Update in Hospital Medicine: Evidence Published in 2013

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In this Update in Hospital Medicine, we present and discuss our choices of influential, practice-changing medical studies that were published in 2013. Two studies look at the prevention and treatment of *Clostridium difficile* infection (CDI), and 4 address intensive care unit (ICU) topics related to transfusion thresholds in severe gastrointestinal bleeding, prone positioning in acute respiratory distress syndrome (ARDS), a drug cocktail for cardiac arrest, and the controversial practice of screening for methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Three studies address optimum inpatient management of diabetes and exacerbations of chronic obstructive pulmonary disease (COPD) and heart failure. Finally, because no hospital medicine year in review would be complete without a study on venous thromboembolism (VTE), we highlight a study that examined the merits of extended VTE prophylaxis with aspirin versus low-molecular-weight heparin (LMWH) in patients undergoing elective hip replacement.

Prevention and Treatment of CDI

Fecal Microbiota Transplant Is More Effective Than Vancomycin for Recurrent CDI

Van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med. 2013; 368:407-15. [PMID: 23323867]

Background: During the past decade, there has been a significant increase in the incidence and severity of CDI resulting in increased mortality and economic burden. Approximately 20% of patients treated for CDI with antimicrobial therapy have a recurrence after their initial treatment course. Patients in this group are at high risk for a second recurrence (approximately 40%), and multiple relapses are not uncommon. Observational studies suggested that fecal microbiota transplantation (FMT) was an effective treatment for patients with recurrent CDI, but no randomized trials had evaluated the benefits and harms of such treatment.

Findings: In this unblinded randomized, controlled trial, patients with a relapse of CDI after at least 1 course of appropriate antibiotic therapy was assigned to 1 of 3 treatment groups: standard therapy with vancomycin, 500 mg orally 4 times per day for 14 days; oral vancomycin for 14 days, followed by bowel lavage on the last day of antibiotic treatment; or oral vancomycin for 4 to 5 days, bowel lavage, and subsequent FMT infusion via a nasoduodenal tube. The primary end point was resolution of CDI-related diarrhea without relapse after 10 weeks.

In the FMT group, 13 (81%) of 16 patients were cured after the first infusion, and 2 of the remaining 3 patients were cured by a second infusion. In contrast, cure rates were 31% in the vancomycin group and 23% in the vancomycin plus bowel lavage group ($P = 0.001$ compared with the FMT group). No statistically significant differences in serious adverse events were noted among the 3 groups.

Cautions: This trial was stopped early for an apparent treatment benefit. When a trial, especially a small one, is stopped prematurely owing to perceived benefit, treatment effects may be exaggerated (1, 2). Furthermore, the trial was unblinded, and the actual efficacy of vancomycin was much less than predicted (60%).

Implications: These results are compelling and consistent with prior observational data that FMT is effective for recurrent CDI. For patients with 2 or more recurrences of CDI, FMT should become first-line therapy. Research is now needed to identify simple protocols to harvest and process donor feces and determine the optimal route of administration.

Largest Probiotic Trial Fails to Show Benefit in Preventing *C. difficile*–Associated Diarrhea

Allen SJ, Wareham K, Wang D, et al. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2013;382: 1249-57. [PMID: 23932219]

Background: *Clostridium difficile*–associated diarrhea (CDAD) is a major cause of morbidity and mortality in hospitalized patients. It occurs most often in older hospitalized adults exposed to broad-spectrum antibiotics, which deplete the normal gastrointestinal flora and allow *C. difficile* to thrive and cause clinical disease. The mainstay of prevention has relied on reducing transmission of the organism and avoiding inappropriate antibiotic use. However, a recent meta-analysis suggested that probiotics, microorganisms that fortify the gastrointestinal flora, result in a large reduction in CDAD and are safe (3).

