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# Hospital Medicine

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ABSTRACT & COMMENTARY

# Can Procalcitonin Predict Need for ICU Admission in Community-acquired Pneumonia Patients?

*By Betty Tran, MD, MSc, Editor*

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

SYNOPSIS: In a prospective cohort study of adults hospitalized with community-acquired pneumonia, higher serum procalcitonin levels on admission were associated with an increased risk of invasive respiratory and/or vasopressor support within 72 hours and improved the performance of pneumonia severity scores in identifying high-risk patients.

SOURCE: Self WH, Grijalva CG, Williams DJ, et al. Procalcitonin as an early marker of the need for invasive respiratory or vasopressor support in adults with community-acquired pneumonia. *Chest* 2016 Apr 20 [Epub ahead of print].

There is significant recent interest in studying procalcitonin (PCT) as a biomarker for the management of critically ill patients with sepsis, as its synthesis and secretion are upregulated by bacterial-specific pro-inflammatory cytokines.[1] Several studies have focused on the use of PCT in diagnosing sepsis, as a prognostic marker in sepsis, and as a guide to antibiotic decisions in sepsis. Research by Self et al adds to the growing literature on PCT by examining whether it is helpful in early severity assessment and risk stratification for patients admitted with community-acquired pneumonia (CAP), particularly with regard to ICU admission.

This was a prospective cohort study of 1,770 adults hospitalized with CAP at three centers in Chicago and two hospitals in Nashville, TN, between 2010 and 2012 who had serum PCT measurements. The primary study outcome was the need for invasive respiratory and/or vasopressor support (IRVS), defined as intubation for respiratory failure or vasopressor administration for septic shock within 72 hours of hospital presentation. Overall, 115 patients required IRVS, with 47 requiring both, 37 requiring respiratory support only, and 31 requiring vasopressor sup-

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[ALERT]

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port only. The area under the receiver operator curve (ROC) for PCT to discriminate between patients with and without IRVS was 0.69 (95% confidence interval [CI], 0.67-0.71), which the authors noted to be higher than the area for WBC (0.54; 95% CI, 0.51-0.56).

Overall, there was a significant association between PCT level and risk of IRVS. For undetectable levels of PCT (< 0.05 ng/mL), the risk of IRVS was 4.0% (95% CI, 3.1-5.1%). For levels of PCT between 0.05 ng/mL and 10 ng/mL, there was a linear risk of IRVS, with each increase in PCT of 1 ng/mL corresponding to a 1-2% absolute increase in IRVS risk. For PCT levels of 5 ng/mL and 10 ng/mL, the risk of IRVS was 14.2% (95% CI, 11-18.1%) and 22.4% (95% CI, 16.3-30.1%), respectively. The risk of IRVS was observed to plateau when PCT levels reached > 10 ng/mL.

The addition of PCT levels to existing pneumonia severity scoring systems such as the ATS Minor Criteria, Pneumonia Severity Index (PSI), and SMART-COP scores increased the area under the ROC curves and improved the risk stratification ability in predicting IRVS for each severity score.

## ■ COMMENTARY

The ability to risk stratify patients with sepsis appropriately has important clinical repercussions. Theoretically, accurate prognostication can result in quicker triage for sicker patients to the ICU and expedite crucial interventions such as appropriate antibiotics, searches for occult infection, and methods of source control.

In the Self et al study, PCT levels on admission for patients hospitalized with CAP strongly correlated with the risk of invasive respiratory and/or vasopressor support, interventions that are performed in the ICU. Specifically, patients with PCT levels of 5 ng/mL and 10 ng/mL were three and five times more likely, respectively, to require IRVS than patients with levels < 0.05 ng/mL. When added to ATS minor criteria, PCT levels improved the ability to accurately identify patients at risk for IRVS who would benefit from admission to an ICU. The authors appropriately acknowledged that the PCT level alone is insufficient in deciding whether to admit a patient with CAP to the ICU. This study suggested yet another unique potential use for PCT in the management of patients with sepsis beyond what has previously been reported in terms of sepsis diagnosis and antibiotic management. There are, however, several issues to consider. First, PCT is mainly upregulated in bacterial infections; its application to non-bacterial pneumonia patients is unclear. Second, its use as a factor in the appropriate triage of sick CAP patients to the ICU will depend on how quickly the value is made available to healthcare providers, especially in the ED. Third, only a single PCT level on admission was used in this study; it may be more helpful to examine changes in PCT over time, as prior studies have reported that changes in PCT rather than absolute values correlate with patient outcomes such as mortality.[2-4] Finally, it is necessary to note that the decision to admit a patient to the ICU is likely to depend on other clinical and social factors besides the risk of IRVS, and PCT levels may not influence decision-making in these situations. Despite its known limitations, it will be interesting to see if PCT will gain more widespread use similar to how clinicians use BNP, lactate, or D-dimer as part of medical decision-making in specific clinical situations. ■

