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Hospital Medicine

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ABSTRACT & COMMENTARY

The Wells Rule May Not Be Reliable for All Patients

By Jennifer A. Best, MD
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Dr. Best reports no financial relationships in this field of study.

SOURCE: Geersing GJ, et al. Exclusion of deep vein thrombosis using the Wells rule in clinically important subgroups: individual patient data meta analysis. *BMJ* 2014 Mar 10;348:g1340. doi: 10.1136/bmj.g1340.

In a patient presenting with leg symptoms, however non-specific, it is appropriate that a physician consider the diagnosis of deep venous thrombosis (DVT), as failure to make this diagnosis can have life-threatening consequences (e.g., pulmonary embolism). Many physicians utilize clinical decision rules such as the Wells score in deciding whether to proceed with additional diagnostic testing and/or treatment. The Wells score assigns an estimated likelihood of DVT, based on the presence or absence of specific clinical factors, including active cancer, paralysis/paresis/immobilization of leg, bedrest >3 days prior, major surgery <4 weeks prior, localized tenderness of the venous system, leg/calf swelling, pitting edema, collateral veins, history of DVT and likelihood of an alternative diagnosis. Scores are categorized as low (<0), moderate (1-2) and high (>3). The Wells rule is often utilized with the D-dimer; studies have shown that patients with a low Wells score and a negative D-dimer need not be anticoagulated empirically prior to additional diagnostic testing. However, some studies evaluating the Wells score have suggested troubling uncertainties. These include a primary care study showing that a combination of Wells and D-dimer resulted in a high number of missed DVT cases and additional concern that the Wells score is inadequate in patients of male sex, with active cancer or with DVT recurrence, as in all these groups the prevalence of DVT is higher than in a general population. Furthermore, patients with active malignancy may have an elevated D-dimer level, whether or not DVT is present. So although

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Hospital Medicine [ALERT]

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the score is well validated in unselected populations, it has been felt that these particular subgroups warrant additional study.

To address these uncertainties, Geersing and colleagues in the Netherlands and Canada pooled individual patient data from 13 studies evaluating patients with suspected DVT. Seven of these studies evaluated the utility of the Wells rule in management decisions, four sought to validate the Wells rule, and two studies aimed to determine whether a positive D-dimer plus an initially normal ultrasound or venogram warranted a serial follow-up study. All selected studies recruited primary care and hospital-based outpatients with suspected DVT; categorized patients by Wells rule (and included data to substantiate this categorization); included D-dimer testing; and documented presence or absence of DVT by compression ultrasonography or venography, or absence of adverse event within 3 months of presentation. These investigators also documented patient age, sex and presence or absence of previous DVT. Where important data were missing (between <1 and 5%, varying by data set), data values were imputed to minimize bias, and discrete data sets were then combined. Several statistical analyses were performed: logistic regression to determine the impact of each patient subgroup on the Wells score, the extent to which a negative D-dimer result contributed to Wells score in excluding DVT, and additional analyses evaluating the heterogeneity of the included studies.

10,002 subjects and 1,864 cases were included in the composite data set; the median age was 59 years, and 62% of patients were female. Nineteen percent of these subjects had proximal DVT. Increasing Wells scores did correlate with higher probability of DVT. However, even in patients with a Wells score of -2, the actual probability of DVT approached 5%, suggesting that the Wells rule alone is not adequate to exclude DVT in these patients. Additionally, with Wells scores up to 1, the probabilities of DVT were nearly doubled in patients with prior DVT and malignancy. Increased DVT probability was also seen in males, but to a lesser degree; overall, no significant differences in Wells performance between men and women were noted. When considering the probably of documented DVT in the setting of negative D-dimer and low Wells score (<1), the failure rate was 1.2%, which was felt to be within limits of acceptability for all groups except of those with malignancy and prior DVT. The combination of low Wells score and negative D-dimer (the "rule-out strategy") was efficient in excluding DVT in all subgroups except patients with cancer.

