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Outcomes in Patients Treated with Therapeutic Hypothermia After In-hospital Cardiac Arrest

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

SYNOPSIS: Current guidelines recommend the use of therapeutic hypothermia in patients with in-hospital cardiac arrest, even though its efficacy has been demonstrated only in randomized trials after out-of-hospital cardiac arrest. This non-randomized, observational cohort study based on a large national registry found that the use of therapeutic hypothermia was associated with lower likelihood of survival and less favorable neurological outcome in patients successfully resuscitated after an in-hospital cardiac arrest.

SOURCE: Chan PS, Berg RA, Tang Y, et al; American Heart Association's Get With the Guidelines–Resuscitation Investigators. Association between therapeutic hypothermia and survival after in-hospital cardiac arrest. *JAMA* 2016;316:1375-1382.

Approximately 200,000 patients suffer in-hospital cardiac arrest annually in the United States. Current American Heart Association (AHA) guidelines recommend the use of a therapeutic hypothermia (or another form of a targeted temperature management [TTM] protocol, i.e., therapeutic normothermia) after both out-of-hospital and in-hospital cardiac arrest. However, its efficacy has been demonstrated only using randomized clinical trials in the specific setting of out-of-hospital cardiac arrest as a result of ventricular fibrillation. This study addresses the very important question of whether or not — similar to out-of-hospital cardiac arrest — therapeutic hypothermia is associated with better survival and neurological outcome for patients with in-hospital cardiac arrest.

This cohort study leveraged data from a large, prospective, national registry of more than 26,000 patients successfully resuscitated after an in-hospital cardiac arrest collected over a 12-year period. Primary outcome was defined as survival to hospital discharge, and secondary outcome was favorable neurological

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[ALERT]

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outcome determined as score 1 or 2 of the Cerebral Performance Category (CPC) scale (good recovery or moderate neurological deficits allowing independent functioning). The registry, if available, also was linked with Medicare files for patients older than 65 years of age to find associations between hypothermia treatment and one-year survival in this subset of patients. Importantly, however, only about 1,500 patients (6% of the entire cohort) received therapeutic hypothermia. These patients were matched to more than 3,700 non-hypothermia-treated patients by a model based on a propensity score that assessed detailed baseline demographic and clinical variables. After adjusting for these variables, using a multivariable logistic regression model, this study found that use of therapeutic hypothermia was associated with lower survival (27.4% vs. 29.2%) and lower likelihood of favorable neurological outcomes at hospital discharge (17.0% vs. 20.5%). At one-year follow-up, there was no difference in survival between the two groups (14.2% vs. 14.1%). These associations were similar for patients with shockable and non-shockable initial rhythms. The authors concluded that therapeutic hypothermia is not associated with better survival or neurological outcomes, and it may be even potentially harmful in the setting of an in-hospital cardiac arrest.

■ COMMENTARY

This non-randomized, cohort study addressed a very pressing gap in our knowledge about whether therapeutic hypothermia is an appropriate choice of treatment for all patients after cardiac arrest or if it should be restricted to patients who were successfully resuscitated after an out-of-hospital cardiac arrest. Although the study was well designed, involved a large number of patients, and was carefully analyzed, it was not randomized and, therefore, it bears several inherent limitations that warrant caution in interpreting the results and the authors' conclusions.

First, a major limitation includes the fact that only 6% of patients with in-hospital cardiac arrest underwent therapeutic hypothermia in this cohort. The inclusion of such a small portion of the population in the main analysis raises important questions regarding generalizability of the results. The authors make a great effort to successfully match a non-hypothermia-treated population with similar demographics, comorbid conditions, likelihood of being treated with hypothermia (e.g., hospital site), circumstances of the resuscitation (such as duration, time of day, day of the week), and post-cardiac arrest interventions (medications and/or devices utilized) using a propensity score matching algorithm. Nonetheless, before propensity score matching, the non-hypothermia-treated cohort (n = 24,615) significantly differed from the hypothermia-treated cohort (n = 1,568) in several important baseline variables: e.g., non-hypothermia-treated patients were older; more likely to be in a telemetry or in an intensive care unit than in the emergency department or other procedural areas; more likely had a non-shockable initial rhythm; and differed in several preexisting comorbid conditions. The results seen after propensity matching may indicate potential ineffectiveness or harm in the small subset of inpatients who are selected to undergo hypothermia treatment under current and evolving clinical practice (distributed over the last 12 years); however, it is unclear at this point if these findings can be applied directly to all patients who suffer an in-hospital cardiac arrest.

