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Title

2013 Literature Update in Hospital Medicine

Permalink

<https://escholarship.org/uc/item/8t95h8bp>

Journal

Hospital Medicine Clinics, 3(3)

ISSN

2211-5943

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Publication Date

2014-07-01

DOI

10.1016/j.ehmc.2014.04.002

Peer reviewed

2013 Literature Update in Hospital Medicine



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KEYWORDS

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

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Fluid and sodium restriction for hospitalized patients with decompensated congestive heart failure provides no significant clinical benefit.
2. Perioperative β -blockers should be given to patients already on them and to patients who need them for an additional clinical reason (eg, recent myocardial infarction and heart failure).
3. In patients with atherosclerotic renal artery stenosis, renal artery stenting did not provide benefit above medical therapy.
4. In patients with diabetic nephropathy, dual angiotensin blockade results in an increase in adverse drug events without confirmed clinical benefit.
5. Eighth Joint National Committee recommendations include the controversial recommendation to increase the systolic blood pressure threshold for treatment of adults aged 60 years or older to 150 mm Hg.
6. In patients with an acute exacerbation of chronic obstructive pulmonary disease, a 5-day course of steroids is as effective as a 14-day course.

CONTINUED

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7. In addition to standard resuscitation therapy for inpatients with cardiac arrest, the combination of vasopressin, steroids, and epinephrine outperformed the combination of epinephrine and placebo.
8. Checking residual gastric volumes for intubated patients receiving enteral feeding decreases caloric supplementation without causing a significant effect on ventilator-associated pneumonia rates.
9. The updated American College of Cardiology Foundation and the American Heart Association cholesterol guidelines focus on moderate-intensity to high-intensity statin use for at-risk groups, rather than focusing on target low-density lipoprotein levels.
10. For patients with recurrent *Clostridium difficile* infection, duodenal stool infusion resulted in improved outcomes when compared with vancomycin monotherapy.

INTRODUCTION

The Update in Hospital Medicine is designed to keep readers informed about the current state of the literature. For this update, we searched journals from mid-January 2013 to February 2014 and sought high-impact articles that had the capability of practice change or practice confirmation for hospitalists. Our initial review yielded 577 articles; from this group, a secondary review targeting those with the highest potential for clinical usefulness yielded 49 articles. From this subgroup, we selected the 10 articles from the year that were most likely to affect patient care.

What is the impact of restricting fluid and sodium intake in patients hospitalized with an acute systolic heart failure exacerbation?

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(12):1058–64.

Background/Purpose

For patients who are admitted with an acute exacerbation of systolic heart failure, clinicians often limit fluid and sodium intake as a nonpharmacologic measure to improve congestion and edema. The evidence supporting this practice is limited.

Study Design

The investigators conducted a randomized controlled trial (RCT) comparing a fluid-restricted (maximum fluid intake, 800 mL/d) and sodium-restricted (maximum sodium intake, 800 mg/d) diet with no restrictions in patients hospitalized with acute congestive heart failure. The patients enrolled had known systolic heart failure and were diagnosed in the emergency department with an acute exacerbation. Patients with chronic renal failure were excluded.

Results

Over a 3-year period, 75 patients were randomized while in the hospital to a restricted diet versus a control diet. There were no significant differences between the 2 groups;

most patients were male, the mean left ventricular ejection fraction was less than 30% in both groups, and ischemia was the most common cause for the heart failure. There were no differences between the 2 groups in terms of weight loss or clinical stability (defined as an improvement in clinical congestion) at 3 days. There were no differences between the groups with regards to dose of diuretics or overall length of stay. Patients randomized to the restricted diet reported significantly worse thirst at the end of the study period (7 days). In addition, at 30-day follow-up, patients in the restricted diet were more likely to be congested, and there was a nonsignificant trend toward higher readmissions in the restricted diet group.

Comment

This is a small but well-performed randomized trial of a fluid-restricted and salt-restricted diet in patients with an acute exacerbation of systolic heart failure, which showed no clinical benefit of the restricted diet and an increase in patient thirst. The investigators postulate a few explanations for the findings, including the ability of diuretics to manage any increase in fluid intake and that restricting sodium may be harmful because it can induce antidiuretic and antinatriuretic systems. This study adds to a few other small studies and raises questions about this practice. Providers should consider the need to fluid and sodium restrict patients with acute exacerbation of systolic heart failure and certainly should not restrict to the point of thirst.

