MISSOURI HOSPITALIST SOCIETY

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Photos: Eagle Bluffs Conservation Area

# MISSOURI HOSPITALIST

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## Hospitalist Update

### New Guidance on Concomitant Use of PPIs and Clopidogrel

Rochelle Parker MD

Over the past year, confusion has ensued as to whether patients who take clopidogrel should also take PPIs. The potential benefits of antiplatelet therapy for patients with CV disease have been amply demonstrated, especially among patients at higher risk for CV events. However, antiplatelet drugs such as clopidogrel increase the risk for upper GI bleeding from pre-existing ulcers and other breaks in the GI tract. Because PPIs suppress gastric acid production, they are often used in concert with antiplatelet drugs in an effort to reduce the risk of GI bleeding. Research published over the last year has suggested an adverse interaction between these drugs that may lessen the antiplatelet effects of clopidogrel and thereby place patients at an increased risk of CV events. The recent publication of a randomized trial (COGENT) of 3761 patients with CV disease who were treated with clopidogrel demonstrated a 56% decrease in GI bleeding in those receiving a PPI compared to those who did not. There is now a published consensus document from three national medical associations supporting the concomitant use of clopidogrel and a PPI in patients with CV disease who are also at high risk of an upper GI bleed; the recommendations from the American College of Cardiology Foundation, the American College of Gastroenterology and the American Heart Association are:

A. Use of PPIs is recommended for patients with a history of upper GI bleeding or for those with multiple risk factors for GI bleeding

B. PPIs are not recommended to reduce upper GI bleeding in patients who have a low risk of upper GI bleeding and who have much less potential to benefit from such prophylactic therapy

C. Future studies are required to assess the impact of concomitant PPI and antiplatelet therapy among the small subset of high-risk CV patients with an impaired ability to metabolize antiplatelet drugs

D. Decisions regarding the combined use of PPIs and antiplatelet drugs (cont)

(cont) must be individualized and not made as a matter of routine.

**DISCUSSION:** Thienopyridine therapy (which includes clopidogrel) as been evaluated as an alternative to or an additive to aspirin therapy (dual antiplatelet therapy) for CV events. The absolute risk reduction from clopidogrel is greater in patients with a higher CV risk, particularly in those with acute coronary syndrome or in those who have had a coronary stent placed.

In patients with ACS without ST segment elevation, dual antiplatelet therapy with clopidogrel and aspirin reduced the risk of cardiac death, MI or stroke from 11.4% to 9.3% compared to aspirin treatment alone; this finding was irrespective of whether patients were revascularized or treated medically but the addition of clopidogrel increased major bleeding from 2.7% to 3.7%. In patients with ST segment elevation MI treated with fibrinolytics, the addition of clopidogrel to aspirin reduced major CV events over 30 days from 10.9% to 9.1% but increased major bleeding complications from 1.7% to 1.9%.

Dual antiplatelet therapy reduces stent thrombosis following percutaneous coronary intervention (PCI); those who receive bare metal stents should be on clopidogrel for at least 1 month while those who receive drug eluting stents are recommended to stay on dual antiplatelet therapy for at least 12 months. For patients with chronic atrial fibrillation who are unable to take vitamin K antagonists, adding clopidogrel to ASA therapy was found to reduce the rate of major vascular events from 7.6% to 6.8% and stroke from 3.3% to 2.4% but was associated with an increased risk of bleeding (2% per year).

Several risk factors for GI bleeding in the setting of antiplatelet therapy have been consistently reported. A history of bleeding or other complications from peptic ulcer disease is the strongest risk factor for upper GI bleeding; advanced age also significantly increases the absolute risk of upper GI bleeding. The use of anticoagulants, steroids or NSAIDs has been associated with GI bleeding, as has the presence of H. pylori infection. The relative risk of GI bleeding increases in concert with the number of adverse risk factors that are present in any given individual. There is limited data on the mortality attributable to GI bleeding in patients on clopidogrel alone or in combination with aspirin but the relative risk for death from a GI bleed has been estimated at 2.5 and GI bleeding appears to be a significant predictor of death, even after adjustment for CV morbidity, age, sex, diabetes, PCI status and concomitant therapy.

