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INSIDE

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How Common is Pulmonary Embolism in Patients with COPD Exacerbations?

ABSTRACT & COMMENTARY

By David J. Pierson, MD

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Dr. Pierson reports no financial relationship relevant to this field of study.

This article originally appeared in the August 2006 issue of Critical Care Alert. *It was peer reviewed by William Thompson, MD.*

Dr. Thompson is Staff Pulmonologist, VA Medical Center, Associate Professor of Medicine, University of Washington. He reports no financial relationship relevant to this field of study.

Synopsis: *In a selected population of patients with known COPD who were hospitalized with acute worsening of respiratory symptoms but did not have usual signs of an infection or other specific process, 25% were found to have pulmonary embolism.*

Source: Tillie-Leblond I, et al. Pulmonary Embolism in Patients with Unexplained Exacerbation of Chronic Obstructive Pulmonary Disease: Prevalence and Risk Factors. *Ann Intern Med*. 2006;144:390-396.

In this study from the University Hospital A Calmette in Lille, France, patients with known COPD who were admitted because of acute respiratory deterioration were evaluated for inclusion in a prospective investigation of the prevalence and risk factors for pulmonary thromboembolism (PE) in this setting. Patients who required intubation were excluded, as were all who had purulent sputum, a history of cold or sore throat, a discrepancy between radiographic findings and the clinical picture, severe hypoxemia, pneumothorax, or iatrogenic intervention (not further defined). Patients who had none of these exclusionary features underwent spiral computed tomography angiography and venous ultrasonography and, if either of these were positive, the patient was classified as having PE. Tillie-Leblond and colleagues recorded demographic and clinical data and calculated the probability of PE using the Geneva score. This score correlates the risk of PE with age, previous PE or deep-vein thrombosis, recent surgery, heart rate, arterial PO_2 and PCO_2, and selected findings on chest radiograph.[1]

Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, selected and reviewed the articles contained within this issue on August 20, 2006.

During the 45-month study, 211 patients met the entry criteria; 197 had complete data and form the basis of the article. Two-thirds of them were admitted from the emergency department and one-third was already in the hospital at the time of referral. One hundred-sixty of 197 patients had had pulmonary function tests within 3 months prior to admission, and their mean FEV1 was 1.56 L (52% of predicted). Mean admission arterial PO_2 and PCO_2 values off supplemental oxygen were 62 and 42 mm Hg, respectively; 29% of the patients had known underlying malignancy.

Forty nine of the 197 patients (25%) met the diagnostic criteria for PE. Clinical factors associated with a statistically significant increased risk for PE were prior PE (risk ratio, 2.43), malignant disease (RR, 1.82), and a decrease in admission PCO_2 of at least 5 mm Hg, compared with previous measurements (RR, 2.10). Among the 197 patients, 9.2% who had a low Geneva score, indicating a low probability of PE, turned out to have PE (95% confidence interval, 4.7%-15.9%). Tillie-Leblond et al calculated the likelihood of PE substituting malignant disease for recent surgery in the Geneva score, and postulated that this might increase its predictive ability.

COMMENTARY

One-fourth of the COPD patients in this study who were admitted with a severe exacerbation without another obvious cause were found to have PE. The diagnosis of PE was more likely to be made among patients with previous thrombosis, underlying malignancy, or an admission PCO_2 at least 5 mm Hg below their baseline value. What can these findings tell us about the likelihood of PE among the patients we manage with COPD exacerbations, or whether we should include a CT angiogram or Doppler study in our admission evaluation of such patients? In my opinion, the answer is "that depends."

From a clinician's perspective, there are some unfortunate omissions in this paper. We are not told how many patients were admitted to Tillie-Leblond et al's unit with COPD exacerbations during the study period, or what proportion of them were considered not to have an infection or other specific cause and were thus referred for possible inclusion. Most COPD patients presenting with an exacerbation have features suggesting infection, and such patients were not included in this study. In fact, the widely used Anthonisen criteria[2] for determining whether a severe exacerbation is present rely on sputum volume and purulence, in addition to an increase in dyspnea for the definition. The study also excluded the most severely ill patients, those requiring intubation and mechanical ventilation. Thus, the patients in this study may have represented a minority of the COPD exacerbations seen at the authors' institution during the study period.