Given that most of the trials in the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) series have been discredited, do perioperative β -blockers provide mortality benefits in patients undergoing noncardiac surgery?

Bouri S, Shun-Shin MJ, Cole GD, et al. Meta-analysis of secure randomised controlled trials of beta-blockade to prevent perioperative death in non-cardiac surgery. *Heart* 2014;100(6):456–64.

Background/Purpose

Both the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) and the European Society of Cardiology (ESC) recommend the use of perioperative β -blockers in certain circumstances. The ESC, as a class I recommendation, encourages the initiation of perioperative β -blockers with dose titration for patients with established coronary artery disease, ischemia on preoperative stress testing, or who are undergoing high-risk surgery. The ESC further recommends, with a class IIa grade, that patients undergoing intermediate-risk surgery should have β -blockers initiated as well. The ACCF/AHA offer as a class IIa recommendation that β -blockers be initiated with dose titration in patients undergoing vascular surgery and who have ischemia on preoperative testing, established coronary artery disease, or more than 1 risk factor. Furthermore, patients undergoing intermediate-risk surgery and who have coronary artery disease or more than 1 risk factor should receive dose-titrated β -blockers. Many of the data for these recommendations rely on a series of publications from the DECREASE trials. The data and conclusions of most of these trials have been discredited. The goal of this meta-analysis was to analyze the remaining data from secured trials to determine if the evidence still supports the previously published guidelines.

Study Design

This meta-analysis included published RCTs comparing noncardiac surgery preoperative β -blocker initiation with placebo in adult patients. The investigators used a systematic review of databases from 1966 to 2013 and a hand-search of previous reviews and meta-analyses. Exclusion criteria included studies that did not compare β -blockers with a placebo treatment, studies in which the β -blockers were given as a 1-time dose, the DECREASE trials, and studies that did not report intention-to-treat data. The primary end point was all-cause mortality at 30 days, inclusive of the in-hospital postoperative period. Nonfatal myocardial infarction (MI), stroke, and hypotension served as secondary end points.

Results

Nine RCTs with 10,529 patients were included in the meta-analysis. β -Blockers increased the risk of mortality by 27% (relative risk [RR] 1.27, 95% confidence interval [CI] 1.01%–1.60%, $P = .04$). The absolute risk increase was approximately 0.5% with a number needed to harm of 200. The 2 DECREASE trials that would have been included in the meta-analysis had they not been discredited showed a nonstatistically significant decrease in mortality (RR 0.42, 95% CI 0.15–1.23, $P = .11$). There was a statistically significant difference between the results from the DECREASE studies and the 9 secure trials. Although β -blockers significantly decreased the risk of MI (RR 0.73, 95% CI 0.61–0.88, $P = .001$), the data from the secure trials showed that β -blockers increased the risk of stroke (RR 1.73, 95% CI 1.00–2.99, $P = .05$) and hypotension (RR 1.51, 95% CI 1.37–1.67, $P < .00001$).

Summary

The discrediting of the DECREASE trials has rocked the perioperative world. Although large observational trials continue to associate β -blockers with improved outcome in patients at high risk who are undergoing high-risk procedures, the data from the RCTs does not support those findings. Although the POISE (Perioperative Ischemic Evaluation) trial dominates this meta-analysis, experts do not agree whether it represents usual practice. Until further large, multicenter trials are completed, the only patients who should receive perioperative β -blockers are those who should be treated with them for other indications (eg, after MI or congestive heart failure) and those who were receiving β -blockers as a chronic medication before surgery.

Does renal artery stenting improve outcomes in patients with renal artery stenosis?

Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014;370(1):13–22.

Background/Purpose

Renal artery stenosis is a common problem, particularly in elderly patients, and may result in hypertension or nephropathy. Use of renal artery stenting to treat renal artery stenosis is common, despite a lack of evidence of benefit. Two randomized trials failed to show that renal artery stenting benefited kidney function, and 3 randomized trials failed to show that renal artery angioplasty improved hypertension. But no trials

have examined whether renal artery stenting reduces adverse renal or cardiovascular events.

