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Literature Update in Hospital Medicine

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KEYWORDS

- Evidence-based medicine • Perioperative medicine • Anticoagulation
- *Clostridium difficile* • Antibiotic usage

This article provides hospitalists with the opportunity to read and understand the most compelling recent research relevant to the practice of hospital medicine. To identify articles to be included in this update the authors independently reviewed the literature for peer-reviewed articles that were published from March 2012 to March 2013. In addition to Medline searches, the authors examined Journal Watch and the American College of Physicians Journal Club reviews of articles. In total, 111 original articles were identified and reviewed. Next, each article was ranked independently by each author in importance (3-point scale) based on the likelihood that it would:

1. Change practice or teaching
2. Modify practice or teaching
3. Confirm practice or teaching

The 9 articles with the highest scores were included in the review. In addition, the authors included 1 additional bonus article that they thought would be of interest.

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HOSPITAL MEDICINE CLINICS CHECKLIST

1. Perioperative statins reduce perioperative myocardial infarctions, atrial fibrillation, and length of stay.
2. Statin use does not increase the risk of intracranial hemorrhage.
3. New oral anticoagulant agents are superior to warfarin in preventing stroke in patients with atrial fibrillation, and may have a better safety profile.
4. In patients with an acute upper gastrointestinal (GI) bleed, the threshold for red blood cell transfusion should likely be a hemoglobin less than 7 g/dL.
5. In patients who have an acute GI bleed while on warfarin, restarting the warfarin after a week may lead to fewer thromboses and lower mortality without increasing the bleeding risk.
6. Patients admitted to the hospital with an exacerbation of chronic obstructive pulmonary disease should receive antibiotics in addition to bronchodilators and steroids.
7. Patients with low English proficiency should receive professional interpreter services on hospital admission.
8. Unnecessary proton pump inhibitors should be discontinued and their use should be limited to patients who cannot tolerate other acid suppression therapies.
9. Treatment with a 7-day course of oral ciprofloxacin should be considered for patients with acute, uncomplicated pyelonephritis.
10. Dogs may be trained to accurately detect *Clostridium difficile* infection by sense of smell on hospital wards.

What effects do perioperative statins have on myocardial infarction, atrial fibrillation, death, and length of stay?

Chopra V, Wesorick DH, Sussman JB, et al. Effect of perioperative statins on death, myocardial infarction, atrial fibrillation, and length of stay. Arch Surg 2012;147(2):181–9.

BACKGROUND/PURPOSE

Despite advances in anesthetic and operative techniques, cardiac complications of surgery are common. Although tools exist to identify patients at high risk for perioperative complications, there are few proven medical interventions to reduce the risk. The purpose of the analysis was to determine the effects of statins, administered in the perioperative period, on the risk of myocardial infarction, atrial fibrillation, death, and length of stay (LOS).

STUDY DESIGN

The investigators performed a systematic review and meta-analysis of 15 randomized, controlled studies. The primary outcomes were perioperative myocardial infarction, perioperative atrial fibrillation, perioperative death, and LOS. The 15 studies examined were determined to be of high quality.

RESULTS

In the pooled analysis, 2292 statin naive patients who were randomized to receive perioperative statins versus placebo (or low-dose statins) were examined. The duration of statin treatment varied across studies (range 7–60 days). In the pooled analysis, statin treatment was associated with a significant reduction in the risk of perioperative myocardial infarction (4.5% vs 8.9%; relative risk [RR], 0.53; 95% confidence interval [CI], 0.38–0.74) and perioperative atrial fibrillation (19.9% vs 36.3%; RR, 0.56; 95% CI, 0.45–0.69). In addition, statin treatment was associated with a 2.2% incidence of death compared with 3.7% among controls, but the difference was not significant (RR, 0.6; 95% CI, 0.34–1.14). There was no heterogeneity among studies for these three outcomes. Treatment with statins was also associated with a significant reduction in LOS (–0.32 days) but there was a high degree of heterogeneity among studies. The investigators did not find evidence that any particular duration of statin treatment was more effective than another, but in most studies patients were treated with statins at least 7 days before surgery.

SUMMARY

Overall, this systematic review and meta-analysis of 15 high-quality randomized controlled trials offers strong evidence that perioperative statins reduce the risk of perioperative myocardial infarction and atrial fibrillation, and may also reduce the risk of perioperative death.

Does statin use increase patients' risk for intracranial hemorrhage?

McKinney JS, Kostis WJ. Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. *Stroke* 2012;43:2149–56.