Additional limitations include lack of detailed data on hypothermia protocols and efficacy of treatments in the registry that may have affected the outcomes; lack of specific information about level of consciousness (i.e., if all patients were comatose at the time of enrollment, however, only patients on mechanical ventilation were included to mitigate this concern); and variability in assessing neurological outcome status at different sites. In addition, there is still a possibility of residual bias in patient selection despite a lot of effort taken to reduce biases, e.g., the indication bias, including a sensitivity analysis that excluded patients who died within the first 24 hours after cardiac arrest that yielded similar results as the main analysis. Most importantly, as this study was not randomized, there may be many other unknown confounders that may have affected the outcomes; therefore, these results cannot be translated readily to clinical practice. Importantly, this study also highlights our lack of knowledge regarding neuroprotective mechanism of hypothermia after severe

brain injuries that could provide some explanation for these results. Indeed, a few studies involving other injury mechanisms, such as severe trauma or bacterial meningitis, showed no benefit or even potential harm of using therapeutic hypothermia. It is plausible that patients who suffer in-hospital vs. out-of-hospital cardiac arrest have different baseline variables and comorbid conditions that may shift neuronal vulnerability or alter the ability to maintain optimal conditions during hypothermia protocols. In addition, the different circumstances of resuscitation efforts in hospital or out-of-hospital settings (e.g., time of initiation of chest compressions, shocks or medications after the arrest) also may influence the possible effects of cooling on various neuronal rescue mechanisms (such as reduction of free-radical formation or halting apoptosis).

In summary, this study addresses a very important question and raises attention to the gap in our knowledge of appropriate utilization of therapeutic hypothermia after cardiac arrest, as well as in our lack of precise understanding of the neuroprotective effects of cooling. Although the results of this study raise some concerns, given the inherent limitations of a non-randomized study design, they should not alter current clinical practice and recommendations to use therapeutic hypothermia after in-hospital cardiac arrest. Nevertheless, these findings strongly emphasize the need for a randomized, prospective clinical trial to establish efficacy of therapeutic hypothermia in patients with in-hospital cardiac arrest. ■

Reported Beta-lactam Allergy Is Associated with More Adverse Events Among Inpatients

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

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

SYNOPSIS: A prospective cohort study from three hospitals determined that patients who did not receive a preferred beta-lactam antibiotic were at greater risk for an adverse event (adjusted odds ratio, 3.1; 95% confidence interval, 1.28-7.89) compared to controls without a beta-lactam allergy.

SOURCE: MacFadden DR, LaDelfa A, Leen J, et al. Impact of reported beta-lactam allergy on inpatient outcomes: A multicenter prospective cohort study. *Clin Infect Dis* 2016;63:904-910.

Many hospitalized patients report a beta-lactam allergy or have one documented in their medical record. This piece of history is important because it frequently prevents the use of a very safe and effective class of antibiotics. Indeed, beta-lactams are the "work horses" of contemporary antibiotic therapy. MacFadden and colleagues investigated the association between beta-lactam allergy labeling and outcomes in hospitalized patients.

The setting for the study was three hospitals in Toronto, Canada, and the population included all inpatients seen by the infectious disease (ID) consultation service between April 2014 and January 2015 on the days that the ID subspecialty residents were present. As part of a quality-improvement project, the investigators prospectively assessed beta-lactam allergy by collecting data on the type of previous allergic reaction such as IgE-mediated, bronchospasm, rash, anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrosis (TEN), drug rash eosinophilia and systemic symptoms (DRESS), angioedema, serum sickness, and "other." Also, they collected patient demographic data (age, sex, pregnancy, and immunocompromised status), referring service, duration of antibiotic therapy, Charlson comorbidity index, and information on antibiotic therapy, including the preferred antibiotic and what antibiotic was chosen initially. Outcome data were recorded later in a second data collection step. The primary outcome measured was the occurrence of any treatment-related adverse event, defined as acute kidney injury while on antibiotics, *Clostridium difficile* infection (CDI) within three months of treatment, suspected drug-related adverse event that required discontinuation, or readmission due to the same infection.