These patients were also not the end-stage patients in whom many exacerbations occur. Most of them would be classified as Stage II or III by the GOLD criteria, based on their baseline FEV1 values. Their exacerbations would not have been judged severe by blood gas criteria: arterial pH values are not provided, but mean admission PCO_2 42 mm Hg and PO_2 62 mm Hg breathing room air would not be expected in many patients presenting with severe exacerbations. In addition, the paper does not include hospital length-of-stay or mortality data on the patients. Thus, clinicians attempting to apply this study's findings to their own practices need to be aware of the selected nature of the patients who were included.

For me, the take-home message of this study is that when patients with known COPD present with an acute clinical deterioration and do not have the usual features of a severe exacerbation, PE should be considered-especially if they have a known malignancy, a history of thrombosis, or an arterial PCO_2 lower rather than higher than expected. The prevalence of PE in the general population of COPD patients presenting with an exacerbation cannot be determined from this study. ■

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Pregnancy and Ischemic Stroke: Is Thrombolysis an Option?

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

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Dr. Jamieson is a consultant for Boehringer Ingelheim and Merck, and is on the speaker's bureau for Boehringer Ingelheim, Merck, Ortho-McNeil, and Pfizer. This article originally appeared in the August issue of Neurology Alert. *It was edited by Matthew E. Fink, MD, and peer reviewed by M. Flint Beal, MD. Dr. Fink is Vice Chairman, Professor of Clinical Neurology, Weill Cornell Medical College, Chief of Division of Stroke and Critical Care Neurology, NewYork-Presbyterian Hospital, and Dr. Beal is Professor and Chairman, Department of Neurology, Cornell University Medical College. Drs. Fink and Beal report no financial relationships relevant to this field of study.*

Synopsis: *rtPA thrombolysis may be used safely in pregnant women.*

Source: Murugappan A, et al. Thrombolytic Therapy of Acute Stroke During Pregnancy. *Neurology*. 2006;66:768-770.

Pregnancy is a prothrombotic state which is rarely associated with ischemic arterial stroke. However, when a stroke occurs, especially in later pregnancy, the options for therapy may be limited. The additional consideration of fetal outcome complicates therapy of the mother, and pregnancy has generally been considered a contraindication for thrombolysis. The confidence and experience in the use of thrombolysis in acute ischemic stroke has increased in the past decade. Although the 3-hour window has remained the standard for intravenous (IV) delivery of recombinant tissue plasminogen activator (rtPA), intra-arterial (IA) delivery has expanded the treatment time and population. The drug is pregnancy category C (unknown safety), with concerns about fetal and maternal hemorrhage risk and teratogenicity. However, animal data have not indicated associated fetal anomalies, and the large molecule does not cross the placenta. Several papers published in 2006 have illustrated that women at different stages of pregnancy can be treated with thrombolysis, either IV or IA, without excess risk to the patient, and with the potential of a viable pregnancy.

Earlier in the year in *Neurology*,[1] a series of 8 patients who underwent IV or IA thrombolytic treatment of ischemic stroke was reported. Half of the patients were treated with urokinase, as opposed to rtPA, and 2 patients had venous, rather than arterial, thrombosis. There was one fatal complication from angioplasty (with death of the fetus), and 3 pregnancies were medically terminated. Two healthy babies were delivered. There was one spontaneous first trimester abortion, as well as a fetal demise due to lethal chromosome abnormalities. Murugappan and colleagues reviewed the medical literature and noted that in the mainly non-stroke related cases of thrombolysis during pregnancy, the premature delivery rate was not increased. There was no indication of teratogenicity.

Case reports note success with the treatment. A woman, 13 weeks pregnant, on subcutaneous heparin because of a mechanical mitral valve, was given standard protocol IV rtPA for a left middle cerebral artery infarct.[2] She was restarted on warfarin for the rest of her uncomplicated pregnancy, and she delivered a healthy baby at 37 weeks.