BACKGROUND/PURPOSE

Several stroke prevention trials have shown that statins significantly reduce the risk of ischemic stroke. One of these, The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, found that atorvastatin reduced overall stroke, but not fatal stroke. A post hoc analysis found that atorvastatin was associated with significantly increased risk of hemorrhagic stroke.

STUDY DESIGN

To determine whether statin therapy increases the risk of intracranial hemorrhage, the investigators performed a systematic review and meta-analysis of 31 randomized controlled trials of statin therapy. In the pooled analysis, 91,588 patients treated with statins and 91,215 control patients given placebo, low-dose statins, or usual care were examined. All studies included in the analysis were randomized controlled trials with blinded outcome assessment.

RESULTS

In the pooled analysis, intracranial hemorrhage occurred in 358 subjects (0.39%) treated with statins versus 318 (0.35%) in the control group. Statin therapy was not

associated with significantly increased risk of intracranial hemorrhage (odds ratio [OR], 1.08; 95% CI, 0.88–1.32). In addition, the investigators found no association between the low-density lipoprotein (LDL) reduction or LDL level achieved and the risk of intracranial hemorrhage.

This analysis could not rule out a small increased risk for intracranial hemorrhage, because an excess of 25 intracranial hemorrhages were noted. To address the possibility of small harm, the investigators compared the magnitude of the possible harm with the magnitude of the benefits of statin therapy. In the same pooled analysis statin therapy prevented 540 strokes and 638 deaths. Thus the benefits of statin therapy far outweighed the possible harm.

SUMMARY

Overall, statin therapy was not associated with significantly increased risk of intracranial hemorrhage. Although a small degree of harm could not be ruled out, the magnitude of the benefits (reduced overall strokes and mortality) far outweighed the possible harm.

Are new oral anticoagulant agents effective and safe for preventing stroke in patients with atrial fibrillation?

Miller CS, Grandi SM, Shimony A, et al. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. *Am J Cardiol* 2012;110:453–60.

BACKGROUND/PURPOSE

Warfarin has been the standard therapy for preventing stroke in patients with atrial fibrillation for many years. Warfarin therapy is limited by the narrow therapeutic window of adequate anticoagulation without bleeding and by the variable dosing among patients, which requires close monitoring. New oral anticoagulant (NOA) agents include direct thrombin inhibitors (eg, dabigatran) and factor Xa inhibitors (eg, rivaroxaban and apixaban). New oral anticoagulant agents offer predictable dosing for most patients, and no need for continuous monitoring. Several randomized controlled trials have shown that NOAs are efficacious in preventing strokes in patients with atrial fibrillation, but none has compared the efficacy among NOAs or examined safety in pooled analyses.

STUDY DESIGN

The investigators performed a systematic review and meta-analysis of 3 randomized controlled trials of NOAs versus warfarin in patients with atrial fibrillation. The 3 trials included 1 each that examined the efficacy of dabigatran, rivaroxaban, and apixaban. In pooled analysis, 44,563 patients randomized to receive an NOA or warfarin were examined. Treatment outcomes included all-cause stroke and systemic embolism, and hemorrhagic stroke. Safety outcomes included major bleeding, intracranial bleeding, and gastrointestinal (GI) bleeding.

RESULTS

In the pooled analysis, treatment with an NOA was associated with significantly decreased risk of all-cause stroke and systemic embolism (RR, 0.78; 95% CI,

0.67–0.92) and hemorrhagic stroke (RR, 0.45; 95% CI, 0.31–0.68) compared with warfarin. In the safety analysis, treatment with an NOA was associated with a significant reduction in intracranial bleeding (RR, 0.49; 95% CI, 0.36–0.66) compared with warfarin. Treatment with an NOA was also associated with a nonsignificant decrease in major bleeding (RR, 0.88; 95% CI, 0.71–1.09) and a nonsignificant increase in GI bleeding (RR, 1.25; 95% CI, 0.91–1.72) compared with warfarin.

It is worth noting that the mean time in the therapeutic range for patients treated with warfarin ranged from 55% to 64% among the three studies. It is likely that warfarin would be more efficacious and safe if a higher time in the therapeutic range could be achieved, but the time in range seen in the studies is approximately what is seen in clinical practice.

SUMMARY

Taken together the three trials examined provide strong evidence that NOAs are superior to warfarin in preventing stroke and hemorrhagic stroke, and likely also have a better safety profile.

At what hemoglobin level should be transfused in the setting of an acute upper GI bleed?

Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013;368:11–21.

BACKGROUND/PURPOSE

Patients with an acute upper GI bleed (UGIB) often require red blood cell transfusion. The optimal hemoglobin level at which to transfuse is unclear.