Findings: In the largest prospective blinded trial to date, approximately 3000 inpatients aged 65 years or older who were about to start antibiotic therapy (or were recently exposed within 7 days) were randomly assigned to receive 2 probiotic strains each of *Lactobacillus acidophilus* and bifidobacterium daily, or placebo for 21 days. The primary

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outcomes were the occurrence of antibiotic-associated diarrhea at 8 weeks and CDAD at 12 weeks.

The incidence of antibiotic-associated diarrhea was similar in the probiotic and placebo groups (10.8% vs. 10.4%, respectively; $P = 0.71$), and in contrast to the meta-analysis, the rate of CDAD did not significantly differ between groups (0.8% vs. 1.2%; $P = 0.35$). The class and number of antibiotics used were the same in both groups.

Cautions: The main limitation of this trial was that the CDAD event rate in the placebo group was lower than predicted (1.2% vs. 4%), which could indicate false-negative results. Furthermore, stool samples to test for *C. difficile* could not be obtained in about 40% of patients.

Implications: Contrary to prior data, this study's negative results suggest that the use of probiotics for prevention of CDAD is complex and incompletely understood. Future research should focus on better understanding of the multiple variables that probably affect efficacy, including types and dosing of probiotic strains, local incidence of CDAD, class of antibiotics used, and host risk factors. Meanwhile, clinicians considering use of probiotics for the prevention of CDAD should be aware that efficacy may vary by strain and that patients' predisposing characteristics and the local frequency of CDAD also play key roles in determining risk.

Issues in the ICU

A Restrictive Transfusion Strategy Reduced Mortality in Patients With Acute Upper Gastrointestinal Bleeding

Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11-21. [PMID: 23281973]

Background: Clinicians routinely transfuse patients with acute upper gastrointestinal bleeding to prevent hemodynamic deterioration. Current transfusion guidelines recommend restrictive rather than liberal transfusion thresholds for hemodynamically stable hospitalized patients (4). Whether this approach applies to patients with acute upper gastrointestinal bleeding is uncertain because such patients were excluded from the original studies that underpinned the guidelines.

Findings: In this trial, 921 patients with acute upper gastrointestinal bleeding were randomly assigned to receive either a restrictive transfusion strategy (when the hemoglobin level decreased to <7.0 g/dL, with a posttransfusion target of 7.0 to 9.0 g/dL) or a liberal strategy (when the hemoglobin level decreased to <9.0 g/dL, with a posttransfusion target of 9.0 to 11.0 g/dL). The primary outcome measure was all-cause mortality within 45 days. The restrictive strategy, compared with the liberal strategy, decreased overall blood transfusions by nearly 60% and reduced all-cause mortality (5% vs. 9%, respectively), further bleeding rates (10% vs. 16%), adverse events (40% vs. 48%), and hospital length of stay (9.6 vs. 11.5 days).

Cautions: These results should not be generalized to all patients with acute upper gastrointestinal bleeding because the mortality analysis was not adjusted for hypovolemic shock and patients with massive bleeding were excluded. In addition, some hesitation in applying the restrictive transfusion targets to all patients with cardiovascular disease may be warranted.

Implications: Clinicians should withhold transfusion in hemodynamically stable patients with acute upper gastrointestinal bleeding until the hemoglobin level decreases to less than 7.0 g/dL. For every 25 patients treated with such a restrictive strategy, clinicians would prevent 1 death at 6 weeks while substantially reducing the use of limited blood supplies. Treatment should be individualized for patients with hypotension in the setting of severe bleeding or those in hypovolemic shock. Although the trial did not include patients with acute lower gastrointestinal bleeding, observed outcomes were consistent with findings seen in other settings. Thus, it seems reasonable to also use a restrictive strategy in patients with hemodynamically stable acute lower gastrointestinal bleeding.

Prone Positioning Benefits Patients With Severe Acute Respiratory Distress Syndrome

Guérin C, Reignier J, Richard JC, et al; PROSEVA Study Group. Prone positioning in acute severe respiratory distress syndrome. N Engl J Med. 2013;368:2159-68. [PMID: 23688302]

Background: Patients with ARDS commonly develop consolidation of the dependent lung regions. Small randomized, controlled trials demonstrate that transitioning patients with ARDS from the supine to prone position improves oxygenation but does not affect patient survival. A meta-analysis, however, suggests that prone positioning might decrease mortality among patients with severely hypoxemic ARDS (5).

