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INSIDE

Methylprednisolone to Prevent Post-Extubation Laryngeal Edema

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

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Dr. Pierson reports no financial relationships relevant to this field of study. This article originally appeared in the August 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 a mixed population of adult ICU patients who had been intubated for at least 36 hours, administration of 80 mg of methylprednisolone over the 12 hours preceding extubation substantially reduced the incidence of post-extubation laryngeal edema and the need for re-intubation.*

Source: Francois B, et al. 12-h pretreatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: A randomised double-blind trial. *Lancet*. 2007;369:1083-1089.

In this multicenter clinical trial from France, Francois and colleagues sought to determine whether methylprednisolone administered prior to extubation would prevent post-extubation laryngeal edema (PELE) and the need for re-intubation. They studied adult patients intubated for at least 36 hours for acute respiratory failure, in whom extubation was planned the following day. In a randomized, double-blind design, they gave such patients either methylprednisolone, 20 mg, or saline intravenously at 12, 8, and 4 hours prior to extubation, and also at the time the endotracheal tube was removed — for a total of 80 mg in the active treatment group. The investigators prospectively evaluated all patients for laryngeal edema (clinically defined as the acute development of upper respiratory obstruction) on 8 examinations over the 24 hours following extubation, and examined the cords visually at the time of reintubation when this was required.

The 2 patient groups were well matched, with 64% male and median age 66 years. Patients had similar frequencies of medical illness (62%), surgical conditions (19%), and trauma (19%). The median duration of intubation prior to randomization was 6 days. Of 761

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patients entered into the study, data from 698 were included in the analysis. PELE developed in 76 of the 343 placebo-treated patients (22%), as compared to 11 of the 355 patients who received methylprednisolone (3%; $P < 0.001$). Re-intubation because of PELE occurred in 14 of 26 (54%) vs one of 13 (8%) patients on placebo vs methylprednisolone, respectively ($P = 0.005$); overall rates of re-intubation were 26/343 (8%) vs 13/355 (4%), respectively ($P = 0.02$). By univariate analysis of the data, patients who developed PELE were more likely to be female, of shorter height, admitted for trauma, and intubated orally with larger endotracheal tubes for a shorter period of time.

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This was a carefully planned, well carried out, rigorously described and reported study, and its results are impressive: administration of steroids for 12 hours prior to planned extubation in patients who had been intubated for 2 days or more reduced the incidence of PELE 7-fold, and also reduced the need for reintubation. Given the seriousness of PELE and the magnitude of the benefit shown in this study, does this mean that the regimen used in this study should become a standard of care in our ICUs? Maybe, and maybe not, as influenced by several considerations.

Are the patients in this study similar enough to my patients, and is Francois and colleagues' experience with PELE and the need for reintubation consistent with what is encountered in my institution? The patient population is well-described, so that readers can judge how well they match up to the patients intubated and ventilated in their ICUs. The more dissimilar the populations (for example, for a neurocritical care unit or one that sees mainly post-operative patients), the more caution would seem appropriate. Although Francois et al cite a previous study that found a 22% incidence of PELE, as observed in their trial, this seems high to me. Perhaps it is related to the care with which this complication was deliberately sought, and an 8% reintubation rate is probably reasonable.

What happens in everyday clinical practice (clinical effectiveness) often does not replicate what is found in the rigorous, carefully-controlled circumstances of a clinical trial [efficacy]. How effectively could the regimen used in this study be implemented in my ICU? Here there may be some problems with ventilatory management and extubation as typically practiced in the United States.

Francois et al evaluated their patients in the evening and determined that they would be extubated the next morning, permitting them to administer the 12 hours of steroids before extubation at the usual time. In this country, decisions to extubate, particularly after several days of mechanical ventilation for acute respiratory failure, as with the patients in this study, are typically made on morning rounds and carried out promptly. This is consistent with the current standard of care. According to the most-often cited weaning recommendations, the 2001 international consensus guidelines,[1] readiness for liberation from mechanical ventilation should be assessed using a spontaneous breathing trial; those who pass this trial should be extubated as soon as possible and not remain intubated any longer than is necessary. Numerous studies have confirmed the correlation between duration of intubation and the incidence of ventilator-associated pneumonia and other complications. The need to wait 12 hours in order to administer a course of methylprednisolone might lead to extubation during the night shift, when staffing may be less and observation for post-extubation difficulties harder to maintain, or holding the patient over until the next morning, essentially adding another day of intubation time.