Strategies to prevent clopidogrel related upper GI bleeding have included histamine (H2) receptor antagonists and PPIs. In a randomized trial of 404 patients with peptic ulcer disease or esophagitis who were taking aspirin, fewer GI ulcers developed over 12 weeks in those assigned to Pepcid therapy compared to placebo; however, in other studies, H2 blockers did not significantly protect those on clopidogrel therapy. In a cohort of 987 patients who were prescribed clopidogrel and aspirin, PPI use was associated with a greater reduction in GI bleeding than use of H2 blockers.

Clopidogrel is a pro-drug, converted in-vivo to an active metabolite that irreversibly binds to the platelet adenosine diphosphate P2Y12 receptor, thereby inhibiting platelet aggregation. Clopidogrel requires hepatic cytochrome P450 metabolic activation to produce the active metabolite. Atorvastatin, omeprazole and several other drugs have been shown to competitively inhibit CYP activation of clopidogrel; to date, however, there is no consistent evidence that these drug interactions impact adverse cardiovascular events and they should not be withheld in patients for whom they have a strong indication. The concomitant use of PPIs may competitively inhibit activation of clopidogrel by CYP2C19, thereby attenuating its antiplatelet effect; coadministration of other CYP2C19 inhibitors may further reduce the efficacy of clopidogrel. Head to head comparison of the various PPIs has not demonstrated any significant difference in their effect on clopidogrel activity and the addition of a PPI to clopidogrel therapy has not been shown to have a consistent impact on the risk for CV events. Since the plasma half-lives of clopidogrel and all available PPIs are less than 2 hours, interactions between these drugs might be minimized by separating the time of their administration, even among poor CYP2C19 metabolizers.

All prescription medications have favorable and unfavorable effects and treatment decisions must be based on whether the potential benefit outweighs the potential for harm. The CV benefits of antiplatelet drugs are over-whelmingly documented, especially for those with ACS or those who undergo PCI. Since their use is also clearly associated with an increased risk of GI bleeding, the challenge for healthcare providers is to determine which patients are more likely to benefit from the addition of PPI therapy despite its potential effect on the activity of clopidogel. Hence the updated, consensus recommendations outlined above.

**REFERENCES:**

Abraham et al., ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update of Expert Consensus on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use, J Am College of Cardiology 2010; 56, No 24, 2051-2066

Bates et al., Clopidogrel-Drug Interactions, State of the Art Paper, J Am College of Cardiology 2011; Vol 57, No 11, March 15, 2011

**CASE REPORT**

VIKESH GUPTA MD, SHIKHA GUPTA MBBS
RAJIV DHAND MD, RAJA GOPALDAS MD

## UNUSUAL CAUSE OF RECURRENT PNEUMONIA

A 24 year old male presented with a 2 week history of cough, high fever and right– sided pleuritic chest pain; the pain radiated to the right clavicle and right arm. He noted associated wheezing and streaky hemoptysis. Treatment of his symptoms had been initiated with oral Levaquin with limited improvement.

The patient reported a history of recurrent pneumonia in his right lung over a period of 3 years. Other PMH was unremarkable with no history of DM, hypertension or TB. His only medication was the prn use of albuterol. The patient smoked cigarettes for 3 years but quit 1 year ago; he denied alcohol or illicit drug use. There was no family history of lung disease or lung cancer.

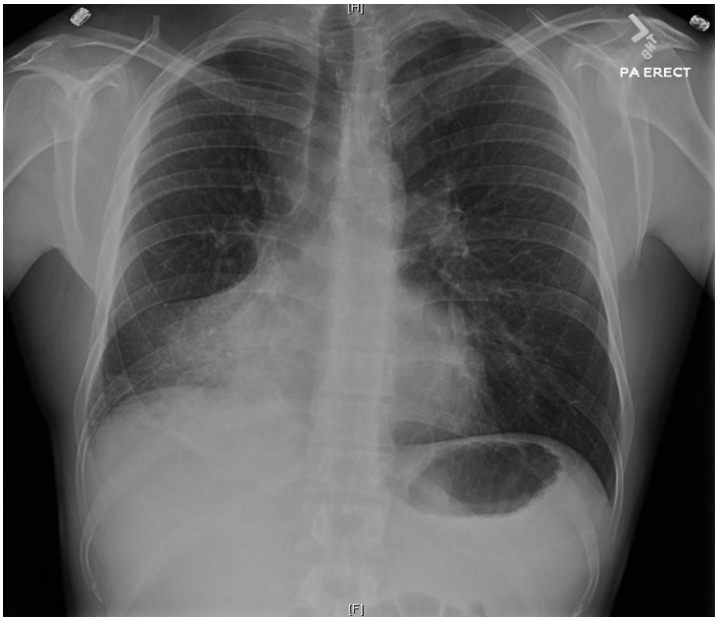
Exam on presentation was remarkable for T 36C, BP 114/77, P 67. He was alert and in no distress. HEENT was entirely normal with no cervical adenopathy. Chest exam was normal except for diminished breath sounds in the right lower lung. Cardiovascular, abdominal and neuromuscular examinations were entirely normal.