Study Design

To determine if renal artery stenting improves outcomes among patients with renal artery stenosis, the investigators performed a multicenter, open-label, RCT, which compared medical therapy alone with medical therapy plus renal artery stenting in patients with atherosclerotic renal artery stenosis and increased blood pressure (BP), chronic kidney disease, or both. All patients received candesartan, amlodipine, and atorvastatin (with or without hydrochlorothiazide) titrated to BP and lipid status. Subjects in the stent group also underwent renal artery stenting of 1 or both renal arteries. The primary end point was the occurrence of a major cardiovascular or renal event (death from cardiovascular or renal causes, stroke, MI, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for dialysis).

Results

Stents were placed in 434 of the 459 patients in the stent group (94.6%) and resulted in a mean reduction of the stenosis from 68% to 16% ($P < .001$). Arterial dissection was the most common angiographic complication, occurring in 11 patients (2.5%).

Renal artery stenting did not lead to fewer cardiovascular or renal outcomes. In the stent group, the primary composite outcome occurred in 35.1% of the patients compared with 35.8% in the medical therapy group ($P = .58$). In addition, there were no significant differences between the treatment groups in death from any cause, stroke, MI, or progressive renal insufficiency. There was no subgroup in which stenting significantly improved outcomes.

Systolic BP (SBP) was lower in the stent group compared with the medical therapy group, but the difference was small (-2.3 mm Hg, $P = .03$) and there was no difference in the number of antihypertensive medications required in the stent group compared with the medical therapy group (mean number of antihypertensives: 3.3 vs 3.5, $P = .24$).

Summary

Renal artery stenting did not provide benefit above medical therapy in patients with renal artery stenosis and hypertension or chronic kidney disease.

Dual angiotensin inhibition with an angiotensin-converting enzyme inhibitor and an angiotensin II receptor blocker decreases proteinuria, but does it safely slow the progression of kidney disease?

Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;369(20):1892–903.

Background/Purpose

Effectively targeting the leading cause of end-stage renal disease (ESRD), diabetic nephropathy, would have important public health implications. Diabetic patients with proteinuria are at high risk of progressing to ESRD. Decreasing proteinuria through the use of medications like angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) have improved ESRD outcomes. A previous study in diabetic patients that treated patients with dual inhibition enrolled subjects

with and without overt proteinuria. Results of that study did not favor dual inhibition. The purpose of this study was to specifically evaluate whether diabetic patients with overt proteinuria would benefit from dual inhibition.

Study Design

The VA NEPHRON-D (Veterans Affairs Nephropathy in Diabetes) trial pitted treatment with an ARB alone (losartan) versus dual inhibition with an ARB (losartan) and an ACEI (lisinopril) in patients with diabetes and albuminuria. The primary outcomes of this multicenter, double-blind, RCT were the first occurrence of a decline in the estimated glomerular filtration rate (GFR) (an absolute decrease of ≥ 30 mL if estimated GFR was ≥ 60 mL at randomization or a relative decrease of $\geq 50\%$ if the estimated GFR was < 60 mL at randomization), ESRD, or death. Safety outcomes, including all-cause mortality, serious adverse events, hyperkalemia, and acute kidney injury, were monitored.

The study enrolled veterans with type 2 diabetes who had an estimated GFR of 30.0 to 89.9 mL per minute per 1.73 m^2 of body surface area and a urinary albumin/creatinine ratio of at least 300 mg/g. Exclusion criteria included known nondiabetic kidney disease, a serum potassium level greater than 5.5 mg/dL, current treatment with sodium polystyrene sulfonate, and an inability to stop proscribed medications that increase potassium.

All patients received 50 mg of losartan per day and had the dose increased to 100 mg per day if potassium levels were less than 5.5 mEq/L and the creatinine did not increase by greater than 30% from the time of enrollment. After tolerating losartan for 30 days or more, patients were randomly assigned in a 1:1 ratio to have either lisinopril or a placebo added to their regimen. The lisinopril or placebo dose was increased every 2 weeks, from 10 mg to 20 mg to 40 mg per day, if the potassium levels were less than 5.5 mEq/L and the creatinine did not increase by greater than 30% from the time of randomization.