If the decision to extubate is made based on the results of an early-morning assessment, could the protocol be abbreviated in order to get the tube out in the next several hours, administering only 2 or 3 doses of steroids beforehand? This question cannot be answered at present. And what if, on reassessment prior to extubation, the decision is made to defer extubation after the steroid course has already begun, as happened a few times during the study and is not uncommon in the unit? Continuing the regimen and extubating the patient the next day would mean giving 200 mg of methylprednisolone rather than 80 mg, the safety and expense of which might become problematic.

Certainly, patients with a history of PELE should receive methylprednisolone prior to planned extubation. Those patients whom the clinician suspects to be at especially high risk for PELE — which according to this study would include small women with large tubes, especially

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Questions & Comments

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those admitted after trauma — would be good candidates as well. As to whether all other patients who will have been intubated for 2 days or more and do not have a specific contraindication should receive steroids prior to extubation — as is recommended in the editorial accompanying the Francois study[2] — I think the jury is still out. I am inclined to await further confirmation of this trial before introducing this regimen this broadly into my own ICU practice. ■

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Pericarditis Triage

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 August 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.*

Source: Imazio M, et al. Indicators of poor prognosis of acute pericarditis. *Circulation*. 2007:115:2739-2744.

Most cases of acute pericarditis are due to idiopathic or viral causes and have a benign prognosis with symptomatic treatment. How to identify those cases due to specifically treatable causes or those cases not expected to do well would be useful to know. Thus, this group from Torino, Italy, studied 453 patients who met criteria for acute pericarditis in the absence of acute myocardial infarction. Patients were included if they met 2 of the following criteria for acute pericarditis: typical pericarditis chest pain, pericardial friction rub, diffuse ST elevation or PR depression on ECG, and new or worsening pericardial fluid on echocardiogram. Myopericarditis was diagnosed if one of the following were present: elevated cardiac enzymes or new focal or diffuse left ventricular dysfunction by echocardiogram. All patients had coronary artery disease excluded by stress nuclear perfusion scintigraphy or coronary angiography. Pericardial tamponade was diagnosed using a combination of clinical and supportive echocardiographic signs. Clinical features in the literature associated with a poor prognosis or specific diagnoses were assessed for their predictive ability. Patients were prospectively enrolled from 1996 to 2004.

Results: A specific cause was discovered in 17% of the patients. Corticosteroid treatment was employed initially in about 25%. Multivariate analysis identified women (RR 1.67), fever (3.56), subacute course (3.97), large effusion or tamponade (2.15), and NSAID failure (2.5) as predictors of a specific cause. Elevated troponin predicted a lower risk of a specific cause (0.37). After a mean follow-up of 31 months, 21% of patients had a complication: recurrence in 18%, tamponade 3%, and constriction 1.5%. Patients with a specific cause had a higher rate of complications (38 vs 18%, $P < 0.001$).

Multivariate analysis showed that women (RR 1.65), large effusion or tamponade (2.51), and NSAID failure (5.50) were predictive of complications. Corticosteroid use was associated with more complications in idiopathic or viral pericarditis (48 vs 14%, $P < 0.001$). Imazio and colleagues concluded that fever, sub acute course, large effusions, or tamponade and NSAID failure may help predict those more likely to have a specific cause of acute pericarditis or those more likely to suffer a complication.

■ COMMENTARY

This is a potentially clinically-useful study, since currently in the developed world acute pericarditis is usually admitted to the hospital. Deployment of this risk stratification scheme could result in sending home the 80% of patients who have a viral or idiopathic etiology who are expected to do well. The predictors include laboratory tests and echocardiography, which would have to be readily available in the acute care setting. Let's look at the multivariate predictors identified. Female sex is not very useful, as it means admitting roughly half the patients. Also, the risk ratio is < 2.0 for this variable, which is not a strong predictor. All of the other predictors have risk ratios > 2.0. Two of the predictors identified predict specific causes and a higher risk of complications, so they would be the most valuable clinically (large effusion or tamponade and NSAID failure). Others are associated with a specific cause only: fever and subacute course. Elevated troponin was associated with lack of a specific cause.