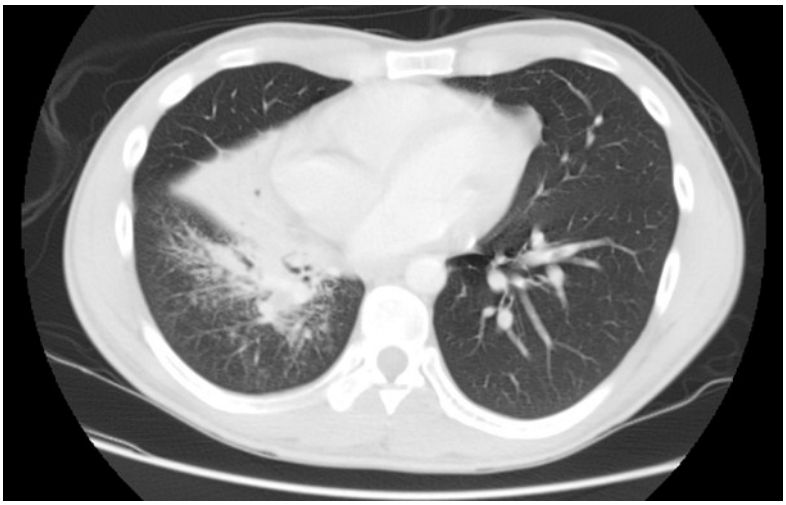
His CBC, CMP and EKG were normal; spirometry did not reveal any obstructive or restrictive defects.

A CXR demonstrated collapse of the right middle lobe and a CT of the chest confirmed the RML collapse and revealed the presence of an obstructing lesion in the right bronchus intermedius (**images on next page**).

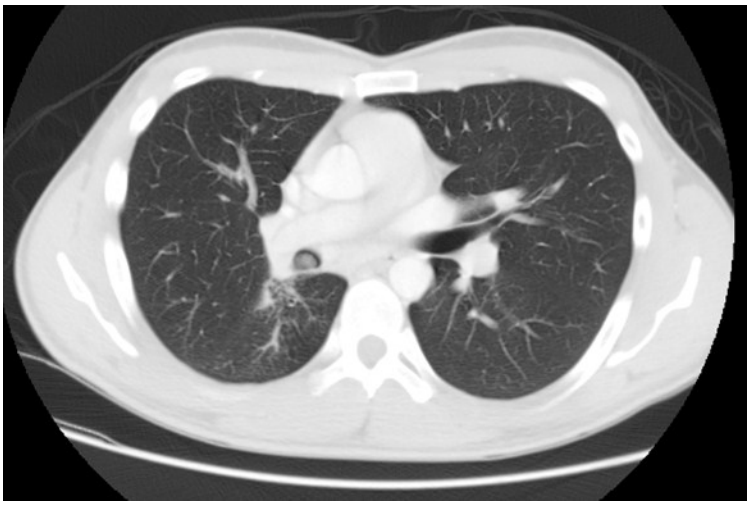
A bronchoscopy was performed and an endobronchial biopsy was obtained; this revealed features typical of carcinoid. Staging with a PET/CT and octreotide scan was negative for metastases. Cardiothoracic Surgery was thus consulted; they performed a right middle lobectomy with a sleeve resection and reconstruction of the right bronchus intermedius.

