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INSIDE

The Efficient Diagnosis of Tuberculosis

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

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Dr. Deresinski serves on the speaker's bureau for Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. This article originally appeared in the July 2007 issue of Infectious Disease Alert. *It was peer reviewed by Connie Price, MD. Dr. Price is Assistant Professor, University of Colorado School of Medicine. She reports no financial relationships relevant to this field of study.*

Synopsis: *In patients with suspected pulmonary tuberculosis who are unable to expectorate sputum, culture of 3 induced sputum samples, all collected on the same day, is an effective and efficient means of diagnosis.*

Source: Brown M, et al. Prospective study of sputum induction, gastric washing, and bronchoalveolar lavage for the diagnosis of pulmonary tuberculosis in patients who are unable to expectorate. *Clin Infect Dis* 2007; 44:1415-1420.

BROWN AND COLLEAGUES EVALUATED THE MOST EFFICIENT means of microbiological diagnosis of tuberculosis in patients. Adults in whom the presence of pulmonary tuberculosis was suspected, based on the presence of compatible abnormalities on chest X-ray, who were unable to produce an expectorated sputum sample, were evaluated in order to determine the relative value of specimens obtained by sputum induction, gastric washing, and bronchoalveolar lavage (BAL). Also studied was the relative value of sputum induction on 3 consecutive days as opposed to obtaining all 3 samples on the same day, approximately 4 hours apart.

Three induced sputum specimens were obtained on a single day, followed by additional morning samples on 2 subsequent days. Analysis of the 79 patients from whom all 5 samples were obtained found that at least one of the 3 specimens collected on a single day were positive in 27 (34%) patients compared to a positive result in 29 (37%; P = 0.63) patients, in at least one of

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the 3 daily induced sputum specimens. There was no correlation between the volume of sputum obtained for testing and the results.

Twenty-one patients whose smears were negative underwent bronchoscopy, and BAL cultures proved to be positive in 5 (24%) — but all 5 had positive day-one induced sputum cultures. In addition, 2 individuals with positive day-one induced sputum samples had negative BAL cultures.

At least 3 induced sputum specimens and 3 gastric washing specimens were available for 107 of the 140 patients enrolled; *Mycobacterium tuberculosis* was recovered in cultures from one or more cultures obtained from 46 (43%) of the 107. At least one of the first 3 induced sputum samples obtained were culture positive in 42 (39%) patients compared to gastric washings from 32 (30%; $P = 0.03$) patients.

COMMENTARY

This is a valuable study from which a number of conclusions regarding the diagnosis of pulmonary tuberculosis in patients unable to provide an expectorated sputum sample can be drawn:

- Culture of 3 induced sputum samples was more sensitive than culture of 3 gastric washings;
- Culture of BAL specimens did not contribute to the diagnosis obtained from the induced sputum samples;
- Collecting induced sputum samples on consecutive days was not superior to obtaining all 3 specimens on a single day.

These results have practical implications for the diagnostic management of patients with suspected pulmonary tuberculosis. The referral center in the United Kingdom where this study was performed has, in fact, altered their procedures as a consequence of these results. In patients unable to expectorate sputum, they no longer perform gastric washings, and instead, obtained 3 induced sputum specimens — all on the same day. Bronchoscopy is performed only in limited circumstances. Thus, in most cases, their entire evaluation is performed in one day. ■

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Emergency Colectomy for Fulminant *C. Difficile* Colitis

ABSTRACT & COMMENTARY

By David J. Pierson, MD
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Dr. Pierson reports no financial relationships relevant to this field of study. This article originally appeared in the July 2007 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. Dr. Thompson reports no financial relationships relevant to this field of study.*

Synopsis: *In this retrospective study of* C. difficile *colitis due to a hypervirulent strain, 53% of 165 patients died. Emergency colectomy was associated with a decreased mortality, especially among very elderly patients, those who were immunosuppressed, those with extreme leukocytosis, those with moderate hyperlactatemia, and those requiring vasopressors.*

Source: Lamontagne F, et al. Impact of emergency colectomy on survival of patients with fulminant *Clostridium difficile* colitis during an epidemic caused by a hypervirulent strain. *Ann Surg*. 2007;245:267-272.