In a review article of 28 published cases of treatment with rtPA in pregnancy,[3] 10 women with stroke were identified. Six of the cases were from an abstract of the recently published paper noted above.[1] One woman with cerebral sinus thrombosis was treated successfully with thrombolysis, and had an uneventful delivery. In the remaining 3 cases (2 IV, one IA), there was good neurological recovery in 2 of the women, and 3 healthy babies were delivered. In the remaining cases where rtPA was given for thrombosed prosthetic cardiac valves, pulmonary embolism, deep vein thrombosis, or fetal complications were rare and felt to be related to the underlying maternal condition, not the thrombolytic therapy. An addendum to the review article reported a woman with a left middle cerebral artery stroke at 23 weeks, treated with IV rtPA, with variable neurological recovery. She delivered successfully at 33 weeks.

Arterial and venous infarcts can be neurologically devastating during pregnancy, with concern about the outcome of both the patient and fetus. While experience with the use of rtPA during pregnancy is still limited, these reported successes encourage the consideration of rtPA in pregnant women with ischemic stroke. As experience with thrombolysis in acute stroke increases, pregnancy does not appear to be an absolute contraindication, especially in the absence of other effective alternatives. Without specific guidelines for its use in pregnancy, the guidelines for rtPA use in general should apply to the woman who suffers an acute ischemic stroke during pregnancy. ■

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Door-to-Balloon Time in STEMI

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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Dr. Crawford is on the speaker's bureau for Pfizer.

This article originally appeared in the August issue of Clinical Cardiology Alert. *It was peer reviewed by Rakesh Mishra, MD. Dr. Mishra is Assistant Professor of Medicine, Weill Medical College, Cornell University; Assistant Attending Physician, NewYork-Presbyterian Hospital. He reports no financial relationships relevant to this field of study.*

Synopsis: *Time to primary PCI is strongly associated with mortality risk and is important regardless of time from symptom onset to presentation and regardless of baseline risk of mortality.*

Source: McNamara R, et al. Effect of Door-to-Balloon Time on Mortality in Patients with ST-Segment Elevation Myocardial Infarction. *J Am Coll Cardiol*. 2006;47:2180-2186.

Although time to reperfusion is correlated with mortality in ST elevation myocardial infarction (STEMI) treated with fibrinolytics, its importance in patients treated with percutaneous coronary interventions (PCI) is less clear. Thus, McNamara and colleagues examined the National Registry of Myocardial Infarction (NRMI) database to explore this issue. From this database of 830,473 acute MI admissions, 29,222 STEMI patients treated by PCI within 6 hours of presentation to 1 of 395 hospitals capable of performing acute PCI were studied. The outcome of interest was in-hospital mortality, and the primary independent variable was door-to-balloon time. Time from symptom onset to hospital arrival (onset-to-door time) and comorbidities that increased risk were also examined.

Results: In-hospital mortality increased significantly with longer door-to-balloon times (< 90 minutes 3%, 120-150 minutes almost 6%). Onset-to-door time was not related to hospital mortality. The relationship of door-to-balloon time to hospital mortality was not affected by clinical characteristics that predict higher risk. McNamara et al concluded that the time from hospital arrival to balloon inflation for acute STEMI patients treated by primary PCI is associated with hospital mortality regardless of symptom onset-to-hospital arrival time and other clinical risk factors for mortality. Efforts to shorten this time could potentially benefit all STEMI patients.

COMMENTARY

This is a large observational study that supports the importance of door-to-balloon time in the treatment of STEMI. Symptom onset-to-door time was not related to mortality, which is somewhat surprising since symptom onset to injection of thrombolytics time has been shown to relate to mortality. The reason for this apparent discrepancy between the 2 types of treatment is not elucidated in this study, but there are some possible explanations. Symptom onset is an imprecise point so, if the patient is unsure of when symptoms started, many would give them the benefit of the doubt and assume it was less than 6 hours. Therefore, they would more likely get PCI, and symptom onset-to-door time would be noncontributory to their outcome. Also, two-thirds of the patients in this study presented within 2 hours of symptom onset, so there may have been less mortality in this timeframe. In addition, some patients died before reaching the hospital, eliminating these higher-risk patients from the pool and making symptom onset-to-door time more benign. Of interest, is that the majority of patients in NRMI had door-to-balloon times of > 90 minutes. This may have improved the spread of times and made it easier to show a relationship to mortality. Finally, door-to-balloon time may be a marker for better hospital care in general. Whatever the reason, it allows us to focus on a more reliable measure that can be shortened by improved systems.