Translating this into practice if a patient with acute pericarditis has a large effusion or tamponade, they should be admitted because these features predict complications and a specific cause. NSAID failure should also be admitted for the same reason, but this is likely to be an unusual presentation. Febrile patients, or those with an indolent course, likely have a specific cause that could be evaluated as an outpatient in some settings. An elevated

troponin and a lack of other high-risk features would reinforce the decision to send the patient home, as long as acute myocardial infarction is excluded. Remember, the most common cause of acute pericarditis in a middle-aged man is acute infarction. These patients were excluded from this study. If you are on the fence about what to do, female sex could be used to tip the balance toward admission.

This study confirms the impression that about 80% of non-infarction-related acute pericarditis is idiopathic or viral, so most patients should not need hospitalization. Based upon their data, the most common specific causes of acute pericarditis are autoimmune disease, neoplasm and tuberculosis with or without HIV. Other bacterial causes are rare (< 1%). This may be different in less developed countries. The study also suggests the notion that steroids should not be the initial therapy of idiopathic/viral pericarditis, as they increase the likelihood of recurrences. Finally, some clinical features, such as warfarin use, trauma and immunosuppressed state were too infrequent to make clear judgment about their risk prediction potential. ■

Endocarditis due to *E. faecalis*: Ampicillin + Ceftriaxone

ABSTRACT & COMMENTARY

By Robert Muder, MD

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Dr. Muder does research for Aventis and Pharmacia.

This article originally appeared in the August 2007 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, and Dr. Price is Assistant Professor, University of Colorado School of Medicine. Dr. Deresinski serves on the speaker's bureau for Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck, and Dr. Price reports no financial relationships relevant to this field of study.*

Synopsis: *The combination of ampicillin and ceftriaxone was effective in treatment of endocarditis due to* E. faecalis. *Efficacy was similar for infections involving isolates with and without high-level aminoglycoside resistance.*

Source: Gavalda J, et al. Brief communication: treatment of *Enterococcus faecalis* endocarditis with ampicillin plus ceftriaxone. *Ann Intern Med*. 2007;146:574-579.

GAVALDA AND COLLEAGUES REPORTED THEIR EXPERIence with treating 43 patients with *E. faecalis* endocarditis using a combination of intravenous ampicillin 2 g every 4 hours and ceftriaxone 2 g every 12 hours for 6 weeks. Twenty-one patients were infected with strains exhibiting high-level aminoglycoside resistance (HLAR) and 22 were infected with non-HLAR strains. Eight of 21 (38%) patients with HLAR *E. faecalis* endocarditis had prosthetic valve infections, as did 10/22 (45%) patients with non-HLAR infection.

Three of 21 patients with HLAR *E. faecalis* endocarditis required surgery, and 7 died during therapy; one of the deaths was due to aspiration pneumonia. All patients who died had negative blood cultures prior to death. One patient died 30 days after therapy due to complications of HIV infection. The remaining 13 patients were free of infection after 3 months of follow-up.

Four of 22 patients with non-HLAR *E. faecalis* endocarditis required surgery, and 4 died during therapy. There were 2 relapses in this group. One patient received ceftriaxone 2 g every 24 hours rather than every 12 hours; he was subsequently cured after treatment with ampicillin plus ceftriaxone 2 g every 12 hours. A patient with an aortic Dacron graft and prosthetic aortic valve suffered a fatal cerebral hemorrhage 21 days after completing therapy. Pre-mortem blood cultures were positive for *E. faecalis.*

In vitro assessment of synergy by time-kill method showed synergistic killing by the combination of ampicillin and ceftriaxone for all 28 isolates tested.