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STROKE ALERT

# Dual Antiplatelet Therapy Appears More Effective Than Single Therapy

***By Matthew E. Fink, MD***

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

SOURCE: Ge F, Lin H, Liu Y, et al. Duel antiplatelet therapy after stroke or transient ischemic attack – how long to treat? The duration of aspirin plus clopidogrel in stroke or transient ischemic attack: A systematic review and meta-analysis. *Eur J Neurol* 2016;23:1051-1057.

The CHANCE study showed that the combination of aspirin and clopidogrel was superior to aspirin alone for reducing the risk of stroke in the first 90 days after a TIA or minor ischemic stroke (*N Engl J Med* 2013;369:11-19). In its 2014 guidelines, the American Heart Association recommended that the combination of aspirin and clopidogrel can be initiated within 24 hours for a minor ischemic stroke or TIA and continued for 90 days. However, the CHANCE trial was performed in China with a discrete ethnic population, and it was not clear if the optimal duration of treatment should be 90 days or longer. In ischemic heart disease, treatment with dual antiplatelet therapy beyond one year is the standard of care in patients who have coronary stents, and this question has been unanswered in patients with transient ischemic attack or stroke. Therefore, the authors performed a comprehensive literature review and meta-analysis, and identified nine randomized controlled trials that included 21,923 patients. In review of these trials, short-term dual antiplatelet therapy significantly reduced the risk of ischemic stroke recurrence by 41% and major vascular events by 30%, without an increased risk of intracranial hemorrhage. Prolonged treatment beyond 90 days reduced the risk of ischemic stroke recurrence by 12% and major vascular events by 10%. However, the risk of major bleeding and intracranial hemorrhage was increased in those patients treated for a longer term. Therefore, it appears that short-term dual antiplatelet therapy appears to be superior to prolonged treatment. However, this difference in outcome needs to be confirmed by further well-designed randomized clinical trials. ■

# Human Adenovirus B7: Severe Infection

***Dean L. Winslow, MD, FACP, FIDSA***

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

SYNOPSIS: Oregon health authorities identified 198 patients from October 2013 until July 2014 with respiratory symptoms and a human adenovirus (HAdv)-positive respiratory specimen. Of the 136 patients (69%) who were hospitalized, 31% were admitted to ICU, 18% required mechanical ventilation and 5 patients died. Patients with HAdV-B7 were more likely to be adults and to have longer hospital stays.

SOURCE: Kendall Scott M, et al. Human adenovirus associated with severe respiratory infection, Oregon, USA, 2013-2014. *Emerging Infectious Diseases* 2016; 22: 1044-1051.

Oregon Public Health Department (OPHD) enlisted 3 major hospitals that perform HAdV testing to participate in the study. Compared to the previous 3 years, during 2013-2014 hospitals in Oregon recorded a 11-fold increase in HAdV cases. For 87% of cases, symptom onset and specimens were collected between January and April 2014. Specimens from 109 patients were typed. Seven HAdV types were identified; HAdV-B7 was most commonly identified (59%). Other types included HAdV-C2, B21, C1, B3, C5, and E4. The genomes from 7 HAdV-positive samples were further studied by sequencing and BamHI and BclI restriction profiling and were found to be identical to HAdV-B7d variants circulating in China in 2009 and 2011. HAdV-C1, C2, and C5 patients were younger (median age 1.2 years), HAdV-B3 or B21 (median age 24 years) and HAdV-B7 (median age 20 years) were older. For all HAdV patients, common symptoms included fever (75%), cough (61%), dyspnea (26%), nausea/vomiting (24%), and rhinorrhea (22%). Pneumonia was seen in 32% of patients and was more common in patients with HAdV-B7 patients 41%) vs. those with other types (26%). More HAdV-B patients (B3, B21- 81%;

B7- 84%) were hospitalized than other types (64%). HAdV-B7 patients had longer hospitalizations. Five patients died and for only 2 of these deaths were specimens available for typing. Both were HAdV-B7.