The ACC/AHA Guidelines recommend a door-to-balloon time of 90 minutes or less, but most available data suggest that it is generally above that in most institutions. The JCAHO and the University Hospitals Consortium averages are just above 120 minutes, and have been there for the last 2 years. Thus, many hospitals have set an internal quality improvement goal of a < 120 minutes. According to the data in this paper, that would correspond to an in-hospital mortality of 4%, whereas < 90 minutes would equate to a 3% mortality. What is necessary to decrease the door-to-balloon time average by 30 minutes to gain 1% in mortality is often not easy. We accomplished it in our hospital with great effort, and have found that it requires constant attention to keep it below 90 minutes.

This study excluded transfer patients since it is very difficult to keep their first hospital door to second hospital balloon time at a reasonable time span unless you have a very coordinated system. Also, most of the study patients were men (71%) and white (86%), so the results may not apply to other populations. Many patients had high-risk features such as hypotension in 10%, tachycardia in 12%, diabetes in 19%, and heart failure in 11%. Those with high-risk features had a higher mortality rate, but the relation to door-to-balloon time persisted. Finally, there was no risk subgroup in which door-to-balloon time < 90 minutes did not reduce mortality relative to longer times. ■

Failed Thrombolysis

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

This article originally appeared in the August issue of Clinical Cardiology Alert. *It was peer review by Rakesh Mishra, MD.*

Synopsis: *Rescue PCI in the setting of early fibrinolytic failure improves mortality, but this is tempered by a possible increase in the risk of thromboembolic stroke.*

Source: Patel TN, et al. A Meta-Analysis of Randomized Trials of Rescue Percutaneous Coronary Intervention After Failed Fibrinolysis. *Am J Cardiol*. 2006;97:1685-1690.

RESCUE PERCUTANEOUS CORONARY INTERVENTION (RPCI) has been advocated for failed thrombolysis in acute STEMI when available, but there is a lack of agreement on the efficacy of this approach. Thus, Patel and colleagues reviewed the English language literature from 1985 to 2004 to find randomized, controlled trials on this topic, and then performed a meta-analysis to evaluate whether RPCI improved outcomes. The primary outcome was short-term mortality (up to 30 days). Secondary outcomes were stroke and heart failure. Five trials were included in the analysis: RESCUE I and II, MERLIN, and REACT. A total of 942 were enrolled in these trials; 405 got RPCI, 395 conservative therapy, and 142 repeat thrombolysis in REACT. The latter patients were excluded. There was no difference in baseline characteristics in the groups. All patients received aspirin; heparin use was variable; stent use varied from 29 to 50%; and glycoprotein IIb/IIIa inhibitor use varied from 3%-55%.

Results: Mortality was reduced 36% (RR 0.64, CI 0.4-1.00, $P = 0.048$) in the RPCI Groups. The number needed to treat (NNT) with RPCI to prevent one death was 25. There were only 11 confirmed thromboembolic strokes; 9 in the RPCI groups, which resulted in a nonsignificant increased risk with RPCI (RR 3.61, CI 0.91-14.27, $P = 0.07$). Heart Failure decreased marginally with RPCI (RR 0.72, CI 0.51-1.01, $P = 0.06$). Patel et al concluded that rescue PCI for failed thrombolytic therapy improves mortality, but may increase thromboembolic stroke.

■ COMMENTARY

Since almost all hospitals with PCI capabilities perform primary PCI for acute STEMI, the issue is whether non-PCI hospitals, which use thrombolysis, should transfer patients with failed thrombolysis to centers where rescue PCI can be done. Prior randomized, controlled trials on this issue have been either very small (28 to 151 patients) angiographic studies (RESCUE) or small clinical studies (MERLIN, REACT, under 300 patients each). Despite the marked differences in trial design, all but RESCUE II (29 patients) showed a trend toward reduced 30-day mortality in the RPCS group, and this was statistically significant on the meta-analysis with a NNT of 25. This is encouraging since the time from chest pain onset-to-arrival in the catheterization laboratory was > 4 hours for all 5 trials. For example, in the MERLIN trial the pain-to-lysis time averaged 180 minutes; the lysis-to-lab time was 146 minutes; and the pain-to-lab time was 326 minutes (almost 5.5 hours).