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E. faecalis strains are generally tolerant to penicillin and ampicillin, i.e., bacterial killing occurs only at antibiotic levels many-fold greater than the MIC. Successful treatment of *E. faecalis* endocarditis usually requires the combination of penicillin or ampicillin plus and aminoglycoside. The combinations result in synergistic killing of *E. faecalis* in vitro and in vivo. For enterococcal isolates exhibiting HLAR, synergistic killing does not occur due the presence of one of several aminoglycoside modifying enzymes. Even if the infecting strain does not exhibit HLAR, the 4-6 week course of treatment required for treatment of enterococcal endocarditis frequently results in significant aminoglycoside toxicity.

The combination of ampicillin + ceftriaxone shows synergism against E. faecalis both in vitro and in an animal model of endocarditis[1,2] whether or not the strain demonstrates HLGR. Efficacy in the animal model was similar to that obtained with ampicillin + aminoglycoside. Addition of an aminoglycoside to the combination of ampicillin + gentamicin did not improve efficacy.

Although not a randomized, controlled trial, the results reported by Gavalda et al are similar to those obtained using the combination of ampicillin + an aminoglycoside for the treatment of non-HLAR *E. faecalis* endocarditis. Thus, ampicillin + ceftriaxone may be reasonably consid-

ered to be first line therapy for HLAR *E. faecalis*. Other potential therapies include linezolid and daptomycin; clinical experience in treating *E. faecalis* endocarditis with these agents is more limited. Nearly all strains of *E. faecalis* are resistant to quinupristin/dalfopristin.

The combination of ampicillin + ceftriaxone is a rational second-line combination for treatment of non- HLAR *E. faecalis* endocarditis in patients at high risk for gentamicin toxicity, such as those with pre-existing renal insufficiency.

Several cautions are in order. The first is that this study was not randomized and involved a relatively small number of patients. The second is that ampicillin/ceftriaxone synergy may not be present if the strain is resistant to ampicillin.[3] Finally, this study should not be extrapolated to treatment of *E. faecium* endocarditis, as *E. faecium* is less susceptible to ampicillin than *E. faecalis*. ■

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Preoperative Anemia and Postoperative Outcomes

ABSTRACT & COMMENTARY

By David J. Pierson, MD

This article originally appeared in the August 2007 issue of Critical Care Alert. It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD.

Synopsis: *In this study of 310,311 veterans aged 65 or older who underwent major noncardiac surgical procedures, 30-day mortality increased 1.6% for every percentage-point decrease in preoperative hematocrit below 39%.*

Source: Wu WC, et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. *JAMA*. 2007:297:2481-2488.

USING DATA FROM 132 US VETERANS HOSPITALS collected in the National Surgical Quality Improvement Program, Wu and colleagues performed a retrospective cohort study of patients aged 65 or older who underwent major non-cardiac surgery between 1997 and 2004. Major surgery included all procedures, elective and emergency, performed in the operating room under general, spinal, or epidural anesthesia. Postoperative mortality and cardiac events (cardiac arrest or Q-wave myocardial infarction) were correlated with preoperative hematocrit values. The latter were divided into 14 groups, from < 18% to ³ 54%, and referenced to a normal range of 39% to 53.9%.

The study cohort was comprised of 310, 311 veterans (98% male, 80% white). Of these, 42.8% had preoperative anemia, defined as hematocrit < 39%, and 0.2% had polycythemia (hematocrit ≥ 54%). Anemic patients had significantly ($P < 0.001$) more diabetes, cardiac disease, neurologic disorders, renal disease, long-term corticosteroid use, and cancer than non-anemic patients. They also tended to be older, inpatients rather than outpatients before surgery, and non-independent in functional status, and to have higher American Association of Anesthesiologists class.

For the entire study population, 30-day postoperative mortality was 3.9% and the cardiac event rate was 1.8%. Both of these outcomes rose monotonically for patients with progressively lower and higher hematocrit levels than normal. For example, the mortality rates were 1.5% for patients with hematocrits of 45.0 to 47.9%, 5.8% with values of 33.0 to 35.9%, 14.9% with values of 24.0 to 26.9%, and 35.4% with values < 18%. There was a 1.6% (95% confidence interval, 1.1%-2.2%) increase in 30-day postoperative mortality associated with every percentage-point decrease in hematocrit level from the normal range. This increase was not just observed in patients with very low hematocrits, and began when the level fell below 39%.