STUDY DESIGN

Investigators enrolled 921 patients who presented to a single hospital in Spain between 2003 and 2009 with an acute UGIB (all presented with hematemesis or melena). Patients were randomized to either a restrictive transfusion strategy (transfuse for hemoglobin less than 7 g/dL) or a liberal strategy (transfuse for hemoglobin less than 9 g/dL). All patients received 1 unit of packed red blood cells before enrollment and all underwent endoscopy within 6 hours of admission.

RESULTS

The 2 most common diagnoses were peptic ulcer disease (49%) and variceal bleeding (21%). Patients in the restrictive strategy were significantly less likely to be transfused (49% vs 86%; $P < .001$). Patients in the restrictive strategy group also had less rebleeding (10% vs 16%; $P = .01$) and a lower mortality at 45 days (5% vs 9%; $P = .02$). Although patients in the restrictive strategy group had a lower hemoglobin at discharge, this difference disappeared by 45 days.

SUMMARY

There are a few minor methodological issues with this study that could limit the ability to generalize from it: all the patients received 1 unit before enrollment, it was not a

blinded study, and all patients had endoscopy within 6 hours. However, given the mounting evidence from other clinical scenarios supporting a restrictive transfusion strategy, this well-done study seems valid and likely should change clinical practice. In general, in the setting of an acute UGIB, clinicians should only transfuse for a hemoglobin less than 7 g/dL or if indicated clinically.

If a patient on warfarin has an acute GI bleed, when is it safe and appropriate to restart the warfarin?

Witt DM, Delate T, Garcia DA, et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. *Arch Intern Med* 2012;172(19):1484–91.

BACKGROUND/PURPOSE

Patients on warfarin (for any indication) are at increased risk for GI bleeding. If they have a bleeding episode, there is little evidence describing the optimal time to restart the warfarin, balancing the risk of recurrent bleeding with the risk of thrombosis.

STUDY DESIGN

Researchers performed a retrospective cohort study to determine the incidence of thrombosis, recurrent GI bleed, and death in patients who had a GI bleed and in whom the warfarin was stopped. Using a large Kaiser database, 442 patients who had a GI bleed on warfarin were identified; the most common indications for warfarin were atrial fibrillation (50%) and venous thromboembolism (25%). Approximately one-third of the patients required intensive care unit (ICU) care for their GI bleed, whereas 25% were discharged from the emergency department. Of these 442 patients, 260 resumed warfarin (59%); the median time to resumption was 4 days. Younger patients, those with mechanical valves, and those who had a lower GI bleed were more likely to resume warfarin. The investigators performed a complex propensity analysis to try to control for confounders.

RESULTS

The risk of thrombosis was significantly lower in those patients who resumed warfarin compared with those who did not (0.4% vs 5.5%; hazard ratio, 0.05; $P < .001$). There was not an increased risk for recurrent bleeding within 90 days in patients who restarted the warfarin (hazard ratio, 1.32; $P = .9$). Restarting anticoagulation was associated with a significant decrease in 90-day mortality (hazard ratio, 0.31; $P = .001$). When examining by time to resumption of warfarin, waiting 7 days may have yielded the best outcomes.

SUMMARY

Clinicians frequently face the complex decision of when to restart the warfarin in a patient who has recently had a GI bleed. Although this study is not perfect, it suggests that restarting warfarin in this setting may lead to fewer thromboses and maybe lower mortality without increasing the risk for recurrent bleeding. Although the data are not

strong enough to do this in all patients and this decision should be made on a case-by-case basis, clinicians should strongly consider restarting. If the decision is made to restart, waiting at least a week is most appropriate.

In patients hospitalized with an exacerbation of chronic obstructive pulmonary disease, is there a benefit to prescribing antibiotics in addition to bronchodilators and steroids?

Stefan MS, Rothberg MB, Shieh MS, et al. Association between antibiotic treatment and outcomes in patients hospitalized with acute exacerbation of COPD treated with systemic steroids. *Chest* 2013;143(1):82–90.

BACKGROUND

There is substantial evidence supporting the use of bronchodilators and steroids in patients hospitalized with a chronic obstructive pulmonary disease (COPD) exacerbation. Although there is reasonable evidence supporting the use of antibiotics in these patients, most of the studies excluded patients who receive steroids. It is not clear whether antibiotics have an added benefit in patients given bronchodilators and steroids for their COPD exacerbations.

STUDY DESIGN

The investigators conducted a retrospective cohort study using a large database of more than 53,000 patients more than 40 years of age who were admitted to an acute care hospital with an exacerbation of COPD (determined by International Classification of Diseases, Ninth Revision coding). Patients admitted to the ICU were excluded and all patients received systemic steroids. Patients given antibiotics in the first 48 hours were compared with those not given antibiotics; multivariable analysis and propensity scoring were performed to control for confounders.