The major concern has been the complication of thromboembolic stroke, which was most notable in MERLIN. Of the 11 such strokes, 7 were in MERLIN; 6 in the RPCI arm and 1 in the conservative arm. There were none to very few in the other trials, and this risk was nonsignificant in the meta-analysis. Of the 6 strokes in the RPCI arm of MERLIN, 3 were periprocedure and 2 resulted in long-term disability. This excess of strokes in MERLIN may be because streptokinase was used almost exclusively in this trial. Also, in MERLIN only, 66% of those randomized to RPCI actually got it. In addition, there was a low rate of stent and GP IIb/IIIa use in MERLIN. Thus, many believe MERLIN is an outlier in this regard and are not concerned about stroke risk. There were no differences in major bleeding in these trials (intracranial, GI), but minor groin bleeding was increased by RPCI as expected.

At this point, rescue PCI should be considered the ideal treatment for failed thrombolysis in acute STEMI unless contraindicated or not feasible. These studies do not provide much information about the timing of RPCI, but it would seem that if RPCI can be accomplished in < 6 hours from pain onset, it should be strongly considered. If this sort of timing is feasible, it raises the issue of whether routine transfer for primary PCI is a better approach. In my experience, unless there is a well-developed special relationship between hospitals to accomplish such transfers on a routine basis in a timely manner, it is better to do thrombolysis first. Organizing an occasional RPCI requires less

coordination and effort overall, but experiences at other centers may dictate a different approach. Despite the simplicity of the time = muscle concept in acute STEMI, selecting the approach that provides the most reperfusion in the least time for all patients remains a challenge. ■

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Risks of Catheter-Related Thrombosis in Cancer Patients

ABSTRACT & COMMENTARY

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This article originally appeared in the August 2006 issue of Clinical Oncology Alert. *It was peer reviewed by VR Veerapalli, MD. Dr. Veerapalli is Staff Clinician, INOVA Fairfax Cancer Center, Falls Church, VA. Dr. Veerapalli reports no financial relationships relevant to this field of study.*

Synopsis: *In a prospective, observational study of 444 patients, there were no cases of symptomatic pulmonary embolus, and postphlebitic syndrome occurred infrequently.*

Source: Lee AY, et al. Incidence, risk factors and outcomes of catheter-related thrombosis in adult patients with cancer. J Clin Oncol. 2006;24:1404-1408.

ONCOLOGISTS ARE BECOMING INCREASINGLY COMfortable with use of central venous catheters (CVC)

particularly for those patients receiving infusional chemotherapy, or who have poor venous access. These have been utilized with a high level of safety and efficacy, yet thrombosis remains a concern for its occurrence may result in morbidity or interrupt chemotherapy schedules or transfusions. The purpose of the current report was to examine the incidence, risk factors, and long-term complications of catheter-related thrombosis (CRT) in adults with cancer.

Consecutive patients with cancer who were treated at the Juravinski Cancer Centre in Hamilton, Ontario, were enrolled in a prospective, observational study. Patients remained on the study as long as the catheter was in place and for 4 weeks thereafter, for a maximum of 52 weeks. Patients with catheter-related thrombosis were followed for an additional 52 weeks from the date of the diagnosed thrombosis. The main end points of the study were symptomatic catheter-related thrombosis, symptomatic pulmonary embolus, postphlebitic syndrome, and catheter lifespan.