Findings: This trial included 466 patients with moderate to severe ARDS (defined as a PaO_2–FiO_2 ratio <150, with FiO_2 ≥0.6; positive end-expiratory pressure ≥5 cm H_2O). All patients received low-tidal-volume ventilation for 12 to 24 hours before being randomly assigned to daily prone positioning or to supine positioning only. Intervention group patients were placed in the prone position within 1 hour of randomization and underwent an average of 4 sessions of proning (mean duration per daily session, 17.3 hours).

At randomization, more than 80% of patients were receiving neuromuscular blockade, and approximately 40% were receiving glucocorticoids. Mortality at 28 days was 16% in the prone positioning group and 33% in the supine positioning group ($P < 0.001$).

Cautions: This intervention is not suitable for all patients with ARDS, such as those with sternotomies or facial

trauma. Placing a patient in the prone position and delivering care safely requires a coordinated, multiteam effort that may necessitate increased staffing and training.

Implications: The survival benefit of prone positioning in this study was dramatic, leaving us to reconcile results of prior trials that reported no such benefit. Treatment focused on patients with severe hypoxemia and was applied quickly and involved prone positioning for 70% of each day; in contrast, the proportion of time spent in prone positioning was much less (about 30% of each day) in prior trials. On the basis of these results, it is time to take a new position on proning: Use it early for most patients with severe ARDS.

A Vasopressin–Steroid–Pressor Cocktail Improves Outcomes in In-Hospital Cardiac Arrest

Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. JAMA. 2013: 310:270-9. [PMID: 23860985]

Background: Aside from aggressive chest compressions and early defibrillation, interventions to improve cardiac arrest outcomes are lacking. A small study using a combination of vasopressin, steroid, and epinephrine (VSE) showed improved survival to hospital discharge but could not assess the effect on neurologic outcomes (6). These data prompted researchers in Greece to perform a randomized trial involving 300 patients with in-hospital cardiac arrest who required at least 1 dose of epinephrine.

Findings: Patients received VSE (20 U of vasopressin and 1 mg of epinephrine per 3-minute cycle for up to 5 cycles, plus 40 mg of methylprednisolone with the first dose of epinephrine) or placebo (saline) plus the standard 1-mg epinephrine dose during each 3-minute cycle. Postresuscitation shock was treated with stress-dose hydrocortisone (300 mg/d for a maximum of 7 days, followed by gradual taper) in the VSE group versus saline in the control group. Therapeutic hypothermia was used to a similar extent in both groups (25%).

Patients who received VSE were more likely than those in the control group to be alive at hospital discharge with neurologically favorable outcomes (14% vs. 5%, respectively). Among 149 patients with return of spontaneous circulation who developed postresuscitation shock, those in the VSE group were also more likely than control patients to be alive at hospital discharge with neurologically favorable outcomes (21% vs. 8%).

Cautions: Postarrest myocardial function and outcomes at 1 year were not reported. It is also unclear to what extent stress-dose steroids contributed to the favorable outcomes in postresuscitation shock; however, a portion of the control group with postresuscitation shock who received open-label hydrocortisone (21%) at the discretion of their attending physicians had more organ failure–free days than those not receiving hydrocortisone.

Implications: Although in-hospital cardiac arrest outcomes remain poor, this intervention represents a new milestone: a pharmaceutical combination that affects important patient-level outcomes. Effects may reflect improved periarrest hemodynamics, shorter resuscitation time, and improved cerebral microcirculatory flow. Expect incorporation of this protocol into cardiac resuscitation guidelines and clinical practice.

