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Advancing Evidence-Based Practice

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Most Likely to Change Clinical Practice

Indranill Basu Ray, MD

Tulane University Heart and Vascular Institute, Tulane University School of Medicine, New Orleans, LA

GASTROENTEROLOGY

In Colorectal Cancer Screening, Multitarget Stool DNA Test Appears to Have Higher Sensitivity Than Fecal Immunochemical Test

Reference: *N Engl J Med* 2014 Apr 3;370(14):1287 – Level 2 (mid-level) evidence

The American Cancer Society and American Gastroenterological Association list both the stool DNA test and the fecal immunochemical test as options for detecting cancer. The diagnostic performance of a new stool DNA test was compared to the fecal immunochemical test for detection of colorectal cancer in a recent cohort study of 11,016 asymptomatic persons aged 50-84 years with average risk for colorectal cancer. Patients with a personal or family history of colorectal cancer or a personal history of colorectal neoplasia, digestive cancer, or inflammatory bowel disease were excluded.

All patients had the multitarget DNA test and fecal immunochemical test done from a single stool sample prior to planned routine screening colonoscopy. The DNA test consisted of a hemoglobin immunoassay plus quantitative molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation, and beta-actin. A total of 9,989 patients (91%) were analyzed after exclusion of 1,027 with uninterpretable or missing results for any screening test. The cutoffs for a positive result were defined as $\geq$183 on the composite score from a logistic regression algorithm for the DNA test and $>$100 ng/mL hemoglobin for the fecal immunochemical test.

During colonoscopy, 65 persons (0.7%) were found to have colorectal cancer and 757 persons (7.6%) had advanced precancerous lesions (advanced adenomas or sessile serrated polyps $\geq$1 cm in greatest dimension).

For detection of any colorectal cancer, the multitarget stool DNA test had a sensitivity of 92.3% vs 73.8% with the fecal immunochemical test (P=0.002). For detection of advanced precancerous lesions, the multitarget stool DNA test had a sensitivity of 42.4% vs 23.8% with the fecal immunochemical test ($P<0.001$). The specificity for no colorectal cancer or advanced precancerous lesion was 86.6% with the multitarget stool DNA test vs 94.9% with the fecal immunochemical test ($P<0.001$). For detection of either colorectal cancer or advanced precancerous lesions, the multitarget DNA test had a positive predictive value of 23.6% and a negative predictive value of 94.7%, and the fecal immunochemical test had a positive predictive value of 32.6% and a negative predictive value of 93.6%.

These results show that stool DNA testing is associated with significantly higher sensitivity than fecal immunochemical testing for detection of colorectal cancer and advanced precancerous lesions at the expense of lower specificity. Further studies are required to determine the optimal interval screening duration and to address other practical aspects of testing, such as stool collection, sufficient DNA, and cost. Randomized trials are needed to determine whether stool DNA testing improves clinical outcomes such as mortality when compared to other screening tests.

GYNECOLOGY

Letrozole Associated with Increased Live Birth Rate Compared to Clomiphene Citrate in Women With Anovulatory Polycystic Ovary Syndrome

Reference: *N Engl J Med* 2014 Jul 10;371(2):119 – Level 2 (mid-level) evidence

Polycystic ovary syndrome (PCOS) affects 4%-8% of women of reproductive age and is a common cause of anovulatory subfertility. Clomiphene citrate is a selective estrogen receptor modulator that induces

Address correspondence to
Indranill Basu Ray, MD
Tulane University Heart and Vascular Institute
Tulane University School of Medicine
1430 Tulane Ave.
New Orleans, LA 70112
Tel: (504) 988-6113
Email: ibasuray@tulane.edu

ovarian stimulation and has traditionally been the first-line therapy for infertility in this patient population. Other treatments such as metformin and aromatase inhibitors have not consistently shown superiority to clomiphene for fertility outcomes. A new randomized trial compared the safety and efficacy of the aromatase inhibitor letrozole to clomiphene for treatment of infertility in 750 women aged 18-40 years with PCOS. Included women had $\geq$1 patent fallopian tube and normal uterine cavity, a male partner with a sperm concentration $\geq$14 million sperm/mL, and mutual agreement with their partner to have regular intercourse during the study period. Women received either letrozole 2.5 mg/day orally or clomiphene citrate 50 mg/day orally on cycle day 3 for 5 days and for up to 5 menstrual cycles.