RESULTS

More than 86% of patients were given antibiotics in the first 48 hours and the most common antibiotic prescribed was a quinolone. Patients prescribed antibiotics had a significantly lower in-hospital mortality (adjusted OR, 0.53; 95% CI, 0.40–0.71). Patients prescribed antibiotics also had lower 30-day readmission rates for COPD (adjusted OR, 0.88; 95% CI, 0.79–0.97). There was no increase in rates of *Clostridium difficile* infection and no antibiotic was superior.

SUMMARY

This well-done retrospective cohort study adds to a large body of evidence supporting the use of antibiotics in the treatment of acute exacerbations of COPD requiring hospitalization. Absent any contraindications, patients admitted to the hospital with a COPD exacerbation should receive antibiotics in addition to bronchodilators and steroids.

When should non-English speaking patients receive professional interpreter services?

Lindholm M, Hargraves JL, Ferguson WJ, et al. Professional language interpretation and inpatient length of stay and readmission rates. *J Gen Intern Med* 2012;27(10):1294–99.

BACKGROUND/PURPOSE

People with limited English proficiency often have difficulty explaining their symptoms during the hospitalizations and understanding their care plan afterward. Low English proficiency is associated with longer LOS, increased risk for serious adverse events after discharge, and higher rehospitalization rates.

STUDY DESIGN

To determine whether timing of professional interpreter services was associated with differences in hospital LOS or 30-day rehospitalization rates, the investigators performed a retrospective, observational study using administrative and clinical data from 3071 adult patients who received professional interpretation services at a large, tertiary care teaching hospital. Professional interpreters at this hospital were screened for bilingual oral and written language proficiency and had more than 90 hours of didactic and practical training before providing services. Patients' LOS and readmission rates were compared with rates when they received interpreter services (none on admission or discharge, on admission only, on discharge only, or on admission and discharge). The analyses were adjusted for patient characteristics, disease severity, and primary language.

RESULTS

LOS at the study hospital ranged from 1 to 85 days, with 75% having LOS less than 6 days. Compared with patients who received interpreter services at both admission and discharge, the LOS of patients who did not receive interpreter services at admission or discharge were 1.49 days longer ($P < .01$). Overall 30-day rehospitalization rate was 17.9%. Rehospitalization rates were significantly higher for patients who did not receive interpreter services on admission and/or discharge (24.3% vs 16.9% interpreter on admission only, 17.6% interpreter on discharge only, 14.9% interpreter on admission and discharge; $P < .001$).

SUMMARY

The chief concern with this observational study is that it may not be possible to generalize the findings to all hospitals, given how thoroughly professional interpreters at the study hospital were vetted and trained. However, the effect sizes reported in this otherwise rigorous study were impressive. To the extent that services are available, hospitalists should involve professional interpreters at the time of admission or at admission and discharge.

Do proton pump inhibitors increase hospitalized patients' risk for C. difficile-associated diarrhea?

Janarthanan S, Ditah I, Adler DG, et al. *Clostridium difficile*-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. *Am J Gastroenterol* 2012;107(7):1001–10.

BACKGROUND/PURPOSE

C. difficile is the most common infectious cause of health care-associated diarrhea in developed countries. Antibiotics remain the primary risk factor associated with *C. difficile*-associated diarrhea (CDAD), but conflicting studies have reported a possible link between proton pump inhibitor (PPI) use and CDAD.

STUDY DESIGN

The investigators conducted a meta-analysis of 23 articles (17 case-control and 6 cohort studies) identified through a PubMed search to evaluate the direction and magnitude of association between PPI use and CDAD. The investigators converted ORs reported in case-control studies to RRs to determine the pooled risk estimates.

RESULTS

The included studies involved a total of 288,620 patients. Overall, PPI exposure was associated with a nearly 70% increased risk for CDAD (RR, 1.69; 95% CI, 1.40–1.97). Systematic assessments of risk for bias found evidence for heterogeneity among the studies but no evidence for publication bias. Sensitivity analyses using random-effects models for all included studies as well as subgroups consisting of only case-control or cohort studies produced similar results.

SUMMARY

Although limited by the absence of controlled trials in the literature, this rigorously conducted meta-analysis contributes to a growing body of evidence that links PPI use to *C. difficile*-associated infections. Unless patients have clear indications for acid suppression, hospitalists should avoid prescribing PPIs and should discontinue their use whenever possible.

Is it safe to treat women with acute pyelonephritis for 7 days?

Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. *Lancet* 2012;380(9840):484–90.