Results

The 4-year study enrolled 1648 patients and randomized 1448 (724 in each group). A primary end point occurred more often in patients in the monotherapy group (21%) compared with the dual therapy group (18.2%), but this difference was not statistically different. Overall, there was no significant difference in mortality (8.3% vs 8.7%, $P = .75$) or ESRD events (5.9% vs 3.7%, $P = .07$) between the monotherapy versus the dual therapy groups. Cardiovascular outcomes also did not differ significantly.

Serious adverse events occurred more often in the dual therapy compared with the monotherapy groups. Acute kidney injury (18.0% vs 11.0%, $P < .001$) and hyperkalemia (9.9% vs 4.4%, $P < .001$) were significantly more prevalent in the dual therapy group.

The study was halted early at the behest of the data and safety monitoring committee.

Summary

This is likely the last study that will evaluate dual versus monotherapy angiotensin inhibition in diabetics. The study was stopped early, even although there was a trend toward improvement in the primary end points and there was a chance that this would have resulted in a statistically significant improvement if the study had continued as planned. The data and safety monitoring committee concluded that the risk of serious adverse events was more likely than the benefit from reducing the primary end point. Dual angiotensin blockade should not be initiated in type 2 diabetics. If it is started, patients must be monitored closely for adverse events. Adverse events are likely to

be more deleterious in the general population outside the trial setting, where monitoring is almost never so close.

What are the recommended goals for treating nonacute hypertension? What are the recommended medications for treating nonacute hypertension?

James PA, Oparil S, Carter BL, et al. Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311(5):507–20.

Background/Purpose

Hypertension is the most common cardiovascular risk factor in the United States. National guidelines for managing this condition were last published more than a decade ago, as the Seventh Joint National Committee (JNC 7) report. This article reports the recommendations of JNC 8.

Design

Panel members appointed to JNC 8 were selected based on their expertise in hypertension and their background in a variety of disciplines relevant to the care of hypertension. The panel members commissioned external systematic review experts to search for only RCTs focusing on adults 18 years or older with hypertension, published between 1966 and 2009. Only trials that enrolled 100 or more patients and reported at least 1 year of follow-up were included. Panel members supplemented this review with 2 independent searches for major, multicentered RCTs of hypertension that involved at least 2000 participants and were published from December, 2009 to August, 2013. Panel members used evidence from these reviews to formulate their recommendations. Evidence-based recommendations (grade A) required agreement by at least two-thirds of panel members; those based on expert opinion (grade E) required agreement of at least 75% of panel members.

Recommendations

The JNC 8 panel made 9 recommendations beyond emphasizing healthy diet, weight control, and physical activity.

Recommendation 1

The panel revised JNC 7 guidelines to recommend that adults 60 years or older be treated to goal SBP less than 150 mm Hg and goal diastolic BP (DBP) less than 90 mm Hg (grade A). The panel also recommended that patients who have been treated to SBP less than 140 mm Hg should continue to take their current antihypertensive medications if they are well tolerated.

Recommendations 2 and 3

Unchanged from JNC 7, the panel recommended that adults younger than 60 years be treated to goal SBP less than 140 mm Hg and DBP less than 90 mm Hg (grade E).

Recommendations 4 and 5

The panel revised JNC 7 guidelines to recommend that both adults with chronic kidney disease and those with diabetes mellitus be treated to goal SBP less than 140 mm Hg and DBP less than 90 mm Hg (grade E).

Recommendations 6, 7, 8, and 9

The JNC 8 panel revised JNC 7 recommendations for prescribing antihypertensive medications. In a general nonblack population, including those with diabetes, the panel recommended giving equal preference to the following antihypertensive medications: thiazide diuretics, calcium channel blockers (CCBs), and ACEIs or ARBs (grade B). In a general black population, including those with diabetes, it recommends giving preference to thiazide diuretics or CCBs (grade B and C). In a population with chronic kidney disease, regardless of race, it recommended including an ACEI or ARB in the treatment regimen (grade B). The panel recommended that clinicians reassess hypertensive patients monthly until they achieve BP goal. If BP goal is not achieved, clinicians should add one of the preferred medication classes (avoiding concurrent use of ACEI and ARB), until the patient achieves BP goal or until they have prescribed all 3 classes (thiazide, CCB, and ACEI/ARB) before adding nonpreferred antihypertensive medications.