The live birth rate was 27.5% for women receiving letrozole vs 19.1% for those receiving clomiphene (P=0.007, number needed to treat [NNT] 12), with no significant differences between groups in the rates of congenital anomalies in live births, pregnancy loss, or twin pregnancy. Compared to clomiphene, letrozole was associated with a significantly decreased frequency of hot flushes, but significantly increased frequency of fatigue and dizziness.

The data from this trial have been incorporated into a new guideline by the Endocrine Society. Although the guideline does not include any recommendations on comparative efficacy of letrozole or clomiphene, it now includes a strong recommendation for clomiphene citrate or comparable estrogen modulators such as letrozole as first-line treatment of anovulatory infertility in women with PCOS. Letrozole has been approved by the US Food and Drug Administration for several breast cancer indications, but is not currently indicated for infertility treatment in women with PCOS.

INFECTIOUS DISEASE

Dalbavancin and Oritavancin Each Have Similar Efficacy to Vancomycin in Patients With Serious Bacterial Skin and Skin Structure Infections

References: *N Engl J Med* 2014 Jun 5;370(23):2169, *N Engl J Med* 2014 Jun 5;370(23):2180 – Level 1 (likely reliable) evidence

Staphylococcus aureus is an important causative agent of skin and soft tissue infections, and methicillin-resistant *S aureus* (MRSA) can be particularly difficult to treat. When MRSA is suspected among hospitalized patients with complicated skin and skin tissue infections, the glycopeptide antibiotic vancomycin is a treatment option. Lipoglycopeptide analogs such as dalbavancin (an analog of teicoplanin) and oritavancin (an analog of vancomycin) share a similar mechanism to their glycopeptide counterparts but have important differences in pharmacologic properties. Two recent studies, one evaluating dalbavancin and the other evaluating oritavancin, assessed whether these analogs were noninferior to vancomycin in patients with acute bacterial skin and skin structure infections.

Dalbavancin was evaluated in a pooled analysis of 2 randomized noninferiority trials with a total of 1,312 adults (mean age 50 years) with acute bacterial skin and skin structure infections. Patients were randomized to dalbavancin 1 g intravenous (IV) on day 1 and 500 mg on day 8 vs vancomycin 1 g or 15 mg/kg IV twice daily for $\geq$3 days and followed to 70 days. Patients in the vancomycin group had the option to switch to linezolid 600 mg orally twice daily to complete 10-14 days of therapy. Fifty-four percent of patients had cellulitis, 25% had major abscess, and 21% had a wound or surgical site infection. All patients had lesions with $\geq$75 cm^2 of erythema plus systemic and symptomatic signs of infection. In patients with a pathogen isolated at baseline, 24% had MRSA and 53% had methicillin-susceptible *S aureus* (MSSA). A total of 45 patients (3.4%) had Gram-positive bacteremia, including 20 patients with *S aureus* bacteremia. The primary outcome was early clinical response, defined as cessation of spread of infection-related erythema plus absence of fever at 48-72 hours. The noninferiority criterion was defined as a lower limit of 95% confidence interval (CI) $\leq$10% for differences between groups in early clinical response. A total of 85% of patients were included in the per-protocol analysis, and 92% were included in the modified intention-to-treat analysis. Early clinical response was observed in 79.7% with dalbavancin vs 79.8% with vancomycin-linezolid in the modified intention-to-treat analysis (noninferiority met). The overall clinical response rate at the end of treatment was 90.7% with dalbavancin vs 92.1% with vancomycin-linezolid in the per-protocol analysis (not significant), with consistent results in the intention-to-treat analysis.