This study has a number of strengths. It is large, including more than 10,000 patients and a high number of DVT cases, but also some drawbacks. Few studies documented adequate blinding between reference test and D-dimer/Wells results. Additionally, many of these studies utilized compression ultrasonography as a reference standard, although it has been shown that this test is less reliable for recurrent events. Citing these considerations, the authors render the following clinical recommendations: 1) The Wells score is useful in estimating the pretest probability of DVT. The 9th ACCP guidelines recommend following a high Wells score with compression ultrasonography and a low Wells score with a D-dimer test. 2) There exists a modified version of the Wells rule, which assigns an extra point to the overall score in the setting of prior DVT. This model has never been validated, but in this population would have improved the failure rate to an acceptable level and is recommended for this unique population. In this modified version, a Wells score of 1 or less, with a negative D-dimer test, would exclude DVT in 1 of 3 patients. This holds regardless of sex, diagnostic setting, or of type of D-dimer assay. 3) These findings hold for all patient subgroups, with the exception of those with active cancer or recurrent thrombosis. ■

ABSTRACT & COMMENTARY

Value of the Physical Examination in Heart Failure

By Michael H. Crawford, MD

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This article originally appeared in the April 2014 issue of Clinical Cardiology Alert. *It was peer reviewed by Ethan Weiss, MD, Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Crawford reports no financial relationships relevant to this field of study, and Dr. Weiss is a scientific advisory board member for Bionovo.*

SOURCE: Caldentey G, et al. Prognostic value of the physical examination in patients with heart failure and atrial fibrillation: Insights from the AF-CHF Trial (Atrial Fibrillation and Chronic Heart Failure). *JACC Heart Fail* 2014;2:15-23.

These investigators from the Montreal Heart Institute asked the question of whether the physical examination was still of value in the modern era of heart failure management that includes the use of biomarkers and echocardiography. They employed the patient population in a trial of heart failure and non-permanent atrial fibrillation (AF) randomized to a rhythm control vs. rate control strategies. The study showed no differences in outcome between the two groups. The physical examination findings were evaluated retrospectively and four signs were studied: peripheral edema, jugular venous distention (JVD), third heart sound, and pulmonary rales. The patients were followed for up to 6 years and the primary outcome was cardiovascular (CV) mortality. Secondary outcomes included all-cause mortality, heart failure-related mortality, sudden death, and heart failure hospitalizations. Of the 1376 patients enrolled, all but seven had data on all four of the physical exam findings. At enrollment, 31% had peripheral edema, 22% had JVD, 15% a third sound, and 13% had rales. Over a mean follow-up of 37 months, 32% died and 25% had at least one heart failure hospitalization. In the univariate analysis, all four of the physical findings were associated with increased CV mortality (hazard ratios [HRs], 1.5-1.9; all $P < 0.004$). On multivariate analysis up against laboratory tests and echocardiographic parameters, peripheral edema (HR, 1.25; 95% confidence interval [CI], 1.00-1.57; $P < 0.05$) and rales (HR, 1.4; 95% CI, 1.08-1.86; $P < 0.02$) remained predictive of CV mortality. Peripheral edema was independently associated with all-cause mortality and heart failure-related death. Rales were independently associated with heart failure-related death and hospitalization. JVD or a third heart sound were not independently associated with any CV outcome. The authors concluded that physical examination signs of congestion are important prognostic indicators in the modern therapeutic milieu of congestive heart failure.

■ COMMENTARY

In the current era where the serial use of echocardiography, brain natriuretic peptide levels, and measures of renal function are often the drivers of therapeutic decisions in heart failure management, it is interesting to see that signs of congestive heart failure on physical examination are still useful predictors of outcome. This study involved patients with left ventricular ejection fractions < 35% and heart failure symptoms within 6 months of enrollment. They were on modern therapy: 86% on angiotensin-converting enzyme inhibitors, 79% on beta-blockers, and 45% on aldosterone antagonists. However, it is not known how many had ventricular pacing. Also, the patients all had a history of non-permanent atrial fibrillation and some were on antiarrhythmic drugs such as amiodarone. Whether the results would apply to other less sick or less well treated populations is unknown, but previous studies would suggest that they would.