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In this study, elderly patients with preoperative hematocrits below the lower limit of normal had worse outcomes, and mortality increased progressively with lower and lower hematocrits. This does not necessarily mean that the anemia was the cause of the worse outcomes, or that raising the hematocrit into the normal range in these patients would have improved their outcomes. Wu et al acknowledge both of these points. In fact, the anemic patients were substantially different from their non-anemic counterparts in a lot of ways that would be expected to push the findings in the direction observed, including being older, having more comorbidities, and being less functional prior to surgery. This suggests that preoperative anemia is a marker for, rather than an independent cause of, worse postoperative outcomes.

This was not an ICU study, and the proportions of patients in the cohort who were critically ill prior to surgery, or managed in the ICU postoperatively, are not given. Only about 8% of the operations were classified as emergent. Wu et al found essentially no relationship

between hematocrit and outcomes in this subset of patients. This may have been because of the overriding effects of comorbidities in these patients, or because the preoperative hematocrit values in the database did not reflect the patients' status at the time of surgery: 21% of the total patient population had no hematocrit recorded within 30 days of the operation. Another interesting finding was that patients who received more than 4 units of transfused blood preoperatively had a reduced rate of postoperative death: the odds ratio was 0.88, with a 95% confidence interval of 0.79-0.98. This supports the notion that recognition and management of serious anemia prior to a scheduled major operation is a good idea.

What should ICU clinicians make of this study's findings in the context of the recent attention focused on hematocrit levels and outcomes in critically ill patients? Studies using large databases have shown associations between lower hematocrits and increased mortality in patients with acute myocardial infarction. However, prospective studies randomizing ICU patients to lower vs higher transfusion thresholds have found that a more liberal transfusion strategy does not improve outcome. It may be that, in general, the presence and severity of anemia are markers for poor prognosis from a multiplicity of disease processes, and that treating the marker per se may not affect the factors responsible for that poorer prognosis. Nonetheless, the present study may prove useful to clinicians in helping to identify patients at increased risk for unfavorable outcomes after elective major noncardiac surgery, so that such patients can be monitored closely if they are in the ICU. ■

New Mechanism of Bacterial Resistance to Aminoglycosides

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD

This article originally appeared in the August 2007 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, and peer reviewed by Connie Price, MD.*

Synopsis: *Methylation of 16S ribosomal RNA (rRNA) has emerged as an important mechanism of resistance to aminoglycosides in pathogens including Enterobacteriaceae and non-fermenters including* Pseudomonas aeruginosa *and Acinetobacter species.*

Source: Doi Y, Arakawa Y. 16S ribosomal RNA methylation: Emerging resistance mechanism against aminoglycosides. *Clin Infect Dis*. 2007;45:88-94.

While use of aminoglycosides to treat gram negative rods has fallen over the last 30 years due to the availability of broad-spectrum beta lactam antibiotics, aminoglycoside antibiotics remain useful for the treatment of some life-threatening infections. Due to increasing prevalence of resistance to beta lactam antibiotics the use of aminoglycosides is occasionally the best option to treat certain infections.

Aminoglycosides exert their bactericidal activity against susceptible pathogens by binding specifically to the aminoacyl site (A-site) of 16S rRNA within the prokaryotic 30S ribosomal subunit and inhibit bacterial protein synthesis. The most common mechanism of resistance to aminoglycosides is enzymatic inactivation of the drug by adenylation, acetylation or phosphorylation (aminoglycoside modifying enzymes). Mutation of the 30S ribosome, defects in cellular permeability (often developing while on therapy), and active efflux are other mechanisms of bacterial resistance to aminoglycosides.

Since aminoglycosides are produced by certain species of actinomycetes, these organisms are intrinsically resistant to the aminoglycosides they produce. In most cases, this intrinsic resistance is caused by ribosomal protection through methylation of specific nucleotides within the A-site of 16S rRNA, which hampers binding of the aminoglycoside.

Recently, clinical strains of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* which produced 16S rRNA methylases were reported.[1,2] These organisms displayed high-level resistance to gentamicin, tobramycin, and amikacin. Since this first publication, the literature has documented identification of new methylase enzymes in other gram negative rods and their spread to different areas of the world.