Oritavancin was evaluated in a randomized noninferiority trial of 968 adults (mean age 45 years) with acute bacterial skin and skin structure infections. Patients were randomized to a single dose of oritavancin 1,200 mg IV vs vancomycin 1 g or 15 mg/kg IV twice daily for 7-10 days with serum trough monitoring and followed to 60 days. Fifty percent of patients had cellulitis, 30% had abscess, and 20% had wound infection. MRSA was isolated in 21% of patients, and MSSA was isolated in 23%. All patients had lesions surrounded by erythema, edema, or induration $\geq$75 cm^2 plus signs and symptoms of systemic inflammation. The primary outcome was a

composite of cessation of spreading or decrease in lesion size, absence of fever, and lack of need for rescue antibiotic at 48-72 hours. The noninferiority criterion was defined as a lower limit of 95% CI $\leq$10% for differences between groups in the primary outcome. A total of 791 patients (82%) were clinically evaluable, and 954 patients (98.5%) were included in a modified intention-to-treat analysis. The primary outcome occurred in 82.3% with oritavancin vs 78.9% with vancomycin (noninferiority met). An investigator-assessed clinical cure occurred in 79.6% with oritavancin vs 80% with vancomycin (not significant). A decrease in lesion area of at least 20% at 48-72 hours was observed in 86.9% with oritavancin vs 82.9% with vancomycin (not significant). No significant differences were seen in the primary outcome in subgroup analyses that separately evaluated patients with MRSA or MSSA.

The findings from these randomized trials demonstrate that dalbavancin and oritavancin have clinical response rates comparable to vancomycin in the management of acute bacterial skin and skin structure infections. Dalbavancin has been approved by the US Food and Drug Administration for treatment of adults with acute bacterial skin and skin structure infections caused by certain susceptible bacteria, including MRSA and MSSA. Cost information was not reported for either agent, and pricing information does not yet appear to be available. In these trials, dalbavancin was administered once weekly and oritavancin was administered as a single dose, whereas vancomycin was administered every 12 hours. The less frequent administration required for dalbavancin and oritavancin and the lack of need to monitor serum levels may make it possible to treat some of these infections on an outpatient basis when they might otherwise have been treated in the hospital. Outpatient treatment could dramatically reduce both the costs and risks of hospitalization. However, the longer duration of action may prove to be a safety concern because any toxic effects may continue for weeks until the agents have been cleared. Also, these trials were designed to compare these lipoglycopeptide agents to vancomycin and do not represent a comparison to standard practice in some cases. For example, in patients with MSSA bacteremia, retrospective cohort studies have demonstrated that nafcillin and cefazolin are associated with reduced mortality compared to vancomycin. For patients with bacteremia who are later shown to have MSSA, it is not clear how these agents compare to standard practice, and the longer half-life of these agents may make switching to optimal treatment more difficult. In addition, it is not clear that a full 14 days of therapy is warranted in all cases, and treatment with a long-acting agent might expose a patient to antibiotics for longer than needed. Longer duration of therapy may also augment the emergence of vancomycin-intermediate *S aureus* and vancomycin-resistant *S aureus*.

PEDIATRICS

Pulse Oximetry Levels May Overly Influence Hospitalization Decision in Infants With Mild to Moderate Bronchiolitis

Reference: *JAMA* 2014 Aug 20;312(7):712 – Level 2 (mid-level) evidence

Pulse oximetry is routinely used to assess and monitor children with bronchiolitis. The American Academy of Pediatrics guideline currently recommends that supplemental oxygen should be used in children with bronchiolitis with oxygen saturation persistently $\leq$89% on pulse oximetry. However, the role of oximetry as part of the decision on whether to admit children to the hospital is unclear. A recent randomized trial of 213 infants aged 1-12 months with mild to moderate bronchiolitis evaluated the effect of oximetry readings on hospitalization rates.