USING LABORATORY RESULTS FROM A RECENT 30-month period for case finding, Lamontagne and colleagues reviewed the medical records of all patients with fulminant *Clostridium difficile*-associated disease (CDAD) who received care in the ICUs of 2 tertiary-care hospitals in Quebec. During the period of this study, Quebec was experiencing an outbreak of a particularly virulent strain of *C. difficile* (hypervirulent toxin type III NAP1/027), which produces levels of toxins A and B that are 16 to 23 times higher than historical strains. Fulminating CDAD was defined as one or more of a positive *C. difficile* cytotoxin assay, endoscopic evi-

dence of pseudomembranous colitis, or histopathologic evidence of pseudomembranous colitis from biopsy, colectomy specimen, or autopsy. All patients who were admitted to the ICU because of the CDAD, or developed it while in the ICU, were included.

Lamontagne et al identified 165 cases of CDAD (in 161 patients) during the study period. Twenty-four percent were healthcare-associated. The patients' ages ranged from 39 to 93 years (median, 75 years). Thirty percent of them were immunosuppressed (leukemia, lymphoma, organ transplantation, neutropenia, and/or > 1 month treatment with corticosteroids). In addition to diarrhea, manifestations of CDAD included abnormal plain abdominal films in 64% of 149 patients, signs of colitis in 78% of 85 abdominal CT scans, and pseudomembranes in 87% of 38 patients who underwent endoscopy. Median peak leukocyte count was 30.9 x 109 cells/L (interquartile range, 20.8-44.1 x 109 cells/L). Serum lactate levels ranged between 0.7 and 23.0 mmol/L (median, 3.1 mmol/L; IQR 2.1-5.6 mmol/L).

Thirty-eight patients (23%) underwent colectomy, which was subtotal or total in 35. Listed indications for colectomy were persistent vasopressor-requiring shock (15 patients), megacolon (11 patients), lack of response to medical treatment (10 patients), and perforation (2 patients). Compared to the patients who did not undergo colectomy, those who did had fewer comorbidities (assessed by Charlson score), higher leukocyte counts (20 x 109 cells/L in 95% vs 73%), and more frequent shock requiring vasopressors (71% vs 52%).

Mortality ascribed to CDAD within 30 days of ICU admission was 87/165 (53%). Thirty-eight (43%) of those deaths occurred within 48 hours of ICU admission. Among the entire cohort, by multivariate analysis, death was more likely to occur in patients aged 75 years or older, who were immunosuppressed, those requiring vasopressors, those in whom peak leukocyte count exceeded 50 x 109 cells/L, and those with lactate levels of 5 mmol/L or higher (all, $P < 0.05$). Mortality among the patients who underwent colectomy was 34%, compared with 58% in patients treated medically ($P = 0.02$). Subgroup analysis suggested that patients most likely to benefit from emergency colectomy were those older than 65, those with leukocyte counts > 20 x 109 cells/L, and those with moderate elevations of serum lactate (2.2-4.9 mmol/L).

COMMENTARY

C difficile, which was identified as the causative agent in pseudomembranous colitis in 1978, has emerged as a pathogen of increasing importance in critical care. The incidence of CDAD appears to be on the rise everywhere, and more and more areas are reporting the emergence of hypervirulent strains associated with increased morbidity and mortality. When patients develop very high leukocyte counts in the ICU — especially exceeding 25 or 30 x 109 cells/L — CDAD should be considered, even if they have not been on multiple or broad-spectrum antibiotics.

This retrospective study highlights the frequency and potential lethality of CDAD, and it suggests that emergency colectomy can be life-saving. However, because of its design, it cannot establish the latter with certainty, nor tell us for sure how to select patients for this procedure. For example, surgeons may have selected patients more likely to survive for colectomy and been reluctant to operate on those with immunosuppression or more comorbidities, influencing the observed mortality differences in those groups. Lamontagne et al acknowledge these and other limitations. In spite of these, however, this study calls needed attention to the seriousness of CDAD today, particularly in the presence of hypervirulent toxin production, and to emergency colectomy as a potentially life-saving procedure. ■

Prophylactic Revascularization Before Vascular Surgery

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco

Dr. Crawford is on the speaker's bureau for Pfizer. This article originally appeared in the July 2007 issue of Clinical Cardiology Alert. *It was edited by Dr. Crawford, and peer reviewed by Rakesh Mishra, MD, FACC. Dr. Mishra is Assistant Professor of Medicine, Weill Medical College, Cornell University; Assistant Attending Physician, NewYork-Presbyterian Hospital.*

Synopsis: *In this randomized pilot study, preoperative coronary revascularization in high-risk patients was not associated with an improved outcome.*

Source: Poldermans D, et al. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery. *J Am Coll Cardiol*. 2007;49:1763-1769.