**Pre-operative CXR shows RML collapse**



**Diagnostic CT Images show RML collapse and an obstructing lesion in right bronchus intermedius**

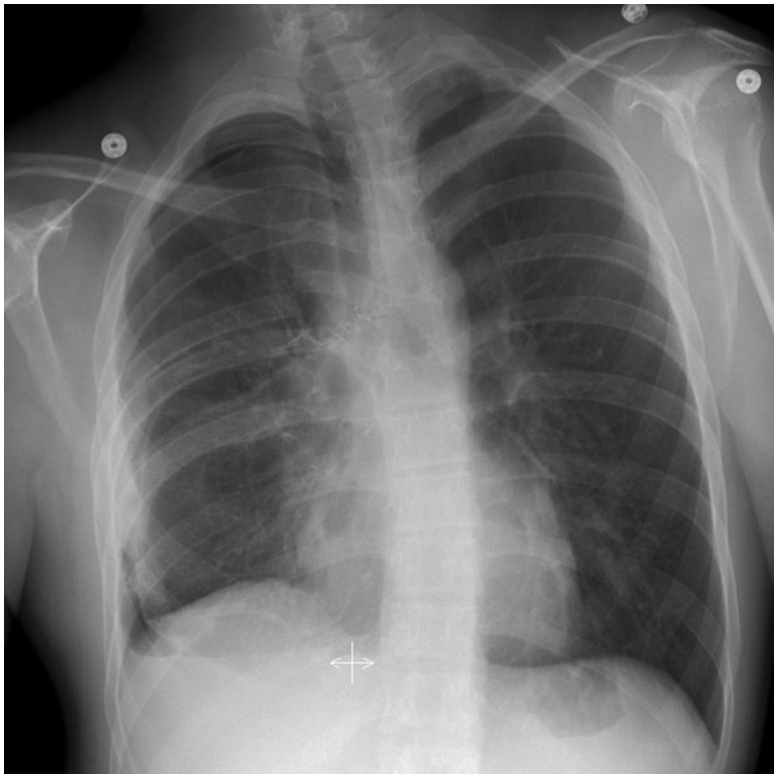


**DISCUSSION:**

Recurrent pneumonia at the same location raises the suspicion of an endobronchial obstruction by a tumor (benign or malignant) or a foreign body. Bronchial carcinoid tumors are a rare group of pulmonary tumors characterized by neuroendocrine differentiation. Most are benign and slow growing but some are malignant and may metastasize.

The clinical presentation is variable and may include cough, hemoptysis, local wheezing, dyspnea and episodes of recurrent pneumonia at the same site. Diagnosis is via a Chest CT and bronchoscopic biopsy. Staging should include a PET/CT and an octreotide scan, as was performed in this case. Surgical resection is the treatment of choice for localized lesions and an effort is made to preserve as much functional lung tissue as possible. Due to the potential for malignant transformation, long term followup is advised.

**POST SURGICAL CXR**



## FROM THE JOURNALS

WILLIAM STEINMANN MD

**Health care system delay and heart failure in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: Follow-up of population-based medical registry data**

Terkleson, JT et al., Ann Int Med 2011; 155:361-367

In patients with a STEMI, delay between contact with a health care system and initiation of reperfusion therapy (a system delay) is associated with increased mortality but data on the associated risk of CHF among survivors is limited. This historical follow-up study used a population based medical registry to assess the risk for CHF admissions or related outpatient visits in patients treated with PTCI within 12 hours of symptom onset and who had a system delay of 6 hours or less. System delays of 60 minutes or less had a long term risk of readmission for or outpatient management for CHF of 10.1% compared to 14.1% for those with delays of 181-360 minutes. The results add further evidence of the benefit of early PTCI in patients with a STEMI. Associated costs were not assessed but likely were markedly increased and deserve further study.

**Off-label use of recombinant factor VIIa in US Hospitals: Analysis of hospital records**

Logan, AC et al., Ann Int Med 2011; 154:516-522

Recombinant factor VIIa is approved for the treatment of bleeding in patients who have hemophilia with inhibitors but has been applied to a wide range of off-label indications. This retrospective data base analysis reviewed 12,644 hospitalizations for patients who received factor VIIa to determine reasons for use of this product.

