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Advancing Evidence-Based Practice

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Most Likely to Change Clinical Practice

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CARDIOLOGY

Compared to Amoxicillin, Levofloxacin and Azithromycin Are Associated With Increased Mortality and Risk of Serious Cardiac Arrhythmia in Older Men

A recent large retrospective cohort study of Veterans Affairs medical centers in the United States evaluated the risk of all-cause mortality and serious cardiac arrhythmia in persons receiving 1 of 3 antibiotics. A total of 1,757,689 treatments with levofloxacin, azithromycin, or amoxicillin to US veterans (mean age 57 years, 89% male) from September 1999 to April 2012 were evaluated [*Ann Fam Med* 2014 Mar-Apr;12(2):121].

At 5 days, the adjusted mortality per million antibiotics dispensed was 384 with levofloxacin ($P<0.001$ vs amoxicillin), 228 with azithromycin ($P<0.003$ vs amoxicillin), and 154 with amoxicillin. At 10 days, the adjusted mortality per million antibiotics dispensed was 714 with levofloxacin ($P<0.001$ vs amoxicillin), 422 with azithromycin (not significant vs amoxicillin), and 324 with amoxicillin. Levofloxacin was also associated with an increased risk of serious cardiac arrhythmia vs amoxicillin at 5 days and 10 days, while azithromycin was associated with an increased risk of serious cardiac arrhythmia vs amoxicillin at 5 days but not at 10 days (level 2 [mid-level] evidence).

These data show that in a US population of predominantly older men, both levofloxacin and azithromycin were associated with an increased risk of all-cause mortality and serious cardiac arrhythmia during the typical dosing cycle for each drug (10 days for levofloxacin and 5 days for azithromycin). This conclusion is strengthened by the large sample size and the use of actual pharmacy dispensing data, rather than prescriptions. The study is limited by its observational design, particularly because of imbalanced patient characteristics within the cohort. Nonetheless, these findings suggest that physicians should consider prescribing medications other than levofloxacin and azithromycin for older patients when multiple antibiotic choices are available, particularly for those with cardiac comorbidities.

INFECTIOUS DISEASE

Combination Ledipasvir/Sofosbuvir With or Without Ribavirin for $\geq$12 Weeks Reported to Have Sustained Virologic Response Rates $>$90% in Adults With Chronic HCV Genotype 1 Infection

The question of when to start treatment for chronic hepatitis C is controversial and uncertain. In patients with hepatitis C virus (HCV) and advanced liver disease, treatment that achieves a sustained virologic response is associated with lower rates of liver-related morbidity and mortality, so treatment is generally recommended. For patients without advanced liver disease, guidelines suggest individualized decision-making. In this group, the absolute rates of adverse clinical events are low and take a long time to develop, so the relative benefit of early treatment is uncertain compared to monitoring and starting treatment later as needed.

For patients in whom therapy is being considered, the combination of recombinant human interferon alpha given as weekly injections and weight-based oral ribavirin has historically been a mainstay of treatment. However, both agents are limited by established adverse reactions: interferon is associated with various flu-like symptoms, depression, and cytopenia, while ribavirin is associated with hemolytic anemia, fatigue, pruritus, and rash. A recent joint treatment guideline from the American Society for the Study of Liver Disease and the Infectious Diseases Society of America includes recommendations for newer direct-acting antiviral agents; however, these

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recommendations were based on small phase 2 studies.

Now, 2 large phase 3 trials have evaluated an oral fixed-dose combination of an HCV nonstructural protein 5A inhibitor (ledipasvir) and a nucleotide polymerase inhibitor (sofosbuvir) in adults with chronic HCV genotype 1 infection [*N Engl J Med* 2014 May 15;370(20):1889 and *N Engl J Med* 2014 Apr 17;370(16):1483]. The first trial (ION-1) included previously untreated patients, whereas the second trial (ION-2) included patients previously treated with peginterferon plus ribavirin (53% also received a protease inhibitor) who had not had a sustained virologic response (serum HCV RNA $<$25 units/mL). In both trials, patients were randomized to ledipasvir/sofosbuvir 90 mg/400 mg orally once daily for 12 weeks vs 24 weeks vs ledipasvir/sofosbuvir at the same dosage plus weight-based ribavirin for 12 weeks vs 24 weeks.

In ION-1, 870 adults (mean age 53 years, 16% with cirrhosis) were randomized, and $>$99% completed treatment and were included in the analyses. The rates of sustained virologic response at 12 weeks after the end of treatment were 99% with ledipasvir/sofosbuvir for 12 weeks, 98% with ledipasvir/sofosbuvir for 24 weeks, 97% with ledipasvir/sofosbuvir plus ribavirin for 12 weeks, and 99% with ledipasvir/sofosbuvir plus ribavirin for 24 weeks. The rate of discontinuation of ledipasvir/sofosbuvir was low in all groups: 0% with ledipasvir/sofosbuvir for 12 weeks, 2% with ledipasvir/sofosbuvir for 24 weeks, 0% with ledipasvir/sofosbuvir plus ribavirin for 12 weeks, and 3% with ledipasvir/sofosbuvir plus ribavirin for 24 weeks. The most common adverse events were fatigue, headache, insomnia, and nausea.