Of the 507 patients who received antibiotic therapy during the study period, 95 (19%) reported a beta-lactam allergy. In the group that reported a beta-lactam allergy and a beta-lactam was considered optimal therapy, 47 (65%) received a beta-lactam, while 25 (35%) received a non-beta-lactam drug. There was an increased likelihood of an adverse event for the patients who did not receive preferred beta-lactam therapy (adjusted odds ratio [OR], 3.18; 95% confidence interval [CI], 1.28-7.89). The adverse events were mostly due to increased rates of readmission and adverse drug reactions, although there

were no significant differences in mortality between the beta-lactam-allergic and non-allergic patients. Moreover, there were no significant differences in outcomes between those patients who reported a beta-lactam allergy yet were given a beta-lactam, compared to patients who did not report a beta-lactam allergy. Further analysis to adjust for possible confounding due to a diagnosis of bacteremia from an unknown primary source did not result in any significant changes to the findings.

■ COMMENTARY

This study is noteworthy because it showed that patients with a reported beta-lactam allergy who did not receive preferred beta-lactam therapy had three times the chance of an adverse event compared to those without a reported allergy. According to the CDC, 10% of the population reports a penicillin allergy, but < 1% of the whole population is truly allergic.[1] Furthermore, approximately 80% of patients with IgE-mediated penicillin allergy lose their sensitivity after 10 years. The findings reported by MacFadden and colleagues support the notion that beta-lactam antibiotics might be appropriate in select patients who report beta-lactam allergies, such as those with non-severe allergy histories. Also, increasing beta-lactam usage in these patients may lead to more cures and fewer adverse events.

One way to objectively assess for beta-lactam allergy is by skin testing. A recent study in which ID fellows at the University of Maryland Medical Center performed penicillin skin testing (PST) showed that 96% of patients tested negative, leading to changes in antibiotic therapy in 84% of cases.[2] As these investigators mentioned, PST can help antibiotic stewardship efforts, reduce antibiotic costs (e.g., less aztreonam use), lead to better clinical outcomes (e.g., using ampicillin instead of vancomycin for enterococcal endocarditis), and is a potential revenue source for ID practices. The study by MacFadden and colleagues, therefore, adds to the growing body of evidence that PST can be used to potentially improve patient outcomes.

There were a few limitations that may have affected the study results. To generate sufficient power, a composite endpoint was used, making it challenging to analyze for individual outcomes. Also, the small sample size may have influenced the incidence of CDI. This is because no increased risk was reported for the beta-lactam-allergic patients, despite receiving alternative antibiotics that are associated with a higher risk for developing CDI, such as clindamycin and fluoroquinolones. Despite these limitations, MacFadden and colleagues have provided robust data about the clinical consequences of reported beta-lactam allergies. Thus, when treating a patient with a beta-lactam allergy for whom a beta-lactam antibiotic would be the best option, clinicians should take a detailed history of the allergy and pursue PST if available. ■

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What Influences ICU Admission?

By Eric Walter, MD, MSc

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

SYNOPSIS: There is widespread variability between hospitals in rates of ICU admission. High ICU utilization hospitals were more likely to use invasive procedures and incurred higher costs than low ICU utilization hospitals with no difference in mortality.

SOURCE: Chang DW, Shapiro MF. Association between intensive care unit utilization during hospitalization and costs, use of invasive procedures, and mortality. *JAMA Intern Med* 2016;176:1492-1499.