THE VALUE OF REVASCULARIZATION BEFORE major vascular surgery in patients with stress-

induced myocardial ischemia has not been tested. Thus, the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) study was conducted in 5 European hospitals and one Brazilian hospital. Among 1880 patients undergoing elective abdominal aorta or infrainguinal vascular surgery, 430 with 3 or more risk factors for coronary artery disease underwent dobutamine echo or dypridamole perfusion scintigraphy. The major inclusion criteria was extensive stress-induced ischemia, which was present in 101 of the 430 patients. They were randomized to medical or revascularization therapy prior to surgery. All patients received perioperative beta-blockers at a dose to keep the resting heart rate between 50 and 65 beats/minute, as long as systolic blood pressure was > 100 mm Hg. Antiplatelet therapy was continued during vascular surgery. The primary end point was the composite of all-cause death and myocardial infarction (MI) until 30 days post surgery. The one-year death and MI rate was a secondary end point.

Results: Two patients died between coronary artery bypass surgery (CABG) and vascular surgery of a ruptured aortic aneurysm. The primary end point was 43% in the revascularization group and 33% in the medical therapy group (OR 1.4, 95% CI 0.7-2.8, $P = 0.3$). Also, the primary end point was not different between those treated with CABG (performed in one-third) or percutaneous coronary revascularization (41% vs 44% during the 1-year follow-up). Poldermans and colleauges concluded that perioperative coronary revascularization in vascular surgery patients with extensive stress-induced myocardial ischemia did not improve post operative or 1-year outcome.

COMMENTARY

The publication of the Goldman Index in the 1970s lead to an industry of preoperative testing for patients with CAD, or those likely to have it based upon risk factors, to detect those with myocardial ischemia who were at highest risk of a perioperative coronary event. But detection-implied treatment was necessary, which spawned such absurdities as doing CABG so someone could have their gallbladder out. Then came perioperative beta-blocker therapy, which demonstrated that many patients considered at risk would do well on such therapy. The Coronary Artery Revascularization Prophylaxis (CARP) trial showed that preoperative revascularization of stable CAD patients did not improve the outcome of major vascular surgery. However, there was a trend in CARP that favored revascularization for very high-risk patients. This hypothesis was tested in the current trial, where only those with extensive stress-induced myocardial ischemia were randomized to revascularization or medical therapy alone. Although the trial was small (101 patients), the results were not encouraging that a larger study would demonstrate the value of revascularization. Thus, it will not likely be done.

The question now is where does this leave preoperative testing? If revascularization does not make a difference, why look for ischemia? These studies did exclude those with significant left main stenosis, but we cannot justify cardiac catheterization in all stable patients for that reason. The only reason to delay surgery for cardiac catheterization would be for the unstable cardiac patient; those with unstable angina, resting ischemia, and stress tests done for symptoms that show high-risk features. Cardiac catheterization in stable or asymptomatic patients — whatever their risk profile — would seem unjustified.

Another interesting feature of this trial is that delaying surgery for cardiac revascularization lead to death from ruptured aneurysms in 2 patients (4%). So the urgency of the surgical situation needs to be considered. Also, aspirin and clopidogrel were not stopped for vascular surgery after coronary stenting, and there was no difference between those on these drugs and those not in bleeding complications. We have to ask our surgeons to rise to the occasion as they do in Europe and Brazil. Almost half the patients in this study had significantly reduced left ventricular ejection fraction. Although this is a legitimate indication for cardiac catheterization if ischemic heart disease is the suspected cause, this study would suggest that this does not have to be done before vascular surgery if the patient is stable. For those interested, the implications of this study are consistent with the ACC/AHA Guidelines. So, experienced clinicians knew these things before this study was done. ■

Are Statin-Induced Myopathic Symptoms Helped by CoQ10?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD

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Dr. Karpman reports no financial relationship to this field of study.

This article originally appeared in the July 15, 2007 issue of Internal Medicine Alert. *It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Clinical Professor, University of California, Irvine, and Dr. Roberts is Clinical Professor of Medicine, Albert Einstein College of Medicine. Dr. Brunton is a consultant for Sanofi-Aventis, Ortho-McNeil, McNeil, Abbott, Novo Nordisk, Eli Lilly, Endo, EXACT Sciences, and AstraZeneca, and serves on the speaker's bureau for McNeil, Sanofi-Aventis, and Ortho-McNeil. Dr. Roberts reports no financial relationship relevant to this field of study.*

Synopsis: *Statin-treated patients who developed symptoms of myopathy should be treated with at least 100 mg daily of coenzyme Q10 for a minimum of 30 days (assuming CPK values and/or other liver function tests are not abnormal) before discontinuing statin therapy.*

Source: Caso G, et al. Effect of coenzyme q10 on myopathic symptoms in patients treated with statins. *Am J Cardiol*. 2007;99:1409-1412.