Universal Decolonization Is More Effective in Preventing ICU Infections Than Targeted Decolonization or Screening and Isolation

Huang SS, Septimus E, Kleinman K, et al; CDC Prevention Epicenters Program; AHRQ DECIDE Network and Healthcare-Associated Infections Program. Targeted versus universal decolonization to prevent ICU infection. N Engl J Med. 2013;368;2255-65. [PMID: 23718152]

Background: Health care–associated infections are an important cause of morbidity, mortality, and health care expenditure, especially in ICU patients. Among the potentially preventable complications of hospitalization, MRSA infection is of specific interest, owing to its protean manifestations, increasing incidence, virulence, and multidrug resistance. Screening for MRSA and contact precautions are the mainstays of prevention, although decolonization is an option in MRSA carriers. How best, if at all, to target decolonization (MRSA carriers or globally) in the ICU is unclear.

Findings: The REDUCE MRSA (Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate Methicillin-Resistant *Staphylococcus aureus*) trial examined targeted and global decolonization versus screening and isolation alone in 43 hospitals. Nearly 75 000 patients in 74 ICUs were randomly assigned into 3 groups. Control group patients were screened and isolated if positive for MRSA. In the second group, MRSA-positive patients were isolated and decolonized with nasal mupirocin and chlorhexidine baths. The third group was not screened for MRSA, but all ICU patients were decolonized. All groups used contact precautions for patients with a history of MRSA.

The rate of MRSA-positive clinical isolates was lowest in the universal decontamination group (hazard ratio [HR], 0.63) versus targeted decolonization (HR, 0.75) and screening with isolation (HR, 0.92). There was a reduction in bloodstream infections with universal decontamination (HR, 0.56) and targeted decolonization (HR, 0.78) compared with screening and isolation (HR, 0.99).

Cautions: Universal decolonization of ICU patients seems to be effective, but the relative effect of mupirocin versus chlorhexidine is unclear. Of concern is the effect of increasing use of mupirocin and chlorhexidine and the development of MRSA or other organism resistance. Reports of chlorhexidine resistance are rare, but mupirocin resistance is well-documented (7, 8).

Implications: Implementation of the techniques involved in this trial is feasible and proven effective in community hospitals. The effects of reducing bloodstream infections are in the interest of both patients and health care institutions. On the basis of the results of this study, hospitals should reconsider the utility of screening and isolation—a practice that impedes direct patient care. In the absence of convincing evidence, laws mandating MRSA screening (which are active in several states) should be abolished.

Inpatient Management of Diabetes, COPD Exacerbations, and Heart Failure

A Simpler Insulin Regimen Results in Similar Glycemic Control Compared With Basal-Bolus Dosing

Umpierrez GE, Smiley D, Hermayer K, et al. Randomized study comparing a basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: basal plus trial. Diabetes Care. 2013;36:2169-74. [PMID: 23435159]

Background: Randomized, controlled trials of patients admitted to general medical and surgical wards have shown that a basal-bolus insulin regimen results in improved glycemic control and fewer complications compared with sliding-scale insulin (SSI). Despite new guideline recommendations to use a basal-bolus regimen as the preferred approach in non–critically ill hospitalized patients, some clinicians remain hesitant, perhaps owing to the complexity of this regimen or fear of inducing hypoglycemia (9).

Findings: In this multicenter trial, 375 adult hospitalized patients with type 2 diabetes were randomly assigned to 1 of 3 insulin regimens:

1. Basal-bolus: glargine given once daily and glulisine given before meals, plus additional corrective glulisine SSI (given at the same time) as needed for blood glucose levels of 140 mg/dL or greater.

2. Basal-plus: glargine given once daily, plus corrective glulisine SSI before meals for blood glucose levels of 140 mg/dL or greater.

3. Glulisine SSI alone before meals for blood glucose levels of 140 mg/dL or greater (no basal insulin). Patients who were receiving nothing by mouth were given corrective glulisine SSI every 6 hours as needed for blood glucose levels of 140 mg/dL or greater.