The major limitation of this study is that it is observational and cannot be adjusted for unknown confounders. For example, rales can be caused by lung disease; a third sound may be due to marked mitral regurgitation; and edema can be due to venous insufficiency. Also, this is a retrospective analysis of a study designed for another purpose, so it is difficult to know how well the physical examination was conducted. Unless each patient is put in the left lateral position and the bell of the stethoscope used, third heart sounds can be missed. In addition, JVD is notoriously hard to determine. Perhaps this is why rales and edema were more predictive than the third sound and JVD.

The new Accreditation Council for Graduate Medical Education mandated resident evaluation system emphasizes the attainment of milestones. At my institution, we are including the mastery of identifying these four physical findings as milestones that the residents should achieve. ■

ABSTRACT & COMMENTARY

Therapeutic Hypothermia: How Cold Is Cold Enough?

By James E. McFeely, MD

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

This article originally appeared in the April 2014 issue of Critical Care Alert. *It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Pierson is Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle, and Dr. Thompson is Associate Professor of Medicine, University of Washington, Seattle. Drs. Pierson and Thompson report no financial relationships relevant to this field of study.*

SYNOPSIS: This large clinical trial of targeted body temperature — 33°C vs 36°C — following cardiac arrest showed no differences in survival or neurological outcome in the two temperature groups.

SOURCE: Nielsen N, et al and the TTM Trial Investigators. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013;369:2197-2206.

Over the last 10 years, induced hypothermia after out-of-hospital cardiac arrest has become the standard of care. This new intervention is based on two studies that were published in 2002 with a total of 352 patients showing improvement in survival and neurologic outcomes in a select group of patients with successful out-of-hospital resuscitation.[1,2] These patients were presumed to have arrests of cardiac origin with initially shockable rhythms. Since that time, use of therapeutic hypothermia has been extended to cardiac arrest with other rhythms and for in-hospital arrests. Questions remained, however, regarding the optimal target temperature and whether the treatment effect was due to induced hypothermia or prevention of fever.

This very large trial of targeted temperature management (TTM) was recently published. A total of 950 unconscious adults were randomized to a TTM goal of either 33°C or 36°C. Primary outcomes were all-cause mortality and a composite score reflecting neurologic function at 180 days. A pre-established protocol was used at 72 hours for neurologic prognosis and withdrawal of care. At the end of the trial, 50% of the 33°C group had died, as compared to 48% of the 36°C group ($P = 0.51$). At the 180-day follow-up, 54% of the 33°C group had died or had poor neurologic function, compared with 52% in the 36°C group. No differences were identified in six predefined subgroups.

■ COMMENTARY

This well-done study was unable to show a benefit of TTM to 33°C as compared with 36°C. If two small studies were enough to change our management to TTM at 33°C, this larger, better-controlled study should make us consider returning to a goal of simply avoiding fever. Much has changed for the better in critical care management in the last 10 years. This may be partly why improved outcomes were seen in both treatment groups in this trial. TTM to 33°C, however, comes with its own set of complications, from the potential need for paralytics and pressors to increased resource utilization from the cooling process. Changing to a philosophy of active fever avoidance rather than rapid cooling will be much easier to implement, with fewer side effects, and (based on this excellent study) equal outcomes.

I would hope for rapid modifications to the international guidelines and local practice to reflect the robust result of this study. Further studies may find subsets of patients who benefit from TTM to 33°C, but until then, 36°C should be our TTM goal. Remember: *Primum non nocere*: first, do no harm. ■

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ABSTRACT & COMMENTARY

Can Occurrence of Delirium Be Predicted by Elevated Proinflammatory Cytokines?

By Linda L. Chlan, RN, PhD, FAAN

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Dr. Chlan reports that she receives grant/research support from Hospira.

This article originally appeared in the April 2014 issue of Critical Care Alert. *It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Pierson is Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle, and Dr. Thompson is Associate Professor of Medicine, University of Washington, Seattle. Drs. Pierson and Thompson report no financial relationships relevant to this field of study.*

SYNOPSIS: This observational study of 224 ICU patients who had serial measurements of C-reactive protein found an association between elevated initial levels and development of delirium. The authors also noted increased delirium incidence in patients whose levels increased on serial measurements.