The genes responsible for these enzymes are mostly located on transposons within transferable plasmids, and are capable of horizontal spread. Some of the organisms carrying these methylases have been shown to coproduce extended-spectrum beta lactamases (ESBLs) or metallo-beta-lactamases contributing to a multi-drug resistant phenotype. Since resistance to multiple aminoglycosides can be due to acquisition of more than one aminoglycoside modifying enzyme, aminoglycoside resistance due to methylase production may not be recognized. The authors of the paper recommend as a screen for methylase-producing organisms that multi-aminoglycoside resistant gram negative rods (as identified by automated susceptibility testing) be subjected to Bauer-Kirby disk susceptibility testing using gentamicin, amikacin and arbekacin disks. (The latter aminoglycoside is not available for therapeutic use in the United States, but demonstration of in vitro resistance to this drug raises the positive predictive value of this method of testing

to ≥ 90%.) The presence of 16SrRNA methylase is suspected when little or no zone of inhibition surrounds any of the aminoglycoside disks. The only definitive confirmation of the presence of these methylases remains PCR. The paper lists the sequences of the specific primers and appropriate thermal cycling conditions.

This is a paper which is of significant clinical relevance. The demonstration of this novel mechanism of antimicrobial resistance is illustration of the propensity of our microbial nemeses to continually stay at least one step ahead of our best attempts to defeat them. ■

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Antithrombotic Therapy for Nonvalvular Atrial Fibrillation

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 August 2007 issue of Clinical Cardiology Alert. *It was edited by Michael H. Crawford, MD, and peer reviewed by Rakesh Mishra, MD.*

Source: Hart RG, et al. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857-867.

In this paper, Hart and colleagues report the results of a meta-analysis of antithrombotic therapy in patients with nonvalvular atrial fibrillation (NVAF). Hart et al identified and included in their database 29 randomized trials that tested various forms of antithrombotic therapy in patients with NVAF. The trials included in the meta-analysis had a total follow-up exposure of 42,450 patient years. The patients had an average age of 71 years and a male to female ratio of 65:35. Results were reported for adjusted dose warfarin compared to placebo or no therapy, antiplatelet therapy compared with placebo or no therapy, and adjusted dose warfarin compared with antiplatelet therapy.

There were 6 randomized trials that compared adjusted dose warfarin to placebo or no therapy. These trials included 2,900 participants who had 186 strokes during a mean follow-up of 1.6 years per participant. Adjusted dose warfarin was associated with a 64% reduction in stroke with similar reductions seen for both disabling and nondisabling strokes. The absolute risk reduction in all strokes was 2.7% per year in the 8 primary prevention trials and 8.4% per year in a single secondary prevention trial. When only ischemic strokes were considered, there was a 67% relative risk reduction associated with adjusted dose warfarin.

There were 8 trials that compared antiplatelet therapy with placebo. These trials involved 4,876 participants who had 488 strokes. When aspirin alone was compared to placebo or no treatment, aspirin was associated with a 19% reduced incidence of stroke. The absolute risk reduction was 0.8% per year for primary prevention trials and 2.5% per year for secondary prevention trials. There were 9 randomized trials that compared warfarin with various doses of aspirin, [3] other trials in which warfarin was compared with other antiplatelet agents and 2 trials where adjusted dose warfarin was compared to low fixed and ineffective doses of warfarin plus aspirin. When adjusted warfarin was compared with antiplatelet therapy alone, warfarin was associated with a 37% reduction in strokes. Among all patients, there was a 52% reduction in ischemic stroke.

The authors also examined several randomized trials that compared adjusted dose warfarin to other antithrombotic agents. There were 3 randomized trials in NVAF involving ximelagatran. There was an 8% reduction in stroke risk with ximelagatran compared to adjusted dose warfarin. Although 19 trials with other agents have been reported, the authors considered that the available data were insufficient for analysis.

The authors also examined major extracranial and intracranial bleeding events and total mortality. Even with the meta-analysis of this size, the frequency of these events is lower than that for ischemic strokes, so that the estimates of the effects of antithrombotic therapies are less precise. Two conclusions were, however, reached. The risk for intracranial hemorrhage was doubled with adjusted dose warfarin but the absolute risk increase was small (0.2% per patient per year) and all-cause mortality was substantially reduced by adjusted dose warfarin vs placebo.