Comment

The JNC 8 panel reviewed only high-quality RCTs, in contrast to past JNC panels, which developed guidelines based on the totality of evidence, including observational studies, meta-analyses, and expert opinion, as well as RCTs. Its recommendations (especially the controversial recommendation increasing the SBP threshold for treatment of adults ≥ 60 years to 150 mm Hg) have received mixed support. Three panel members withdrew from authorship before publication, and 5 of the remaining 16 panel members published a separate minority view arguing that absence of RCT evidence for treating to SBP less than 140 mm Hg in older populations is not necessarily evidence for the absence of benefit.¹ National performance standards, such as HEDIS (Healthcare Effectiveness Data and Information Set) measures, are based on JNC 7 recommendations. Whether JNC 8 will change these standards remains uncertain.

Does treating patients with acute exacerbation of chronic obstructive pulmonary disease with a 5-day course of steroids produce similar reexacerbation rates as treatment for 14 days?

Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA* 2013;309(21):2223–31.

Background/Purpose

International guidelines recommend treating acute chronic obstructive pulmonary disease (COPD) exacerbations with 7 to 14 days of systemic glucocorticoid medications. However, observational studies and a Cochrane review reported no difference in clinical outcomes among patients who receive short versus long courses of steroids.

Study Design

The investigators conducted a randomized controlled noninferiority trial of 314 patients who presented with acute COPD exacerbation to 1 of 5 Swiss teaching hospitals. Patients were randomized to receive a short course (5 days) or a long course (14 days) of systemic steroids. All patients were treated with 40 mg intravenous methylprednisolone on the first day and 40 mg oral prednisone on each subsequent day. All

patients also received nebulized short-acting bronchodilators 4 to 6 times a day as needed, inhaled glucocorticoids/long-acting β_2 agonist twice a day, tiotropium once daily, and a 7-day course of broad-spectrum antibiotics. Investigators were blinded to group allocation. Patients were followed for 6 months, and loss to follow-up was less than 4%. The primary outcome was time to next COPD exacerbation, defined as an acute clinical deterioration requiring interaction with a clinician.

Results

Patients in the intervention and control groups were well matched at baseline. In intention-to-treat analysis, 56 patients (35.9%) in the short-term treatment group and 57 patients (36.8%) in the conventional treatment group experienced COPD reexacerbations within 180 days (P value for noninferiority = .006). Time to reexacerbation also did not differ between the 2 groups. Among patients who experienced reexacerbation, the median time to event was 43.5 days (interquartile range [IQR], 13–118 days) in the short-term treatment group and 29 days (IQR, 16–85 days) in the conventional treatment group. Analysis of prespecified subgroups and secondary end points also found no significant differences among the treatment groups in terms of glucocorticoid use before enrollment, GOLD (Global Initiative for Chronic Obstructive Lung Disease) classification, FEV₁ (forced expiratory volume in first second of expiration)/FVC (forced vital capacity) change, mortality, incidence of hyperglycemia, or infection rates. Patients in the short-term treatment group had shorter lengths of stay (median 8 days, IQR 5–11 days vs median 9 days, IQR 6–14 days).

Comment

This high-quality, randomized noninferiority clinical trial shows that a 5-day course of steroids is equally effective as treating for 14 days for most acute COPD exacerbations.

Can vasopressin and steroids improve outcomes in cardiac arrest resuscitation?

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(3):270–9.

Background/Purpose

A pilot study performed in 2009 by the same investigators suggested that vasopressin, steroids, and epinephrine (VSE) improved survival for hospitalized patients treated for cardiac arrest when compared with epinephrine and placebo. Unlike the 2005 AHA guidelines, the 2005 European Resuscitation guidelines did not suggest vasopressin as an alternative to epinephrine; epinephrine was the preferred first-line agent.