ICU services comprise 13.4% of total hospital costs and more than 4% of national health expenditures. Yet, the decision as to which patients should be cared for in the ICU largely is subjective. Chang and Shapiro used administrative data to compare ICU use across 94 hospitals in Washington state and Maryland for diabetic ketoacidosis (DKA), pulmonary embolism (PE), upper gastrointestinal bleed (UGIB), and congestive heart failure (CHF). The primary outcomes were risk-adjusted mortality, use of invasive procedures, and hospital costs. Invasive procedures were defined as use of central venous catheters for any of the diagnoses, mechanical ventilation in DKA, thrombolytics in PE, and esophagogastroduodenoscopy in UGIB. Analyses were adjusted for both patient level and hospital level factors. Logistic regression models were used to predict ICU admission rates for

each hospital during hospitalizations for each diagnosis. Hospitals also were dichotomized into higher (> 50th percentile for predicted ICU utilization rate) and lower ICU utilization (50th percentile and below) groups.

There was wide variability in rates of ICU admission for each diagnosis (16.3%-81.2% for DKA, 5.0%-42% for PE, 11.5%-51.2% for UGIB, and 3.9%48.8% for CHF). High ICU utilization was associated with increased use of invasive procedures in all four conditions. Increased ICU utilization was associated with higher hospital costs despite comparable lengths of stay. Severity of illness was lower among patients in high ICU utilization hospitals. Hospital mortality did not differ between hospitals with high and low ICU utilization. Correlations between ICU utilization rates for all four conditions were high.

■ COMMENTARY

The ICU is inherently a heterogeneous unit. In the same ICU, we may admit a patient with severe hypotension next to a patient with malignant hypertension. The unit admits a patient presenting with severe bleeding, followed by a patient suffering from portal venous thrombosis. This heterogeneity may explain why so many ICU trials have produced negative results. The variability in admission rates described by Chang and Shapiro highlight another layer of ICU heterogeneity.

In many ways, these results should not be surprising. The decision to admit someone to the ICU is subjective. It will be influenced not only by the patient's severity of illness, but also hospital size, number of ICU beds, bed availability, nurse ratios, physician comfort, reimbursement, and more. Chang and Shapiro found that institutional factors appeared to influence the decision to admit to the ICU more so than patient level factors. High ICU utilization hospitals admitted patients with all four studied conditions frequently to the ICU despite a lower severity of illness. The influence of these institutional factors may be understandable in some circumstances. In this study, smaller hospitals were higher ICU utilizers. It may make sense to admit a patient with DKA to the ICU in a smaller hospital in which floor nurses may not have the time or expertise to manage an insulin drip. However, these results also suggest that many patients may not need ICU care, as there was no difference in mortality between hospitals with high and low utilization. The decision to admit patients to the ICU may expose patients to potential harms, since invasive procedures such as central lines, thrombolytics, intubation, and EGD were used more often by high ICU utilizer hospitals.

These results present significant implications for future studies evaluating ICU outcomes and costs. There may be too much variability from hospital to hospital to compare ICU costs or outcomes directly across hospitals and regions without accounting for both institutional and patient level factors. We simply cannot compare sepsis-related organ failure assessment scores and Charlson comorbidity indices. Future studies must try to better understand the institutional factors that affect the decision to admit a patient to the ICU. At the individual level, ICU physicians and directors must critically consider the reasons why or why not staff chooses ICU level of care for a patient. With a better understanding of the factors that affect the decision to admit to the ICU, clinicians can better determine when ICU level care truly is needed. ■

Vasopressin as a Single Vasopressor Agent in Patients with Septic Shock

By Samuel Nadler, MD, PhD

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

SYNOPSIS: The use of vasopressin as a vasopressor for septic shock produced similar outcomes as the use of norepinephrine.

SOURCE: Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early vasopressin vs. norepinephrine on kidney failure in patients with septic shock: The VANISH Randomized Clinical Trial. *JAMA* 2016;316:509-518.

There has been continuous interest in the use of vasopressin for patients who suffer septic shock. Norepinephrine (NE) continues to be the recommended first-line vasopressor, but since the VASST trial in 2008, the use of vasopressin as an adjunct vasopressor has become widespread.[1] That trial demonstrated that the addition of low-dose vasopressin (0.03 U/min) improved the mortality of patients in a subgroup of patients with less severe septic shock (defined as need for NE < 15 mcg/min). Other studies have implied that vasopressin may produce a synergistic effect with corticosteroids to prevent renal dysfunction. The Vasopressin as Initial Therapy in Septic Shock (VANISH) trial sought to determine if early vasopressin use as compared with

standard NE infusions would improve patient outcomes.