THE MOST COMMONLY USED METHOD FOR DECREASing cholesterol production is by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) using statin drugs which have proven to be extraordinarily effective and safe[1-3] and, in addition, outcome studies have clearly demonstrated their incredible effectiveness in both the primary and secondary prevention of myocardial infarctions and strokes.[4] Since the biosynthetic pathway inhibited by statin drugs is shared by ubiquinone (coenzyme Q10), this vital component of the mitochondrial electron transport system[5] is usually significantly reduced in patients receiving statin therapy,[9-13] thereby affecting oxidative phosphorylation and mitochondrial adenosine triphosphate (ATP) production, which may result in impaired muscle energy metabolism and contribute to the development of myopathy and muscle symptoms.[6,7]

Recognizing that the clinical studies determining whether or not coenzyme Q10 supplementation would improve muscle symptoms in patients receiving statin therapy had not been previously performed, Caso and colleagues studied 32 patients before and after treatment with coenzyme Q10 or vitamin E (control group) for one month.[8] Myopathic symptoms were defined as the development of muscle pain alone or accompanied by other symptoms, such as muscle weakness and/or fatigue. In a double-blinded protocol, patients who had been treated with statins and who developed myopathic symptoms were randomly treated with either 100 mg per day of coenzyme Q10 or 400 IU of vitamin E orally. After coenzyme Q10 treatment for 30 days, pain severity decreased by 40%, and interference with daily activities, because of the pain, decreased by 38%, whereas no change in pain severity or interference with daily activities due to pain was noted to occur in the control group which had been treated with vitamin E.

COMMENTARY

Only a small fraction of the millions of people in the United States who have been treated with statin drugs have developed severe myopathy which, in the worst cases, can lead to severe myoglobinuria, acute renal failure, and even death; in fact, this complication, although occurring in only a small numbers of patients, was also associated with a small number of deaths, which led to the relatively recent withdrawal of cerivastatin from the US markets. Toxic myopathy occurs in only approximate 0.1% of statin users and, fortunately, the myopathy usually resolves when statin therapy is discontinued. In a small published study, patients could accurately identify blinded statin therapy by carefully assessing their functional capacity and muscle strength.[7] Most physicians have characteristically reassured their patients that their muscular aches and pains were most likely not due to statin therapy (especially if serum CPK determinations proved to be normal); however, it should now be recognized that the Caso study[8] results suggest that deficiency of coenzyme Q10 resulting from statin therapy may be contributing to, or even causing, the myopathic symptoms. Their study was an extremely small one, utilizing a total of only 32 patients, but the results reached statistical significance and, therefore, their conclusions should be carefully considered.

In summary, it is important to recognize that the vast majority of patients who report muscular symptoms while on statin therapy do not have chronic or subacute myopathy and, therefore, statin therapy should, in most cases, not be discontinued unless the CPK becomes elevated (although CPK elevation has not been clearly demonstrated to be a sensitive marker to detect or assess statin-related myopathies). Even

though the results of the study were so impressive, it must be recognized that it was an extremely small clinical study which will hopefully lead to a larger, double-blinded, well controlled study. However, for the time being, the proven efficacy of statin therapy for primary and secondary prevention of cardiovascular disease, especially in high-risk cardiac patients mandates that statins should not be discontinued in patients complaining of muscular aches and pains but rather, it would now appear to be appropriate to consider treating these patients with at least 100 mg of coenzyme Q10 daily for at least 30 days assuming that their CPK enzyme values and/or liver function tests do not become significantly abnormal. Of course, many physicians will already have elected to prescribe coenzyme Q10 prophylactically when prescribing statin drugs in order to hopefully avoid the development of myopathic symptoms but, for those statin-treated patients not already receiving coenzyme Q10, 100 mg of coenzyme Q10 daily for at least 30 days should be considered as a therapeutic option before the statin drug is discontinued in the patient who presents with new onset of myopathic symptoms and who does not have a significant increase in CPK values or liver function tests. ■

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Major Hemorrhage on Warfarin in Elderly Patients

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant.

This article originally appeared in the July 2007 issue of Clinical Cardiology Alert. It was edited by Michael Crawford, MD, and peer reviewed by Rakesh Mishra, MD.

Synopsis: *Stroke prevention among elderly patients with atrial fibrillation remains a challenging and pressing health concern.*

Source: Hylek EM, et al. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation. 2007;115: 2689-2696.