All infants had oxygen saturation $\geq$88% (mean 97% in each group) at baseline and were randomized to oximetry measurements that were artificially elevated by 3% above true values vs true oximetry values. The primary outcome was hospitalization within 72 hours or hospital care for $\geq$6 hours because of concerns about respiratory distress. The primary outcome rate was 25% with artificially elevated oximetry display vs 41% with true oximetry display (P=0.005). No significant between-group differences were seen in the amount of supplemental oxygen administered in the emergency department, in the length of hospital stay, or in the rate of unscheduled medical visits for bronchiolitis.

Pulse oximetry is one of several factors used to evaluate the need to admit an infant with bronchiolitis to the hospital, and clinical findings such as respiratory distress or feeding difficulties may indicate a need for hospital admission irrespective of oxygen saturation values. The findings from this trial are consistent with those of a previous observational study that found that oxygen saturation levels were a significant predictor of hospital admission after emergency department evaluation for moderate to severe bronchiolitis. However, the ability to interpret these new results is limited by the fact that most infants in the study had near-normal oxygen saturation at baseline (mean oxygen saturation was 97%, and only 13% overall had oxygen saturation $<$94%). Nonetheless, these findings suggest that there may be an overreliance on pulse oximetry in deciding whether to admit infants with mild to moderate bronchiolitis to the

hospital. These data highlight the need to avoid weighing a single finding in isolation, rather than viewing it as one piece of a larger clinical picture.

PULMONARY MEDICINE

Thrombolytics for Patients With Intermediate-Risk Pulmonary Embolism: An Analysis of 2 Recent Systematic Reviews

References: *J Thromb Haemost* 2014 Jul;12(7):1086, *JAMA* 2014 Jun 18;311(23):2414

Results from 2 recent systematic reviews each evaluating the safety and efficacy of thrombolytics vs anticoagulants in patients with intermediate-risk pulmonary embolism (PE) have reached different conclusions because of differing methodologies. After diagnosing a patient with a PE, the next step is to do a risk assessment to guide decision-making regarding anticoagulation vs thrombolysis. The decision depends on several factors, including the hemodynamic stability of the patient and the patient's estimated risk of bleeding. The current American College of Chest Physicians guidelines suggest the use of thrombolytics for 2 groups of patients:

- Patients with acute PE associated with hypotension and without high bleeding risk
- Select patients with acute PE not associated with hypotension and with low bleeding risk whose initial clinical presentation or clinical course after starting anticoagulant therapy suggests high risk of developing hypotension

However, the evidence for the comparative safety and efficacy of thrombolytics vs anticoagulants in most patients with intermediate-risk PE has been limited. Intermediate-risk PE (also referred to as submassive PE) has been defined as hemodynamic stability with right ventricular dysfunction or myocardial injury, and this definition is consistent in guidelines from both the American Heart Association (AHA) and the European Society of Cardiology (ESC). A previous Cochrane review of 8 randomized trials with 679 adults with PE found insufficient evidence to support the use of thrombolytic therapy but did not include an analysis specific to patients with intermediate-risk PE. Two recent systematic reviews have compared thrombolytics vs anticoagulants in this specific patient population.

The first systematic review identified 6 randomized trials comparing thrombolytics (alteplase or tenecteplase) vs heparin in 1,510 patients with intermediate-risk PE. The systematic review found no significant differences in either all-cause mortality (risk ratio 0.72, 95% CI 0.39-1.31) in an analysis of all trials or risk of major bleeding (risk ratio 2.07, 95% CI 0.58-7.35) in an analysis of 5 trials with 1,474 patients. However, the CIs for both mortality and major bleeding could not rule out clinically important differences between the thrombolytics and heparin.

The second systematic review identified 16 randomized trials comparing thrombolytics vs anticoagulants and included a separate analysis of 8 trials with 1,775 patients who had intermediate-risk PE. This systematic review included all of the trials included in the review mentioned above, as well as 2 additional trials for the mortality analysis and 3 additional trials for the major bleeding analysis. The inclusion of these trials resulted in statistically significant differences for both decreasing mortality (odds ratio 0.48, 95% CI 0.25-0.92) and increasing major bleeding (odds ratio 3.19, 95% CI 2.07-4.92) in analyses of all 8 trials.