The VANISH trial was a factorial (2 x 2), multicenter, double-blind, randomized, controlled trial that included 421 adult patients with sepsis as defined by systemic inflammatory response criteria with suspected or known infection. All patients underwent adequate fluid resuscitation yet required vasopressors. Patients were randomized to vasopressin (up to 0.06 U/min) or NE (up to 12 mcg/min) as a first vasopressor. If this intervention did not restore mean arterial pressure > 65 mmHg, patients also were randomized to receive hydrocortisone (50 mg intravenously every six hours for five days, then tapered) or placebo as an additional treatment. If patients remained hypotensive despite administration of both study drugs, additional open-label vasopressors were added. Exclusion criteria included previous vasopressor use during hospitalization, need for steroid treatments, endstage renal failure, known mesenteric ischemia, or vasospastic diseases such as systemic sclerosis. The primary outcome was kidney failure-free days up to 28 days. Secondary outcomes included renal replacement therapy, mortality and organ failure-free days, and Sequential Organ Failure Assessment scores.

Overall, the treatment groups were well balanced at baseline and received similar amounts of fluid. Study drugs were started within three hours of diagnosis, and the mean arterial pressures were similar in all groups. Two patients in the NE group received open-label vasopressin and were included in the intent-to-treat analysis. There were no significant differences in kidney failure-free days, mortality, new organ failure, or the need for renal replacement therapy in comparisons of vasopressin vs. NE or with the use of hydrocortisone. There also were no differences in duration of mechanical ventilation, ICU length of stay, hospital length of stay, time to shock reversal between groups, and no significant increase in adverse events.

■ COMMENTARY

The VANISH trial did not detect a statistically significant difference in primary or secondary endpoints. In the study's power calculations, the sample size was chosen to detect a 20-25% relative risk reduction of kidney failure assuming an incidence of acute kidney failure of 30-50%. There was an incidence of renal failure of 40.6-49.5% in the four study groups. The absolute difference in kidney failure in the vasopressin vs. NE groups was -5.1% (95% confidence interval, -15.2% to 5%), which represents a relative risk reduction of 11.3%. Thus, this study was not powered to detect this degree of renal protection. Interestingly, the greatest benefit in terms of use of renal replacement, incidence, and duration of kidney failure (although not statistically significant, either) was in non-survivors.

Compared with NE, this study also showed that vasopressin statistically and non-significantly trended toward higher 28-day mortality (30.9% vs. 27.5%), ICU mortality (28.4% vs. 25.0%), and hospital mortality (33.3% vs. 29.4%). The time to shock reversal tended to be longer with vasopressin by six hours, the use of inotropes was greater by 6.7%, and there were greater rates of digital ischemia and acute coronary syndrome. Thus, while it may be expected that a larger trial may detect a small change in renal protection with vasopressin, it is equally likely that it will show increased mortality, length of stay, and complication rates that seem to be more important endpoints. If the benefit is greatest among non-survivors, as previously suggested, this is not truly an overall benefit.

The VANISH trial may be interpreted in the context of the prior VASST study. VASST added vasopressin to NE infusions and was a larger trial (n = 802). A notable difference in baseline demographics in this study was that the vasopressin arm was statistically younger (59.3 vs. 61.8 years; $P = 0.03$). Despite this difference, no statistically significant improvement was observed in the primary endpoints of 28-day mortality or secondary endpoints of 90-day mortality, days free of organ dysfunction, mechanical ventilation, use of renal replacement therapy, corticosteroid use, length of stay, or serious adverse events. Given that both VASST and VANISH did not demonstrate efficacy in their primary or secondary endpoints, reconsider the widespread use of vasopressin. ■

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Warning: Reactivation of Hepatitis B Virus Coinfection During Treatment of Chronic Hepatitis C Virus Infection

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Prior to initiation of hepatitis C virus treatment with direct-acting antivirals, patients should be screened for hepatitis B virus coinfection. Those who are hepatitis B virus-infected should receive ongoing monitoring for flares and reactivation of hepatitis B.