RECENTLY, THE IMPORTANCE OF ANTICOAGULAtion with warfarin in patients with atrial fibrillation and risk factors for stroke has been established in

clinical trials and emphasized in recent guidelines. The major complication of anticoagulant therapy is bleeding, and there is always a risk/benefit ratio which must be considered whenever warfarin is prescribed. In this paper, Hylek and colleagues report an inception cohort study designed to define the rate of major hemorrhage in atrial fibrillation patients starting warfarin therapy. Patients were eligible for inclusion if they were over 65 years of age, had atrial fibrillation verified by an ECG, and were starting warfarin therapy, which would be managed by a single, onsite anticoagulation clinic. Patients were enrolled on the first day of warfarin and followed throughout the first year of therapy. The end points analyzed were: major hemorrhage, time to termination of warfarin, and physician reasons for discontinuation. For this study, a hemorrhage was considered major if it was either fatal, required greater than or equal to 2 units of packed red blood cells, or involved a critical site. Each patient was classified according to the CHADS2 scheme for known risk factors of stroke. Concurrent medications were obtained from electronic medical records. Use of over-the-counter agents, such as aspirin or nonsteroidal anti-inflammatory drugs was also recorded.

The study cohort eventually included 472 patients. Of these, 47% were female and 54% were over 75 years of age, with 153 patients (32%) over 80 years of age. With the use of the Outpatient Bleeding Risk Index, 95.3% were classified as intermediate risk and 4.7% as high risk for major hemorrhage with warfarin therapy. During the study, the following proportion of patient times were spent within the following INR ranges: 2.0 to 3.0 (58%), below 2.0 (29%), between 3.1 and 4.0 (11%), and 2% greater than or equal to 4.0.

During the first year after starting warfarin, major hemorrhages were noted in 26 patients (5.5%). These included: 9 intracranial hemorrhages, 11 gastrointestinal bleeds, one retroperitoneal bleed, one hemothorax after a fall, one ocular bleed, one hemarthrosis, and 2 nose bleeds severe enough to require transfusions. The major hemorrhage rate was 7.2 per 100 person-years, with a rate of intracranial hemorrhage of 2.5%. Increased age was associated with increased risk of bleeding. Patients 80 years of age or older had a bleeding rate of 13.1 per 100 person-years vs 4.75 for those under age 80. Several risk factors for hemorrhage were identified: INR range greater than or equal to 4, older age, and first 90 days after initiation of therapy. During the first year of therapy, warfarin was discontinued in 134 patients. Although perceived maintenance of sinus rhythm was the most common cause (65 patients), safety concerns led to discontinuation in many others, particularly in those 80 years of age or older. There was a strong correlation between bleeding risk and an elevated CHADS2 score, demonstrating an important overlap between risks for bleeding and stroke.

Hylek et al conclude that in general clinical practice, the risk of bleeding may be higher than has been estimated from prior randomized trials. These observations indicate that stroke prevention among the highest risk patients remains a challenge.

COMMENTARY

Stroke is the most serious complication of atrial fibrillation. Randomized clinical trials have clearly shown that warfarin decreases this risk by about 67% in an intention-to-treat analysis, and has an even greater effect in an on-therapy analysis. However, many of the patients studied in these trials had already tolerated warfarin for some period of time before enrollment, and patients thought to be at particularly high risk of bleeding were excluded. For some studies, this was more than 35% of the patients screened for participation. As a result, the annual rates of major bleeding were relatively low (1.4% to 4.2%) in these trials and in some other large scale trials in atrial fibrillation. In this paper, Hylek et al show that "real world" anticoagulation of elderly patients with atrial fibrillation is still a major clinical problem. By studying an inception cohort, they mimicked the situation when a clinician makes a decision to start warfarin therapy. Even though all patients were followed systematically by an experienced anticoagulation clinic, the major hemorrhage rate in the first year of therapy was 7.2%, and much higher in those patients 80 years of age or older. An important observation was the risk factors for stroke and for bleeding overlap, making clinical decisions even more difficult.

How should clinicians react to these data? Clearly both stroke risk and bleeding risk must be considered before starting anticoagulation. The need for concomitant drugs that might increase bleeding risk (eg, aspirin, anti-inflammatory drugs, other platelet inhibitors) must be evaluated at each visit and, in many cases, these drugs should be discontinued. Very careful monitoring to prevent excessive anticoagulation is needed, especially in patients over 80. ■

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; and

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

Readers are Invited

Readers are invited to submit questions or comments on material seen in or relevant to Hospital Medicine Alert. Send your questions to: Leslie Hamlin — Reader Questions, *Hospital Medicine Alert*, c/o AHC Media, PO Box 740059, Atlanta, GA 30374. ■