SOURCE: Zhang Z, et al. Prediction of delirium in critically ill patients with elevated C-reactive protein. *J Crit Care* 2014;29:88-92.

Delirium is an unfortunate consequence of the ICU stay for many patients hospitalized for a critical illness or injury, occurring in up to 80% of patients depending on target population and assessment methods. In the past, delirium was viewed by clinicians as "something that just happened to ICU patients." However, findings from studies over the past few years have documented the adverse and detrimental influence of delirium on morbidity and mortality in critically ill patients. Numerous factors — including sepsis, metabolic factors, medications, illness severity, alcohol abuse, older age, and inflammation that occurs with critical illness or infection — contribute to the occurrence of delirium. The study by Zhang and colleagues reviewed here aimed to determine if one proinflammatory cytokine, C-reactive protein (CRP), could be used as a predictor for the development of delirium in a sample of ICU patients in China.

A total of 223 patients (54.1% mechanically ventilated) were enrolled in this prospective, observational study from one 24-bed medical-surgical ICU. Patients had a Glasgow Coma Scale score of ≥ 10, a Richmond Agitation Sedation Scale of -3 or higher, and were expected to remain in the ICU for a minimum of 48 hours. Patients with delirium at ICU admission or those with an acute brain injury (stroke, trauma, hemorrhage, or subdural hematoma) were not enrolled. Participants were predominantly male (63%) with a mean age of 57 years. Obtaining CRP levels is a standard of practice on this ICU; levels were obtained on ICU admission and 24 hours later. Nurses received training in administration of the Confusion Assessment Method-ICU, and performed all delirium assessments at ICU admission and every 8 hours each study day. Clinical variables (demographic data, medical diagnosis, illness severity [APACHE II], drinking and cigarette smoking history, application of physical restraints) were abstracted from the medical record. Analyses included change in CRP levels correlated with the clinical variables of illness severity, age, gender, intubation, history of drinking and smoking, use of physical restraints, and length of hospital stay.

The study participants had median APACHE II scores of 13 (inter-quartile range, 9-17), frequently had physical restraints applied (47.8%), with 26.1% known as heavy alcohol users and cigarette smokers. An overall prevalence of delirium was reported at 24.2%. Not surprisingly, delirium was more common in older, mechanically ventilated patients with higher illness severity scores and longer ICU stays. Higher levels of CRP were associated with delirium, in that for every 10 mg/mL increase in CRP from admission, there was a 7% increase in the risk for delirium. Further, patients with higher levels of CRP at ICU admission were more likely to develop delirium during the ICU stay, particularly in those with higher illness severity scores. The investigators concluded that elevated levels of CRP in patients with higher illness severity scores at ICU admission may be predictive of the occurrence of delirium during the ICU stay.

■ COMMENTARY

Delirium is an acute event that can fluctuate over the course of an ICU stay. It is complex and there are many clinical and patient-specific factors that are

known contributors to this ICU-acquired syndrome. Likewise, inflammation is a very complex biological process that is confounded by critical illness, infectious processes, and medications. This makes it extremely difficult to single out one marker of inflammation given the complex interrelationships among the numerous pro- and anti-inflammatory biomarkers. Many times, these biomarkers exist in extremely miniscule amounts in the blood, while others may not even be detectable depending on the sensitivity and specificity of the assay. However, CRP is a non-specific biomarker of inflammation that increases 10,000-fold in response to stimuli, making it a strong candidate to investigate in the development of delirium when examining inflammatory processes.

Zhang and colleagues reported that changes in CRP from ICU admission resulting in higher levels of this proinflammatory cytokine during the ICU stay were predictive of the development of delirium, particularly in those patients who had higher illness severity scores. This finding is significant in that other investigators have attempted to link inflammatory biomarkers with the development of delirium — findings from these investigations have been inconsistent across studies. The significant findings by Zhang et al may be due to several factors, including expertise in obtaining and interpreting biomarkers (given CRP is routinely obtained for analysis in their ICU) and the careful selection of participants. Further, the investigators recommend serial measurement of CRP, given that changes toward higher levels of CRP were predictive of delirium development in their sample.