■ COMMENTARY

This study demonstrates that HAdV infections have become more common in the United States in the past few years and the predominant genotype is identical to the type which circulating commonly in China. HAdV-B7 appears to preferentially affect older patients/young adults than other types and to cause more severe disease. This reminds me of the outbreak of severe HAdV-B2 (type 14) about 10 years ago in US military recruits[1], which resulted in the deaths of several of these young, previously healthy service members. My personal interest in this disease was activated by being involved in the care of a young, previously healthy man in his late 20's who was hospitalized at Stanford recently with multilobar pneumonia requiring mechanical ventilation who also developed acute renal failure requiring hemodialysis support for many weeks. No FDA-approved drugs exist for treatment of systemic adenovirus infections, although both cidofovir and ribavirin have been used in isolated cases. Cidofovir may have some clinical utility (our patient received this drug) but this agent has significant toxicity[2]. ■

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ABSTRACT & COMMENTARY

# TAVR Without On-site Cardiac Surgical Backup: Fringe Procedure, or Wave of the Future?


***By Jeffrey Zimmet, MD, PhD***

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



SYNOPSIS: Data from transcatheter aortic valve replacement procedures performed at German hospitals without on-site cardiac surgery shows relatively low rates of major complications and mortality similar to hospitals with full surgical programs.


SOURCE: Eggebrecht H, Bestehorn M, Haude M, et al. Outcomes of transfemoral transcatheter aortic valve implantation at hospitals with and without on-site cardiac surgery department: Insights from the prospective German aortic valve replacement quality assurance registry (AQUA) in 17,919 patients. *Eur Heart J* 2016 May 17 [Epub ahead of print].

Since its commercial introduction just a few years ago, transcatheter aortic valve replacement (TAVR) has become rapidly integrated into the standard of care for aortic stenosis patients at elevated risk for surgery. The early model encouraged performance of the procedure in a cath lab or hybrid operating room, with full cath lab and surgical teams, and with cardiopulmonary bypass and cardiac surgical equipment at the ready should an emergency arise requiring open surgical intervention.

Guidelines from the European Society of Cardiology recommend performing TAVR procedures only at hospitals with cardiac surgery available on site. The situation in the United States is even more restrictive, limiting TAVR to a subset of cardiac surgical centers that meet particular operator- and institution-specific requirements.

In Germany, regulations requiring on-site cardiac surgical backup for TAVR have been relaxed as part of an effort to increase access to this procedure. As a prerequisite for performing TAVR, these hospitals were required to evaluate patients as part of a heart team with visiting cardiac surgical specialists from external, collaborating hospitals. The data from 2013-2014 have been

published, comparing transfemoral TAVR procedures at institutions with and without cardiac surgery.

Between the beginning of 2013 and the end of 2014, 17,919 patients in Germany underwent transfemoral TAVR. By 2014, 22 hospitals were performing this procedure without on-site surgical backup vs. 75 with surgery. Of these, 1,332 underwent TAVR at hospitals without on-site cardiac surgery.

One concern has been that performance of TAVR at non-cardiac surgery centers would lead to a detrimental change in patient selection. Patients undergoing TAVR at non-cardiac surgical hospitals were significantly older (82.1 vs. 81.1 years; $P < 0.001$), belonged to higher NYHA CHF class, and were more likely to present with a history of coronary disease, peripheral arterial disease, COPD, and neurologic events. As a result, patients undergoing TAVR at non-cardiac surgical hospitals had a higher calculated risk of surgical mortality according to both the GAV-score and the logistic EuroSCORE. Nearly 84% of patients underwent TAVR as elective procedures.

Procedure times were longer in hospitals without on-site cardiac surgery (110.3 ± 48.2 vs. 79.3 ± 44.8 min; $P < 0.001$), although fluoroscopy times were similar. Total procedural complications were lower in non-cardiac surgery centers (8.4% vs. 11%; $P = 0.004$), while catastrophic complications, including annular rupture, aortic dissection, and device embolization, were similarly rare (all < 1%) in both groups.

While the composite of complications that could potentially benefit from open cardiac surgery were similar between groups (3.4% vs. 3.9%), conversion to open sternotomy was less likely at non-cardiac surgical sites (0.3 vs. 0.7%). In-hospital mortality (3.8 vs. 4.2%; $P = 0.396$), myocardial infarction, stroke, and vascular complications were all similar between groups.