From 2000-2008, off-label use of factor VIIa in academic and non-academic hospitals increased more than 140 fold. Adult and pediatric cardiovascular surgery, body and brain trauma and intracranial hemorrhage were the most common indications for its use. In conclusion, off-label use of factor VIIa in the hospital setting far exceeds its use for approved indications. This pattern raises concern about the use of factor VIIa in conditions for which strong supporting evidence is lacking.

**Interventions to reduce 30-day re-hospitalization. A systemic review**

Hansen, LO, Ann Int Med 2011; 155:521-528

About one in five Medicare fee-for-service patients discharged from the hospital is re-hospitalized within 30 days. Beginning in 2013, hospitals with high-risk standardized readmission rates will be subject to a Medicare reimbursement penalty. This study reviewed the literature to evaluate studies aimed at reducing re-hospitalization within 30 days of discharge. Forty-three articles covered 12 distinct interventions; pre-discharge interventions included patient education, medication reconciliation, discharge planning and pre-discharge scheduling of followup visits while post-discharge interventions included followup phone calls, patient activated hotlines, direct communication with the ambulatory provider, ambulatory provider followup and post-discharge home visits. Bridging interventions included transition coaches, provider continuity across the inpatient and outpatient settings and patient-centered discharge instruction. This comprehensive literature review points to the lack of information to support definitive action plans and concluded that no single intervention alone was regularly associated with a reduced risk for 30 day re-hospitalization.

**Synopsis of the National Institute for Health and Clinical Excellence Guidelines on management of transient loss of consciousness**

Cooper, PN et al., Ann Int Med 2011; 155: 543-549

Transient loss of consciousness is common and often leads to an incorrect diagnosis, unnecessary investigation or inappropriate subspecialist referral. In August, 2010, the National Institute of Health and Clinical Excellence published guidelines that addressed the initial assessment and the most appropriate specialist referral for persons who have experienced transient loss of consciousness. The Synopsis describes the principal recommendations concerning these issues.

The recommendations include:

Persons with uncomplicated faint, situational syncope or orthostatic hypotension should receive electro-cardiography but do not otherwise require immediate additional investigation or specialist referral.

Persons with features that suggest epilepsy should be referred to a Neurologist for further evaluation.

Brief seizure-like activity is often associated with syncope from any cause and should not be accepted as a sign of epilepsy.

Persons with a suspected cardiac cause for their transient loss of consciousness or persons for whom a cause cannot be determined after an appropriate initial assessment should be referred to a Cardiologist for additional evaluation.

This article deserves a full read since the subject is complicated and decision-making in the course of its workup is often challenging for the clinician.

## ID CORNER

WILLIAM SALZER MD

INFECTIVE ENDOCARDITIS—DIAGNOSIS, TREATMENT AND MANAGEMENT OF COMPLICATIONS

These Guidelines are not new but I have found them to be very useful in the management of patients with infective endocarditis and refer to them often as an Infectious Disease consultant.

Baddour, LM et al., Infective Endocarditis—Diagnosis, Antimicrobial Therapy and Management of Complications, AHA Scientific Statement, Circulation 2005; III:e394-e433

http://circ.ahajournals.org/cgi/reprint/111/23/e394?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&searchid=1129901552991_5861&stored_search=&FIRSTINDEX=0&minscore=5000&search_url=http%3A%2F%2Fcirc.ahajournals.org%2Fcgi%2Fsearch&journalcode=circulationaha

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## MISSOURI HOSPITALIST CALENDAR

**Sleep Medicine 2012**, January 26-29, Phoenix; register via www.chestnet.org

**41st Annual Critical Care Congress**, Society of Critical Care Medicine, February 4-8, Houston; register via www.sccm.org

**Fundamentals of Mechanical Ventilation for Providers**, February 23, Northbrook, Illinois; register via www.chestnet.org

**Hospital Medicine 2012**, Society of Hospital Medicine, April 1-4, San Diego Convention Center; register via www.hospitalmedicine.org

**American Geriatrics Society Annual Meeting**, May 2-5, Seattle, Washington; register via www.americangeriatrics.org

Please direct all comments, ideas and newsletter contributions to the Editor:

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**Please forward this newsletter to Hospitalists that you might know!**