This study is limited in that only one proinflammatory cytokine was examined at two collection points. Given that other biomarkers are known to be associated with delirium, the findings from this study provide only a limited snapshot of the contributions of inflammatory biomarkers to the development of delirium. Further, inflammation can fluctuate over the course of critical illness, which supports the investigators' recommendation to obtain serial measurements of biomarkers over the course of ICU stay. Perhaps intervention strategies to prevent delirium are needed for all ICU patients, with special attention to those patients deemed to be at higher risk for the development of delirium given its significant impact on morbidity and mortality. ■

ABSTRACT & COMMENTARY

The Importance of the CSF Specimen for Antibody Determination in NMDA Receptor Encephalitis

By Bianca D. Santomasso, MD, PhD
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Dr. Santomasso reports she is a stockholder in Novartis.

This article originally appeared in the April 2014 issue of Neurology Alert. *It was edited by Matthew E. Fink, MD, and peer reviewed by M. Flint Beal, MD. Dr. Fink is Professor and Chairman, Department of Neurology, Weill Cornell Medical College and Neurologist-in-Chief, New York Presbyterian Hospital, and Dr. Beal is Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center. Dr. Fink is a retained consultant for Procter & Gamble, and Dr. Beal reports no financial relationships relevant to this field of study.*

SYNOPSIS: The data from this large cohort of patients confirm the importance of submitting cerebrospinal fluid for assessment when NMDA receptor encephalitis is suspected.

SOURCE: Gresa-Arribas N, et al. Antibody titers at diagnosis and during follow-up of anti-NMDA receptor encephalitis: A retrospective study. *Lancet Neurol* 2014;13:167-177.

Since its discovery in 2007, anti-N-methyl-D-aspartate (NMDA) receptor encephalitis has entered the mainstream of neurology as an important and potentially treatable form of autoimmune encephalitis. The disorder predominantly affects young women and children, and can occur with or without tumor association (usually an ovarian teratoma in roughly half of patients). Neurologic improvement usually occurs with immunotherapy and resection of teratoma if one is present; however, relapses and refractory cases are also seen and incompletely understood.

Patients with anti-NMDA receptor encephalitis present with a subacute onset and stereotyped course characterized by psychosis, memory deficits, seizures, and language disintegration that progresses into a state of unresponsiveness, with catatonic features often associated with abnormal movements

and autonomic and breathing instability. Establishing the diagnosis depends on detection of an IgG antibody targeting the GluN1 subunit of the NMDA receptor. The two principle techniques that have been used for antibody testing in this disorder are 1) immunohistochemistry of brain tissue (which produces a highly characteristic pattern of reactivity); and 2) a cell-based assay (CBA) of human embryonic kidney 293 cells expressing the GluN1 subunit of the NMDAR. It is typically thought that these two assays complement each other for laboratory quality assurance of the diagnosis. However, the authors of this study mention that reports by others have suggested that serum testing using only CBA is sufficient for the identification of NMDA receptor antibodies and the diagnosis of NMDA receptor encephalitis. Therefore, they set out to clarify the appropriate antibody testing by directly comparing the sensitivity and specificity of different NMDA receptor antibody techniques in paired serum and cerebrospinal fluid (CSF) samples.

In this study, the authors retrospectively examined a large cohort of patients and report the sensitivity and specificity of paired serum and CSF samples by immunohistochemistry-based and cell-based assays. Two hundred fifty patients with NMDA receptor encephalitis (established by antibody positivity in both immunohistochemistry and cell-based assays) were compared with 100 control patients with encephalopathy. The authors found that all patients with anti-NMDA receptor encephalitis have anti-GluN1 antibodies in the CSF (100% detectable with both techniques), but antibodies in serum are found less often: 91% with immunohistochemistry and 86% with the cell based assay, suggesting that false-negative cases can occur when only serum is used. Put another way, the diagnosis of anti-NMDA receptor encephalitis would be missed in 13% of patients if only serum and a cell-based assay were used. Using a live cell-based technique actually worsened the serum results. None of the 100 paired serum and CSF samples from control samples showed NMDA receptor antibodies with either of the techniques (specificity 100%).