The authors conclude that in patients with NVAF, warfarin reduces stroke by approximately 60% and death by 25% compared with no antithrombotic therapy. Antiplatelet therapy reduces stroke by approxi-

mately 20%. The data support the current guideline recommendations.

COMMENTARY

This meta-analysis of a large number of studies involving antithrombotic therapy in patients with nonvalvular atrial fibrillation provides a useful resource for physicians making decisions about anticoagulation in patients with NVAF. The data clearly show that warfarin should be the gold standard against which new therapies are compared, but also indicate that alternative therapies may be appropriate in patients with few or no risk factors for stroke. The problems and complications for warfarin therapy are well summarized. Unfortunately, it appears that the bleeding complications, the major complication associated with warfarin therapy, are strongly related to the intensity of antithrombotic therapy, and safer yet equally effective alternatives to warfarin have not yet been identified.

In 2006, the guidelines for anticoagulation in patients with nonvalvular atrial fibrillation were revised. They recommend oral anticoagulation for all patients with atrial fibrillation unless there are contraindications or the patient is under age 60 without any heart disease or risk factors for atrial fibrillation (lone atrial fibrillation). For the latter patients the benefits of aspirin vs the risk of bleeding has not been established. The results of this meta-analysis can be used as a reference for the recommendations made in these guidelines. ■

CME Questions

16. In the study by Francois et al, 20 mg of methylprednisolone given 4 times over the 12 hours preceding extubation (80 mg total) resulted in which of the following outcomes?

a. A 7-fold reduction in the development of post-extubation laryngeal edema.
b. A 2-fold increase in the overall need for reintubation.
c. A 3-fold increase in the development of nosocomial pneumonia.
d. A decrease in the need for reintubation that was observed only in trauma patients.

17. In the study or preoperative anemia and postoperative outcomes in elderly VA patients:

a. transfusion to a hematocrit greater than 35% improved outcomes.
b. preoperative anemia with a hematocrit less than 39% worsened postoperative outcomes.
c. preoperative anemia was an independent risk factor for postoperative mortality.
d. The association of anemia and postoperative complications was seen only in the subset of ICU patients.

18. Based on the study of poor prognostic signs in patients presenting with acute pericarditis, which of the following was NOT predictive of a higher risk of complications or a specific cause being identified?

a. A subacute or indolent presentation
b. A large effusion or tamponade
c. NSAID failure
d. Fever
e. An elevated troponin

Answers: 16. (a); 17. (b); 18. (e)

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. ■

Dear *Hospital Medicine Alert* Subscriber:

This issue of your newsletter marks the start of a new continuing medical education (CME) or continuing nursing education (CNE) semester and provides us with an opportunity to review the procedures.

Hospital Medicine Alert, sponsored by AHC Media LLC, provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options and physician office practices. Our intent is the same as yours — the best possible patient care.

Upon completing this program, the participants will be able to:

1. review pertinent safety, infection control, and quality improvement practices;
2. discuss diagnosis and treatment of acute illness in the hospital setting;
3. review current data on diagnostic and therapeutic modalities for common inpatient problems.

Each issue of your newsletter contains questions relating to the information provided in that issue. After reading the issue, answer the questions at the end of the issue to the best of your ability. You can then compare your answers with the correct answers provided in an answer key in the newsletter. If any of your answers were incorrect, please refer back to the source material to clarify any misunderstanding.

At the end of the semester, you will receive an evaluation form to complete and return in an envelope we will provide. Please make sure you sign the attestation verifying that you have completed the activity as designed. Once we have received your completed evaluation form, we will mail you a letter of credit. This activity is valid 24 months from the date of publication. The target audience for this activity is principal investigators and clinical trials nurses.

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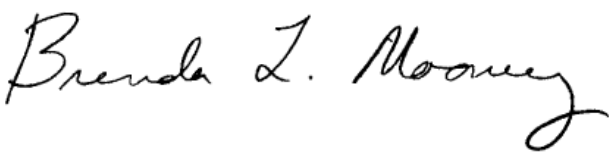

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