Of the 444 patients enrolled, 19 (4.3%) had symptomatic CRT over 76,713 patient days of follow-up. The median time to CRT was 30 days, and the median catheter lifespan was 88 days. By multivariate analysis, 3 significant risk factors became apparent. These were 1) more than one insertion attempt (odds ratio [OR] = 5.5; 95% confidence interval [CI], 1.2-24.6; $P = 0.03$); 2) ovarian cancer (OR = 4.8; 95% CI, 1.5-15.1; $P = 0.01$); and 3) previous central venous catheter insertion (OR = 3.8; 95% CI, 1.4-10.4; $P = 0.01$). Of the 19 patients with catheter-related thrombosis, 9 were treated with anticoagulants alone, 8 patients were treated with anticoagulants and catheter removal, and 2 patients did not receive anticoagulation. None of the 19 patients had recurrent CRT or symptomatic PE, and postphlebitic symptoms were infrequent.

Thus, Lee and colleagues concluded that in patients with cancer, the incidence of symptomatic CRT is low and long-term complications are uncommon.

COMMENTARY

This was a rigorous, prospective analysis of the incidence of symptomatic CRT in patients with cancer and the results were encouraging. The incidence of symptomatic CRT was low (4.3%), and certain risk factors became apparent. These included difficulty at the time of the insertion, prior central venous catheter, and the presence of ovarian cancer. The low incidence of CRT was similar to that found in other studies although all the methodologies were quite different.[1,2]

The risk identified in ovarian cancer patients is a curious finding. Lee et al carefully reviewed those cases and could find no evidence for specific histologic subtype but did find that these patients were heavily pretreated at the time of CVC insertion, and there was a high incidence of poor peripheral venous access in these patients. Thus, it is quite possible that vessel injury from multiple venipunctures and the heavy prior use of cytotoxic chemotherapy were the important contributing factors rather than any specific biological characteristic of the underlying ovarian cancer.

Of note, this study did not find prophylaxis with anticoagulation reduced the risk of symptomatic CRT. However, Lee et al were quick to point out that this was not the purpose of the current report, and the numbers were insufficient to make a confident statement in this regard. Nonetheless, other recent reports have also questioned the value of routine anticoagulant prophylaxis.[3,4] Certainly, the published reports to date suggest no therapeutic value for routine or low dose anticoagulation therapy in those with CVC and, possibly, an increased risk of bleeding.

Thus, in summary, the study demonstrated a low risk of symptomatic catheter-related thrombosis in cancer patients. Although this was from a single institution, the evaluation was thorough, and there were a sufficient number of patients to accept the study conclusion with confidence. Because there was a low incidence of symptomatic CRT and because there was no control over type of cancer therapy, anticoagulant prophylaxis and treatment of the CRT, the identification of risk factors was likely to be incomplete and additional studies will be required to confirm those identified and possibly establish others. Nonetheless, we can conclude that symptomatic catheter-related thrombosis is an uncommon occurrence in the general cancer patient population and the risk of symptomatic pulmonary embolus, or even postphlebitic syndrome is very low. ■

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CME Questions

19. In pregnant woman who present with an acute ischemic stroke, tissue plasminogen activator:

a. has been shown to increase the risk of placental hemorrhage.
b. should not be used because of its known teratogenicity.
c. should only be given directly into the affected cerebral artery.
d. has been shown not to increase fetal risk when given intravenously.
e. increases the risk of fetal intracerebral hemorrhage.

20. In the article by McNamara et al, mortality in patients who undergo percutaneous coronary intervention is relative to:

a. hospital arrival time to coronary balloon inflation time (door-to-balloon time).
b. chest pain onset time to hospital arrival time (onset-to-door time).
c. hospital arrival time to catheterization lab arrival time (door-to-door time).
d. All of the above
e. None of the above

21. According to the article by Tillie-Leblond et al, patients hospitalized for an unexplained COPD exacerbation were more likely to have had a pulmonary embolism if:

a. they had an underlying malignancy.
b. they had a previous episode of thrombosis (DVT or PE).
c. they had a $PaCO_2$ at least 5 mm Hg below their baseline value.
d. All of the above.
e. None of the above

Answers: 19. (d); 20. (a); 21. (d)

CME Objectives

The objectives of *Hospital Medicine Alert* are to:

• review pertinent safety, infection control, and quality improvement practices;

• discuss diagnosis and treatment of acute illness in the hospital setting;

• review current data on diagnostic and therapeutic modalities for common inpatient problems. ■