The authors then went on to do quantitative studies with antibodies using antibody titers. From a smaller group of patients for whom serial clinical data (modified Rankin Score) and specimens were available, antibody titers were determined with brain immunohistochemistry and prognostic significance of these antibody titers are reported. Results from their multivariate analysis showed that patients with higher antibody titers in serum or CSF at diagnosis were more likely to have poor outcome or the presence of a teratoma or both. Additionally, patients with a tumor were more likely to have antibodies detectable in serum than those without a tumor. There was also a possible association between good clinical outcome and early decrease of CSF antibody titers during the first month of the disease, but this was not statistically significant. The change in titers in CSF correlated better with clinical relapses than that in serum, but an association between the change in antibody titers and symptoms along the course of disease in this study was not seen. By last follow-up, most patients had a decrease in their serum and CSF titers regardless of clinical outcome, with possible explanations being either a slow spontaneous fading of the immune response or a burned-out stage of the disease. For unclear reasons, after clinical recovery, 24 of 28 CSF samples and 17 of 23 serum samples from patients remained antibody positive. Finally, the authors found that the same epitope specificity (amino acid 369 of GluN1) is present in all tested patients, regardless of their clinical outcome or stage of disease.

■ COMMENTARY

The most important point to be taken from this study is that CSF antibody determination is crucial in the initial diagnostic testing for suspected cases of NMDA receptor encephalitis. Examination of serum alone is not sufficient and could lead to a delay in neoplasm diagnosis and immunotherapy initiation in up to 13% of patients. In practice, any patient presenting with suspected autoimmune encephalitis should have both serum and CSF submitted to a commercial laboratory to optimize detection of the more than 20 antibodies (including anti-GluN1) classified as pertinent to autoimmune encephalopathy, since some individual autoantibodies are more readily detected in one specimen type or by a specific assay method.

Assay methods are known to influence sensitivity and specificity. Studies that test serum with cell-based assay alone have identified anti-GNuN1 antibodies in patients with schizophrenia, Creutzfeldt-Jakob disease, Parkinson's disease, and in healthy individuals; these findings could not be reproduced in studies that used both cell-based assays and brain immunohistochemistry in serum and CSF samples. False positives resulting in misdiagnosis of a cognitive disorder as autoimmune might lead to erroneous use of potentially toxic immunotherapy.

The finding that patients with high antibody titers and little or no decrease of CSF antibodies in the first months of the disease are less likely to have a good outcome than those with low titers or a clear decrease in CSF titers is intriguing, but it needs confirmation with prospective studies. Further studies should also investigate whether the level of antibody that persists after clinical recovery predicts relapses and need for chronic immunotherapy. In the meantime, while we wait for prospective studies to confirm CSF antibody titers as a potential prognostic biomarker, a recent large study of 577 patients suggests that clinical assessment of the patient is most important for informing clinical decisions along the course of disease.[1] ■

Reference

1. Titulaer MJ, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. *Lancet Neurol* 2013; 12:157-165.

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CME QUESTIONS

1. Ceasing investigation for deep venous thrombosis in light of a negative D-dimer and a low Wells score is a reasonable strategy in all patients EXCEPT:

a. Men
b. Hospital outpatients
c. Patients with active malignancy
d. Patients with a quantitative D-dimer result

2. In the study by Nielsen and the Targeted Temperature Management investigators, patients who were comatose after cardiac arrest and randomized to either 33°C or 36°C had:

a. A higher all-cause mortality but improved neurologic function in the group managed with a goal temperature of 33°C
b. No significant differences in overall outcome
c. A lower all-cause mortality but worsened neurologic function in the group managed with a goal temperature of 36°C
d. No difference in all-cause mortality but improved neurologic function in the group managed with a goal temperature of 33°C

3. In the analysis by Caldentey and colleagues, which of the following physical exam findings were independently predictive of heart failure-related deaths in patients with CHF:

a. Poor capillary refill
b. Jugular venous distention (JVD)
c. A third heart sound (S3 gallop)
d. Rales (crackles)

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.