Study Design

The investigators conducted a randomized placebo-controlled double-blind study from 2008 to 2010 at 3 Greek tertiary-care centers. They enrolled 300 patients who experienced in-hospital cardiac arrest, excluding 32 who had a return of spontaneous circulation before medication administration. All remaining patients received care according to the 2005 European Resuscitation guidelines, but were randomized into 2 groups: the VSE group (20 units of vasopressin with each of the first 5 cycles of

cardiopulmonary resuscitation [CPR], along with methylprednisolone 40 mg during the first cycle and a subsequent hydrocortisone taper over 8 days) and the placebo group (saline without vasopressin or steroids).

Results

Return of spontaneous circulation was significantly improved in the VSE group: 83.9% versus 65.9% (odds ratio [OR] 2.98, $P = .005$). Survival to hospital discharge was similarly improved in the VSE group: 13.9% versus 5.1% (OR 3.28, $P = .02$). There was no significant difference between groups with regard to hospital length of stay, days in the intensive care unit, or days on the ventilator.

Summary

In addition to standard resuscitation therapy for inpatients with cardiac arrest, the combination of VSE outperformed the combination of epinephrine and placebo.

How will ventilator-associated pneumonia rates be affected if residual gastric volumes are not monitored for intubated patients receiving nasogastric tube feeds?

Reignier J, Mercier E, Le Gouge A, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. *JAMA* 2013;309(3):249–56.

Background/Purpose

For mechanically ventilated patients receiving enteral nutrition, it is common practice to measure residual gastric volumes in an effort to decrease rates of ventilator-associated pneumonia (VAP). However, numerous recent studies have suggested that suspending enteral nutrition in the setting of high residual gastric volumes places patients at risk for malnutrition without affecting VAP rates. The investigators of the present study sought to determine the effect of not monitoring residual gastric volume on VAP rates and on nutrition delivery to the patient.

Study Design

The investigators conducted a randomized multicenter noninferiority trial, in which the intervention was not to check residual volumes for intubated patients receiving nasogastric enteral nutrition. They enrolled 449 patients, excluding patients with expected duration of intubation of less than 48 hours, previous gastrotomy/jejunostomy, or gastrointestinal bleeding. Patients in the control group had residual gastric volumes checked per protocol; these were not checked in the intervention group. In both groups, enteral feeding was changed in the setting of vomiting; in the control group, it was also changed for residual gastric volumes higher than 250 cm³.

Results

There was no difference in VAP rate in the intervention (no residual checked) versus control arm (16.7% vs 15.8%, 90% CI –4.8%–6.7%). Rates of vomiting were increased in the intervention arm (39.6% vs 27%; $P = .003$), as were rates of

achievement of the caloric target (OR 4.95). There were no differences between groups in length of stay or 90-day mortality.

Summary

Clinicians do not need to check residual gastric volumes for intubated patients receiving enteral feeding, because this practice decreases caloric supplementation without effecting VAP rates.

What is the optimal management of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults?

Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2013. [Epub ahead of print].

Background/Purpose

There have been numerous RCTs since the last major guidelines on the management of cholesterol in adults were published in 2002 (Adult Treatment Panel III). This expert guideline sought to update recommendations for optimal treatment.

Design

An expert panel was convened by the National Heart, Lung, and Blood Institute (NHLBI) and members reviewed all RCTs, systematic reviews, and meta-analyses up to 2013 that examined the impact of treatment of blood cholesterol on cardiovascular disease (CVD) risk. All evidence quality was rated according to usual standards. Initial recommendations were then reviewed by additional experts in the NHLBI as well as 4 experts nominated by the American College of Cardiology (ACC)/AHA. The guidelines were endorsed by the ACC/AHA as well as multiple other national CVD organizations.

Results/Recommendations

To help clinicians estimate CVD risk, the panel developed the pooled cohort equations, risk calculators based on 5 large cohorts that allow for CVD risk assessment that is sex-specific and race-specific as well as including stroke as an outcome. The expert panel had several key recommendations.

Recommendation 1

The panel endorsed the ACC/AHA Lifestyle Management Guideline,² which encourages healthy lifestyle habits for all persons, including regular exercise and avoiding smoking.