Although the specific analyses used in the 2 systematic reviews had small differences, the main reason for the opposing findings is the choice of which trials to include. Although exclusions were not described in detail, the smaller systematic review describes exclusion of the Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) trial because of inclusion criteria that do not specifically address right ventricle dysfunction or myocardial injury. This trial randomized 121 patients to either alteplase or heparin/enoxaparin but used inclusion criteria that do not match the definitions of right ventricle dysfunction or myocardial injury described in the AHA or ESC guidelines above. As a consequence, inclusion of this trial may not be appropriate for conclusions in patients with intermediate-risk PE, suggesting that the mortality benefit for thrombolytics may not be valid. At the same time, this systematic review excluded 2 additional trials from the major bleeding analysis without explanation, calling into question the finding of no between-group difference for this outcome.

This analysis highlights important aspects of the critical appraisal of systematic reviews, namely the need to clearly define the population of interest and to determine how closely the studies included in the review adhere to this definition. The fact that the mortality and major bleeding outcomes are dependent on what studies are included in the analyses adds a level of uncertainty to the findings that makes it difficult to draw strong conclusions for either safety or efficacy. Future randomized trials, such as the PEITHO (Pulmonary Embolism Thrombolysis) trial, will help clarify this. At this point, any mortality advantage for thrombolytics is uncertain, while at the same time there is a reasonable concern of increased risk of major bleeding with thrombolytics compared to anticoagulants in this patient population.

RHEUMATOLOGY

Hydroxychloroquine May Not Improve Symptoms of Primary Sjögren Syndrome in Adults

Reference: *JAMA* 2014 Jul 16;312(3):249 – Level 2 (mid-level) evidence

Sjögren syndrome is a chronic autoimmune disorder characterized by exocrine gland dysfunction resulting in dryness, pain, and fatigue. Hydroxychloroquine is an immunomodulator that is frequently prescribed for patients with primary Sjögren syndrome who present with general symptoms such as fatigue, arthralgia, and myalgia. However, despite its widespread use, clinical data supporting the efficacy of hydroxychloroquine are limited. A recent randomized trial of 120 adults with primary Sjögren syndrome compared hydroxychloroquine 400 mg orally daily vs placebo for 24 weeks.

All patients had been taking stable doses of nonsteroidal antiinflammatory drugs, oral corticosteroids, pilocarpine, or topical cyclosporine for at least 4 weeks, and concurrent use of these agents was allowed throughout the trial. The primary outcome was a $\geq$30% decrease in symptom scores on at least 2 of 3 scales assessing dryness, pain, or fatigue. The proportion of patients achieving the primary outcome was 17.9% with hydroxychloroquine vs 17.2% with placebo (odds ratio 1.01, 95% CI 0.37-2.78). Hydroxychloroquine was associated with a nonsignificant decrease in mean pain scores (P=0.06), and there were no significant differences in mean scores for fatigue or dryness. Serious adverse events were reported by 3.6% of patients taking hydroxychloroquine vs 4.9% of patients taking placebo (no P value reported).

Clinical evidence supporting hydroxychloroquine for primary Sjögren syndrome has mostly been confined to small open-label studies. A randomized crossover trial previously failed to demonstrate any symptomatic improvement associated with hydroxychloroquine despite improvements in surrogate markers of disease. However, that trial was limited by a small sample size. The results from this new and much larger trial confirm the previous findings and provide more compelling evidence that hydroxychloroquine does not appear to improve symptoms of primary Sjögren syndrome. Furthermore, use of hydroxychloroquine requires periodic ophthalmologic examinations because of a dose-related risk of retinopathy.