The basal-plus regimen resulted in glycemic control similar to the basal-bolus regimen, and both were superior to SSI alone. Glycemic control within the target range (70 to 140 mg/dL) was highest for the basal-plus regimen (42%) compared with the basal-bolus (37%) and SSI (32%) regimens ($P = 0.045$). Hypoglycemia (blood glucose level <70 mg/dL) occurred in 16%, 13%, and 3%, of patients in the basal-bolus, basal-plus, and SSI groups, respectively ($P = 0.009$). The rate of severe hypoglycemia (blood glucose level <40 mg/dL) was 1% or less in all 3 groups.

Cautions: These results are not generalizable to all inpatients, because patients with severe hyperglycemia and those receiving a total dose of insulin greater than 0.4 U/kg per day were excluded. For such patients, a basal-bolus approach may be preferred.

Implications: This study strengthens existing evidence that basal insulin is necessary for optimal glucose control in hospitalized patients with type 2 diabetes. Clinicians now have an effective alternative regimen in "basal-plus," which is simpler to use and achieves similar glycemic control. Future trials should focus on elucidating its effects on more meaningful outcomes, such as hospital complication rates and mortality.

A 5-Day Course of Corticosteroids in COPD Exacerbations Is Equally as Effective as Traditional Dosing

Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCED randomized clinical trial. JAMA. 2013;309:2223-31. [PMID: 23695200]

Background: Although randomized trials showed that patients with COPD exacerbations benefited from systemic corticosteroids, the trials used different doses and durations of steroid therapy, which has led to practice variation. The 2013 Global Initiative for Chronic Obstructive Lung Disease guidelines (10) recommend a 10- to 14-day course of systemic corticosteroids (30 to 40 mg of prednisolone) for COPD exacerbations.

Findings: Swiss researchers randomly assigned 314 patients (>85% with severe or very severe airflow limitation and baseline mean FEV_1 of 31%) with acute COPD exacerbations to receive 5-day or 14-day courses of glucocorticoids (40 mg of intravenous methylprednisolone in both groups on day 1, followed by oral prednisone, 40 mg/d). Most patients were hospitalized (92%), and both groups received a 7-day course of antibiotics, short-acting bronchodilators, inhaled glucocorticoids, and long-acting β-agonists twice daily plus tiotropium.

Intention-to-treat analysis revealed no difference between the 5-day and the 14-day course of therapy in terms of repeated exacerbations within 6 months (36% vs. 37%, respectively), time to repeated exacerbation, death from any cause, or need for mechanical ventilation. Adverse events were similar in the 2 groups, but the median length of hospital stay was significantly shorter in the 5-day treatment group (8 vs. 9 days). The cumulative steroid dose was reduced by 65% in the 5-day treatment group over the study period.

Cautions: The patient population in the study had severe to very severe COPD, with at least a 20–pack-year tobacco history. The results may not be generalizable to nonsmokers or those with less severe disease; however, the latter seems unlikely. It is also unclear whether physicians will

readily withhold further systemic corticosteroid dosing in patients who have completed a 5-day course yet still meet criteria for inpatient treatment.

Implications: In patients presenting to the emergency department with acute exacerbations of COPD, 5 days of systemic glucocorticoid therapy was noninferior to a 14-day course while significantly reducing glucocorticoid exposure. When it comes to steroids and treatment of COPD exacerbations, less is definitely more, and most patients should be treated with a 5-day course of therapy.

Sodium and Water Restriction Is Not Beneficial in Hospitalized Patients With Heart Failure

Aliti GB, Rabelo ER, Clausell N, et al. Aggressive fluid and sodium restriction in acute decompensated heart failure: a randomized clinical trial. JAMA Intern Med. 2013;173:1058-64. [PMID: 23689381]

Background: Patients hospitalized with acute decompensated heart failure are frequently placed on low-sodium, volume-restricted diets despite inconclusive data supporting their use. Although this restriction seems to make prima facie sense, patients may perceive fluid and salt restriction as draconian measures. Does the low-fluid, low-salt paradigm make a difference to patient outcomes?