It is worth noting that, similar to prior reports, in-hospital mortality was very high for all patients requiring emergent cardiac surgery for TAVR complications (50% in non-cardiac surgery hospitals and 62.5% in hospitals with on-site surgery; $P = 0.694$).

The authors argued that serious complications from TAVR have declined markedly over time with increased experience and better devices, and that their data support the safety of performing this procedure at sites without on-site cardiac surgical backup.

## ■ COMMENTARY

It is remarkable to note that more than 1,300 TAVR procedures were performed in German hospitals without on-site cardiac surgery over the short period from 2013 to 2014. Figures for mortality and life-threatening complications were low and were similar when compared to centers with cardiac surgery. The authors claimed their data support the feasibility and safety of this approach. Does this mean expanding TAVR to non-cardiac surgical centers is a good idea?

To explore this further, let's look at the data closely. Compared to centers with cardiac surgery, those without had significantly lower institutional procedure volumes. This translated to longer procedure times, as well as higher rates of at-least-moderate aortic insufficiency and higher rates of permanent pacemakers, both of which can be affected by operator and institutional experience. Mortality did not significantly increase, and this is undoubtedly positive. Although the number of procedures analyzed here was substantial, it is likely not large enough to show a difference in low-frequency outcomes such as mortality and emergent cardiac surgery.

### OTHER CONCERNS

It should also concern clinicians that patient selection was significantly different at non-cardiac surgery centers, compared with the more experienced hospitals with both cardiology and cardiac surgery on site. Although this did not translate into a statistical difference in mortality, one could wonder whether the heart team model is consistently applied within this paradigm.

Although the rates of emergent cardiac surgery with TAVR have fallen to below 1%, and the odds of surviving such a complication — even in a center with on-site surgery — are low, it is difficult to discount the notion that small numbers of lives might be saved by the immediate availability of cardiac surgery.

I am not yet convinced that the issue of access to these mainly elective procedures is compelling enough to expand outside of established cardiac surgical centers. In the United States, we might expect steady expansion of TAVR procedures to more hospitals that currently offer cardiac surgery; however, the inclusion of hospitals without cardiac surgery on-site is most likely not on the immediate horizon. ■

PHARMACOLOGY UPDATE

# Buprenorphine Implant for Subdermal Administration (Probuphine)

***By William Elliott, MD, FACP, and James Chan, PharmD, PhD***

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**Drs. Elliott and Chan report no financial relationships relevant to this field of study.**

The FDA has approved the first buprenorphine implant for the treatment of opioid dependence. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine was previously approved as oral and sublingual tablets. The implant is marketed as Probuphine.

## INDICATIONS

Buprenorphine implant is indicated for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (< 8 mg/day).[1]

## DOSAGE

A trained professional inserts the buprenorphine implant subdermally in a patient's upper arm, leaving the implant there for six months before removal.[1] It should be used as part of a complete treatment program that includes counseling and psychosocial support. Each ethylene vinyl acetate implant (2.5 mm diameter x 26 mm length) contains 80 mg of buprenorphine HCl (74.2 mg of buprenorphine base).

## POTENTIAL ADVANTAGES

The implant provides a more convenient form of delivery with sustained medication for six months. This form of buprenorphine offers convenience and eliminates the risk of the patient forgetting to take the medication or someone stealing it, factors the FDA considered advantageous during the approval process.

## POTENTIAL DISADVANTAGES

The implant contains 80 mg of a drug that could be expelled or removed, resulting in accidental exposure or misuse.[1] Insertion and removal of the implants are associated with the risk of migration, protrusion, expulsion, and nerve damage from the procedure.[1] Most frequent adverse events were implant-site pain, pruritus, and erythema.[1]

## COMMENTS

The efficacy of the buprenorphine implant was demonstrated in one randomized, double-blind, double-dummy, six-month study in 178 subjects.[1] Study subjects met the DSM-IV-TR criteria for opioid dependency as a primary diagnosis and were clinically stable on sublingual buprenorphine at a dose of no more than 8 mg/day.[1]

Healthcare providers attested to the clinical stability based on a checklist that included no reports of illicit opioid use, no withdrawal symptoms, no hospital admissions or ED visits in the past 90 days, low to no desire to use illicit opioids, stable living and work environments, and compliance with clinical/behavior/cognitive visits.