VASCULAR MEDICINE

Addition of Extended-Release Niacin/Laropiprant to Statin-Based Therapy Increases Risk of Serious Adverse Events and Does Not Decrease Risk of Major Vascular Events in Patients With Vascular Disease

Reference: *N Engl J Med* 2014 Jul 17;371(3):203 – Level 1 (likely reliable) evidence

For several decades, observational studies have shown correlations between certain lipid markers and the risk of major vascular events. Several of these markers have been evaluated as potential targets for the prevention or management of vascular disease. Niacin (also called nicotinic acid or vitamin B3) is an essential human nutrient that increases high density lipoprotein (HDL) cholesterol concentrations through several different mechanisms. Improvements in clinical outcomes in patients at risk of cardiovascular disease have been demonstrated with reduction in low density lipoprotein (LDL) cholesterol concentration. However, although increased HDL cholesterol concentrations are correlated with lower risk of vascular events in observational studies, it has remained unclear whether the addition of niacin to statin-based therapy actually helps decrease the risk of major vascular events. A recent large randomized trial evaluated the addition of a combination of niacin and laropiprant (a prostaglandin inhibitor used to prevent flushing) in patients with vascular disease receiving statin-based therapy.

A total of 42,424 patients aged 50-80 years with a history of myocardial infarction, cerebrovascular disease, peripheral arterial disease, or diabetes entered an unblinded run-in period with simvastatin followed by added ezetimibe if necessary until LDL cholesterol-lowering therapy was standardized, plus extended-release niacin/laropiprant. Afterwards, 25,673 patients without clinically significant adverse events during run-in continued statin therapy and were randomized to extended-release niacin/laropiprant 2 g/40 mg per day orally vs placebo. The primary outcome was major vascular events, defined as a composite of nonfatal myocardial infarction, coronary-related death, stroke, and arterial revascularization.

During median 3.9 years follow-up, the rate of major vascular events was 13.2% with extended-release niacin/laropiprant vs 13.7% with placebo (not significant). In addition, extended-release niacin/laropiprant was associated with an increased rate of fatal or nonfatal serious adverse events compared to placebo (55.6% vs 52.7%, $P<0.001$, number needed to harm 34). The increased serious adverse events with niacin/laropiprant included infections, gastrointestinal bleeding, disorders of glucose metabolism, and other events associated with gastrointestinal, respiratory, or musculoskeletal systems. Extended-release niacin/laropiprant was also associated with a

nonsignificant increase in all-cause mortality compared to placebo (6.2% vs 5.7%, $P=0.08$).

The findings from this new trial are also consistent with those of the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health) trial, which also found no reduction in vascular events with extended-release niacin compared to placebo in patients receiving statin therapy. Furthermore, this new trial showed that the use of combination niacin/laropiprant increases the rate of adverse events. In addition, the adverse event rate observed in this trial underestimates the true adverse event rate associated with treatment because patients experiencing adverse events during the unblinded run-in period were excluded from the trial. Many adverse events observed in the new trial, including infection and gastrointestinal bleeding, were not expected based on previous studies evaluating niacin such as AIM-HIGH and may be associated with laropiprant as opposed to niacin itself. Also, although niacin/laropiprant was associated with substantially increased HDL cholesterol concentrations, the baseline HDL cholesterol levels were not substantially below the normal threshold (about 44 mg/dL in each group). Thus, the interpretation of these findings is less clear for patients with low or very low HDL cholesterol levels in the population towards which niacin treatment is primarily targeted.

Collectively, the current evidence shows no evidence of benefit (through effects on HDL concentrations or otherwise) and an increased rate of adverse events with extended-release niacin in this patient population. Combination niacin/laropiprant has not been approved by the US Food and Drug Administration and has had its marketing authorization withdrawn by the European Medicines Agency based on the results of this new trial.

Level 1 [likely reliable] Evidence: research results addressing clinical outcomes and meeting an extensive set of quality criteria that minimize bias.

Level 2 [mid-level] Evidence: research results addressing clinical outcomes and using some method of scientific investigation, but not meeting the quality criteria to achieve level 1 evidence labeling.

Level 3 [lacking direct] Evidence: reports that are not based on scientific analysis of clinical outcomes. Examples include case series, case reports, expert opinion, and conclusions extrapolated indirectly from scientific studies.

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