Recommendation 2

The benefits of statin therapy outweigh the risks in 4 groups:

1. Those with known CVD (eg, acute MI, stroke, transient ischemic attack) for secondary prevention
2. Those with low-density lipoprotein cholesterol (LDL-C) levels of at least 190 mg/dL for primary prevention

3. Those aged 40 to 75 years old with diabetes and LDL-C levels of 70 to 189 mg/dL for primary prevention
4. Those aged 40 to 75 years old without diabetes and with a 10-year CVD risk of at least 7.5% (based on the pooled cohort equations) for primary prevention

Note: the investigators did not find evidence to comment on statin use in patients who receive hemodialysis or have New York Heart Association class II, III, or IV heart failure.

Recommendation 3

Patients on statins should be monitored for adherence, response to therapy, and adverse effects within 4 to 12 weeks of initiation or change in statin therapy. Alanine aminotransferase levels should be checked before initiation; hepatic function and creatine kinase levels should not routinely be monitored but can be checked based on symptoms.

Recommendation 4

There is an inadequate evidence base to make recommendations for the use of treatment goals to guide therapy; patients should remain on the appropriate statin unless they have complications. The guidelines also make specific recommendations about which statin to prescribe for the different scenarios outlined earlier as well as more specifics regarding response to therapy and side effects.

Comment

These updated cholesterol guidelines were a significant departure from previous guidelines, which advocated for treating to achieve specific LDL-C goals dependent on the level of risk. These experts believed that there was inadequate evidence to advocate for this approach. The specific guidance for the groups in whom the benefits outweigh the risks should help clinicians make decisions about appropriate therapy. There has been subsequent controversy since publication of these guidelines regarding the pooled cohort equations (which determine which patients are included in group 4), including accusations that they overestimate cardiovascular risk and lead to overtreatment with statins. The controversy has reached *The New York Times*.³ Clinicians should be advised that until the calculators are validated, they should be used cautiously to estimate risk. However, overall, these guidelines were rigorous and well done and provide clear guidance on optimal cholesterol management.

Is duodenal infusion of donor stool efficacious for the treatment of recurrent Clostridium difficile infection?

van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013;368(5):407–15.

Background/Purpose

Recurrent *Clostridium difficile* infection is common, occurring in 15% to 25% of patients treated for an initial infection, and antibiotic failure rates for the treatment of recurrent infection are high. Observational studies of duodenal infusion of feces from a healthy donor suggest that the treatment is effective. However, RCTs have not been performed.

Study Design

This is an open-label, RCT comparing 3 treatment regimens in patients with recurrent *C difficile* infection: (1) vancomycin alone, (2) vancomycin plus bowel lavage, or (3) abbreviated vancomycin, bowel lavage, and stool infusion. The primary outcome was cure of infection without relapse within 10 weeks after the initiation of therapy. Study subjects were patients with a relapse of *C difficile* infection after at least 1 course of antibiotic therapy. Critically ill patients, patients with immunodeficiency, and patients who required ongoing treatment with antibiotics for other infections were excluded. Stool donors were healthy volunteers. Donor stool was screened for parasites, *C difficile*, and enteropathogenic bacteria. Donor blood was screened for human immunodeficiency virus, human T-cell lymphotropic virus, hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus, and parasites.

Results

Forty-three patients with median of 3 recurrences of *C difficile* were enrolled in the trial. The trial was stopped early after an interim analysis reported clear benefit to the stool infusion group and relapse in most patients in both control groups. In the patients randomized to stool infusion, 81.3% were cured after the first infusion and 93.8% were cured after a second infusion. In contrast, 30.8% of patients randomized to vancomycin only were cured and 23.1% of patients randomized to vancomycin plus lavage were cured. Measurements of fecal microbiological diversity were low in patients before stool infusion and increased significantly to the level of donor diversity after infusion. After stool infusion, most subjects had diarrhea (94%). In addition, cramping (31%) and belching (19%) were reported.

Summary

Although this study was small, it represents the strongest evidence to date that treatment with duodenal stool infusion, compared with vancomycin, resulted in better outcomes in patients with recurrent *C difficile* infection, including patients with multiple previous recurrences.

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