Subjects were randomized to buprenorphine implants and placebo sublingual tablets or sublingual buprenorphine/naloxone and placebo implants. Supplemental dosing with sublingual buprenorphine/naloxone was allowed if clinically appropriate. Efficacy was based on four randomly scheduled urine toxicology screens and patients self-reporting to detect opioid use over the six-month period. Subjects in the buprenorphine arm who required supplemental buprenorphine were considered as non-responders.

The proportion of subjects with no evidence of illicit drug use was 63% for the implant and 64% for usual sublingual buprenorphine/naloxone. The implant appears to be less effective if the daily buprenorphine dose is > 8 mg. In two studies in subjects stabilized on 12-16 mg/day, the success rate for the implant was about 30% at weeks 17 to 24, which was similar to sublingual buprenorphine, in one study and 37% for the full 24 weeks in the second study.[2,3]

## CLINICAL IMPLICATIONS

Buprenorphine (with or without naltrexone) and methadone are approved and effective drugs for management of opioid dependence.[4,5] Buprenor-

phine, in contrast to methadone, can be prescribed in an office-based setting as opposed to a federally authorized opioid treatment clinic.[6,7] The implant provides another option for those who have been stabilized on low-to-moderate doses of sublingual buprenorphine.

The implant is only available to certified healthcare providers through the PROBUPHINE REMS Program. Prescribers and providers who plan to insert or remove the implants must successfully complete a live training program. Cost was not available at the time of this review. ■

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STROKE ALERT

# Cerebral Microbleeds: Risk Factor for Symptomatic Intracerebral Hemorrhage


***By Matthew E. Fink, MD***

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

SOURCE: Tsivgoulis G, Zand R, Katsanos AH, et al. Risk of symptomatic intracerebral hemorrhage after intravenous thrombolysis in patients with acute ischemic stroke and high cerebral microbleed burden. A meta-analysis. *JAMA Neurol* 2016;73:675-683.

Cerebral microbleeds (CMBs), as visualized on gradient-echo or susceptibility-weighted MRI, are considered markers of bleeding-prone cerebral microvessels and constitute a significant and independent predictor of future intracerebral hemorrhage. However, the risk of these abnormalities in patients undergoing thrombolysis is uncertain, and observational studies have shown conflicting results. The authors undertook a literature review and meta-analysis to investigate the association of a high cerebral microbleed burden (> 10 CMBs on pre-IV thrombolysis MRI) and the risk of symptomatic intracranial hemorrhage following thrombolysis for acute ischemic stroke. Symptomatic hemorrhage was defined as any intracranial bleed with neurological worsening ≥ 4 points on the NIH stroke scale score. After a comprehensive literature review, nine studies were identified comprising 2,479 patients with acute ischemic stroke. The risk of symptomatic intracranial hemorrhage after thrombolysis was found to be higher in patients who had CMBs compared to patients without CMBs (risk ratio = 2.36). A higher risk for hemorrhage was detected in patients with a high CMB burden (> 10 CMBs) when compared with patients who had 0 to 10 CMBs (risk ratio = 12.10). The presence of cerebral microbleeds and a high CMB burden on pretreatment MRI were independently associated with symptomatic intracranial hemorrhage in patients treated for acute ischemic stroke with thrombolysis. CMB burden should be included as part of the individual risk stratification formula for patients when the decision is being made to administer IV thrombolysis. ■

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## CME QUESTIONS

**1. In the prospective cohort study by Self and colleagues, the addition of a procalcitonin level in patients with community-acquired pneumonia was shown to:**

a. Have no effect on risk stratification for predicting need for ICU admission when combined with other clinical severity scores

b. Correlate with the need for invasive respiratory support or vasopressors

c. Predict the need for antibiotics

d. Correlate with the need for renal replacement therapy

**2. In the case series from Kendal Scott, et al., the incidence of pneumonia in patients with human adenovirus B7 (HAdV-B7) was:**

a. 5%

b. 26%

c. 41%

d. 75%

**3. In the meta-analysis performed by Ge and collaborators, dual antiplatelet therapy after minor ischemic stroke or TIA was most clinically efficacious with regards to benefit-harm ratio for:**

a. No period of time; dual anti-platelet therapy did not provide additional benefit over aspirin alone in this setting

b. Short-term, up to 90 days

c. Medium-term, up to 180 days

d. Long-term, up to 1 year

## 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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