BACKGROUND/PURPOSE

Acute pyelonephritis is a common infection among women of all ages. Prior studies have shown that treating with either trimethoprim-sulfamethoxazole or a

fluoroquinolone results in high rates of clinical or bacteriologic cure. However, the optimal duration of antibiotic therapy for this condition is unclear.

STUDY DESIGN

The investigators conducted a multicenter, double-blind, randomized controlled non-inferiority trial of 248 adult, nonpregnant Swedish women who were presumptively diagnosed with acute pyelonephritis. Women were included if they were 18 years old or older, had a fever greater than or equal to 38.0 C, and one of the following symptoms: flank pain, costovertebral angle tenderness, dysuria, urgency, or frequency. They were excluded if they had an indwelling urinary catheter, intermittently catheterized their bladder, used antibiotics within 72 hours of enrollment, or had any contraindications to fluoroquinolone therapy. Randomized patients received ciprofloxacin 500 mg twice a day for either 7 or 14 days. Outcomes were assessed at 10 to 14 days after treatment (short-term follow-up) and at 42 to 63 days after treatment (long-term follow-up). The investigators excluded 69 women (28%) who did not meet inclusion after enrollment (eg, diagnosis other than pyelonephritis), and 23 women (13%) who had incomplete follow-up. Among the remaining 156 patients, 16 (22%) in the 7-day treatment group and 26 (32%) in the 14-day treatment group had positive blood cultures.

RESULTS

At early follow-up, women who received 7 days and 14 days of ciprofloxacin experienced high cure rates (97% vs 95%; P for noninferiority, .004). Both groups also experienced similar rates for clinical failure/recurrent urinary tract infection (3% in 7-day group vs 4% in 14-day group). At long-term follow-up, rates for cure (93% vs 93%) and clinical failure (7% vs 7%) also were similar in both groups, but patients treated for 7 days were significantly less likely to experience a mucosal yeast infection (0% vs 6%, $P = .04$). The investigators found no significant differences in cure rates between treatment in the subgroup of patients with positive blood cultures ($P = .62$).

SUMMARY

The ability to generalize from this study is limited to fluoroquinolones and to moderately ill patients with uncomplicated infections. Nevertheless, this rigorous study provides hospitalists with a convenient, short-course treatment option that can facilitate early discharge and improve medication adherence in the post-acute care setting.

Can a dog be trained to recognize *C. difficile* infection?

Bomers MK, Agtmael MA, Luik H, et al. Using a dog's superior olfactory sensitivity to identify *Clostridium difficile* in stools and patients: proof of principle study BMJ 2012;345:e7396.

BACKGROUND/PURPOSE

C. difficile infection is a common complication of hospitalization and is becoming more frequent, severe, and refractory to standard treatment. Rapid diagnosis of

C. difficile infection is essential for the timely initiation of infection control measures and treatment.

STUDY DESIGN

In this proof-of-principle study the investigators trained a single beagle to smell and recognize toxigenic strains of *C. difficile*. For training, *C. difficile* was cultured on standard media under anaerobic conditions. The dog was exposed to the cultured strains by using sticks, fabrics, and metals that had been placed in contact with the cultures for varying periods of time. The dog was trained by a professional dog trainer to sit or lie down when it detected *C. difficile*. After training, the dog was tested with 100 stool samples, half from patients with *C. difficile* infection, and half from controls. In addition, to determine the dog's ability to identify *C. difficile* infection in a clinical setting, the dog was taken to the hospital wards and to patient rooms. Using a blinded case-control design, the investigators tested the dog on 30 patients with confirmed *C. difficile* infection, and 270 control patients.

RESULTS

The dog performed well when tested on stool samples (sensitivity 100%, specificity 94%). The dog also performed well when identifying *C. difficile* infection in patients in hospital rooms (sensitivity 93%, specificity 97%). The dog registered an inconclusive response in only 7 of 300 patients. However, this study has several limitations. Although the dog trainer was blinded to the status of patients when the dog was tested on the hospital wards, there were several mechanisms that may have unblinded the trainer and biased the results. First, the patients were presented in blocks of 10 with 1 positive patient in each block, allowing the trainer to anticipate only 1 positive in each block. Next, many of the patients with *C. difficile* infection were placed in isolation rooms, which may have unblinded the trainer. In addition, there may have been other clinical cues that may have allowed the trainer to guess whether a patient had *C. difficile* infection. Because of these potential biases, it is likely that the study design resulted in an overestimation of the dog's performance.

SUMMARY

Despite the limitations, this study is a proof of principle and suggests that *C. difficile* may be detected quickly in a clinical setting, allowing the rapid initiation of infection control measures and treatment.