c. A shorter hospital length of stay

d. A greater rate of treatment failure

e. All of the above

2. Agar, et al., conducted a double-blind, randomized controlled trial that compared risperidone, haloperidol, and placebo in addition to managing precipitants and supportive care for the management of delirium in elderly palliative care patients. In that study, the optimum regimen with regards to mortality, side effects, and clearing of delirium was:

a. Risperidone

b. Haloperidol

c. Risperidone plus haloperidol

d. Placebo

e. No difference; all regimens were equal to each other

3. In the observational study by Breidthardt and colleagues, hemoconcentration during the treatment of an acute heart failure exacerbation was associated with what outcome(s):

a. Reduced 90-day mortality

b. Increased frequency of worsening renal function

c. Greater reduction in B-type natriuretic peptide (BNP)

d. Greater weight loss

e. 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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