Findings: This small randomized, controlled trial involved 75 patients with acute systolic heart failure (mean age, 60 years; mean left ventricular ejection fraction, 0.26). Of these, 38 patients were randomly assigned to strict salt and fluid restriction (daily maximum intake, 800 mg of sodium and 800 mL of fluid) and 37 received more liberal diets (3 to 5 g of sodium and >2.5 L of fluid per day). The primary end points were weight loss and clinical stability at 3 days, as measured by a clinical congestion score. Secondary end points were 30-day rehospitalization rates and self-reported thirst at 7 days.

The investigators reported no statistically significant difference between the 2 groups in the primary end points; mean weight loss was 4.42 kg in the restricted intake group and 4.67 kg in the liberal intake group. Thirst was greater in the restricted than liberal intake group, as measured on a scale of 1 to 10 (5.1 vs. 3.4, respectively). The 30-day rehospitalization rate did not significantly differ, although it was higher in the restricted intake group than the liberal intake group (11 vs. 7 patients).

Cautions: Only 9% of the screened patients ended up in the study. The randomization may have occurred up to 36 hours into the admission, by which time a response to therapy may have already occurred. The total sodium and fluid ingestion was not provided, nor was the mean total dose of diuretics. No conclusions can be drawn in stable outpatients with heart failure.

Implications: There is no evidence that patients hospitalized for acute heart failure who are placed on strict sodium and fluid restrictions have better outcomes than those placed on less restrictive diets, despite the traditional use of this approach. In preventing rehospitalization, finding a proper level of homeostasis among medication, intake, and volume status would seem reasonable. Severe intake restrictions probably further activate the renin–angiotensin–aldosterone system along with vasopressin, leading to both fluid retention and increased consumption of salt and fluid after discharge. Despite the study limitations, it seems counterproductive to severely restrict sodium and fluid intake in patients with acute heart failure.

Extended VTE Prophylaxis in Hip Replacement

Aspirin Is Noninferior to LMWH for VTE Prevention After Elective Hip Replacement

Anderson DR, Dunbar MJ, Bohm ER, et al. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. Ann Intern Med. 2013;158:800-6. [PMID: 23732713]

Background: Venous thromboembolism after total hip arthroplasty is a common complication that has significant potential for morbidity and mortality. Prolonged pharmacologic prophylaxis (up to 35 days after surgery) reduces the rate of VTE but is costly and increases bleeding risk. Aspirin, a much cheaper alternative, has also been used for VTE prevention but carries its own risk for adverse effects. Which agent is superior?

Findings: The EPCAT (Extended Prophylaxis Comparing Low Molecular Weight Heparin to Aspirin in Total Hip Arthroplasty) trial was a multicenter, blinded, randomized comparison of aspirin and LMWH in 12 tertiary care centers in Canada. A total of 778 patients were initially treated with 10 days of LMWH followed by 28 days of either low-dose aspirin (81 mg) or dalteparin (5000 U subcutaneously). At 90-day follow-up, 5 patients in the LMWH group and 1 patient in the aspirin group had VTE, demonstrating that aspirin was noninferior ($P < 0.001$) but not superior to dalteparin. Clinically important bleeding rates were similar between the 2 groups: 1 major event and 4 nonmajor events (1.3% of patients) with LMWH and no major events and 2 nonmajor events (0.5%) with aspirin.

Cautions: The study population had a large range of exclusion criteria (only 18% of screened patients participated), and the trial was stopped early owing to recruitment problems. Adherence to therapy was self-reported and not checked. The total treatment time of 38 days is longer than the previously studied 35 days.

Implications: For patients initially treated with LMWH, longer-term prevention with aspirin seems equivalent to LMWH at a much lower cost. However, this trial involved a selected population and results might not be generalizable to other populations or other major orthopedic procedures. This leads to further questions, including the optimal duration of LMWH therapy before switching to aspirin and the relative merits of aspirin versus the newer

oral anticoagulants. Given the high incidence of perioperative myocardial infarction after total hip arthroplasty, there may be a secondary benefit in the use of aspirin.

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