SOURCE: FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM523499.pdf. Accessed Oct. 17, 2016.

The FDA identified a total of 24 cases of confirmed reactivation of hepatitis B virus (HBV) coinfection during treatment of hepatitis C virus (HCV) infection with direct-acting antivirals (DAA). The patients' HCV genotypes were heterogeneous. Reactivation of HBV occurred a mean of 52 days after initiation of treatment of HCV infection, with most cases occurring within 4-8 weeks. Two patients died as a consequence, while another required liver transplantation. The characteristics of the HBV coinfection prior to reactivation were variable: Seven had detectable HBV DNA, four were HBsAg positive but DNA negative, three were negative for both, and the results were unknown for the remaining 10.

After HBV reactivation, at least 12 of the 24 received treatment with either tenofovir or entacavir, and at least six received no treatment. Anti-HBV treatment was delayed in at least five of the 12, and one of these patients died; it was possibly delayed in at least three others, including the patient who required transplantation. DAA therapy was discontinued in eight patients when transaminase elevation was recognized. Overall, the FDA described the following as being the commonly encountered sequence: "… initiation of DAA-based HCV treatment, rapid drop of HCV RNA to undetectable levels within 1-2 weeks after normalization of transaminase levels (if they were elevated), followed by a rise in HBV DNA with or without increase in transaminases between weeks 4-8."

As a consequence of these observations, the FDA now requires that a Boxed Warning be added to the drug labels of the currently approved DAAs. This warning directs healthcare providers to screen and monitor for flare-ups and reactivation of HBV coinfection in patients receiving these drugs. Screening should include testing for both HBsAg and anti-HBc, with quantitation of plasma HBV DNA prior to initiation of DAA in those with serological evidence of infection. In those with HBV coinfection, in addition to clinical evaluation, monitoring should include serial measurement of HBsAg, HBV DNA, transaminase levels, and bilirubin, both during and after treatment of HCV infection.

■ COMMENTARY

The fact that this adverse event was not observed during the clinical trials required for FDA approval has a simple explanation: Coinfection with HBV excluded patients from participation. Flares had been observed during treatment with regimens that included interferon-alpha, but this is confounded by the complexity of the effects of the latter, which has both antiviral and immunomodulatory activities.

The mechanistic explanation for these flares and reactivations during receipt of DAA therapy is not known. It is of interest that plasma levels of HCV generally exceed those of HBV in coinfected patients, suggesting the possibility of an undefined interaction between the two. One reasonable potential explanation for the occurrence of reactivation and flares is that prevention of HCV replication may alter the local hepatic milieu such that local nonspecific immune activity is increased, leading to hepatic damage in the presence of HBV coinfection.[1] ■

REFERENCE

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CME INSTRUCTIONS

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CME QUESTIONS

1. In the non-randomized observational cohort study by Chan and colleagues, therapeutic hypothermia for inpatient cardiac arrest was found to be associated with which outcome:

a. Improved survival at hospital discharge in patients under age 55 years.

b. No difference in survival at one-year follow-up

c. Improved neurological outcomes at hospital discharge

d. Improved neurological outcomes at one-year follow-up

e. Increased risk of pulmonary embolism

2. In the randomized controlled trial of vasopressin versus norepinephrine as a single agent for use in patients with septic shock (VANISH), vasopressin use was associated with which of the following outcomes:

a. Vasopressin was associated with improved 28-day survival

b. Vasopressin was associated with a decreased incidence of renal failure

c. Vasopressin was not associated with any statistically significant improvement in outcomes

d. Vasopressin was associated with a decrease in ICU length of stay

e. Vasopressin was associated with a statistically significant increase in adverse events

3. What outcomes were seen in the study of hospitalized patients who report a beta-lactam allergy and received antibiotic therapy:

a. Approximately 65% of patients received a beta-lactam antibiotic despite the reported allergy.

b. There was a higher incidence of adverse events in the group who did not receive a beta-lactam, including more adverse drug events.

c. There was no difference in mortality between the beta-lactam allergic and non-allergic patients.

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.

[IN FUTURE ISSUES]

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