In ION-2, 441 adults (mean age 56 years, 20% with cirrhosis) were randomized, and $>$99% completed treatment and were included in the analyses. The rates of sustained virologic response at 12 weeks after the end of treatment were 94% with ledipasvir/sofosbuvir for 12 weeks, 98% with ledipasvir/sofosbuvir for 24 weeks, 96% with ledipasvir/sofosbuvir plus ribavirin for 12 weeks, and 99% with ledipasvir/sofosbuvir plus ribavirin for 24 weeks. No patients discontinued treatment because of adverse events, and the most common adverse events were fatigue, headache, and nausea.

The ION-1 and ION-2 trials (level 3 [lacking direct] evidence) demonstrate that an all-oral fixed-dose combination of ledipasvir/sofosbuvir for 12-24 weeks is associated with sustained virologic response rates $>$90% without the need for interferon or ribavirin. This finding was true even in patients who had not had a sustained virologic response to interferon-based therapy, a group considered more difficult to treat. These results are the basis for a new drug application for the ledipasvir/sofosbuvir combination.

Other direct-acting antiviral agents have also shown promising results in early trials and are easy to administer with short duration of treatment, few contraindications, and minimal side effects reported. The arrival of these agents will almost certainly reshape the management of patients with hepatitis C infection. However, the very high cost of treatment for these new agents (estimated to exceed $90,000 per course in some cases) represents a serious limitation to their use in clinical practice, particularly in developing countries. This new study does not address the issue of when to initiate treatment for patients with chronic hepatitis C, but after clinicians decide to treat with antiviral therapy, this new evidence suggests a less toxic but expensive combination can achieve high rates of sustained virologic response.

NEUROLOGY

CAM-S Severity Score May Help Predict 90-Day Mortality and Length of Stay in Hospitalized Patients $\geq$70 Years Old Without Delirium

The Confusion Assessment Method (CAM) is a validated assessment tool that can reliably identify delirium in different patient populations and can be used to screen for delirium on hospital admission. A recent prospective cohort study evaluated a new CAM-Severity (CAM-S) score to predict adverse outcomes in hospitalized patients $\geq$70 years old [*Ann Intern Med* 2014 Apr 15;160(8):526].

The derivation cohort included 300 patients $\geq$70 years old from the Successful Aging After Elective Surgery study who were scheduled for major surgery and did not have delirium on hospital admission. The validation cohort included 919 similar hospitalized patients from the Project Recovery study.

The short-form CAM-S score (range 0-7 points) was used to categorize patients into 4 risk groups: none, low, moderate, and high. In the validation cohort, 90-day mortality was 7% among 598 patients with no risk factors, 15% among 91 patients in the low-risk category, 16% among 128 patients in the moderate-risk category, and 27% among 102 in the high-risk category (P for trend $<$0.001) (level 2 [mid-level] evidence).

Similarly, adjusted mean length of hospital stay was 6.5 days with no risk factors, 8.8 days for the low-risk category, 11.1 days for the moderate-risk category, and 12.7 days for the high-risk category (P for trend $<$0.001).

Higher CAM-S short form scores were also associated with increased risk of new nursing home

placement, functional decline, and cognitive decline (P for trend <0.001 for each risk).

The prediction of adverse patient outcomes with the CAM-S short form was consistent with a 10-item CAM-S long form (range 0-19 points). This new tool provides useful information that may help predict adverse outcomes, guide treatment decisions, and potentially monitor response to treatment in some patient populations.

VASCULAR MEDICINE

Diagnostic Algorithm Using Clinical Prediction Score, D-Dimer Testing, and Ultrasound Predicts Upper Extremity Deep Vein Thrombosis

Both cancer and the use of central venous catheters have been shown to be common risk factors for upper extremity deep vein thrombosis (UEDVT) [*J Thromb Haemost* 2005 Nov;3(11):2471], and a recent systematic review concluded that peripherally inserted central catheters are associated with higher risk of UEDVT than other central venous catheters [*Lancet* 2013 Jul 27;382(9889):311]. Previously, a clinical prediction score has been shown to help predict UEDVT in patients with clinically suspected disease [*Thromb Haemost* 2008 Jan; 99(1):202].

A new study evaluated a diagnostic algorithm that uses the clinical prediction score to guide testing with D-dimer and compression ultrasound. The scoring system gives 1 point each for the presence of venous material (such as a catheter), localized pain, and unilateral pitting edema, and subtracts 1 point if a plausible alternative diagnosis exists. For patients who score 1 point or less, the initial test of the algorithm is a serum D-dimer that if negative can rule out a UEDVT. If the D-dimer is elevated, a compression ultrasound is done. For patients with a score of 2 or 3, the algorithm starts with a compression ultrasound. If the ultrasound is positive, a UEDVT is diagnosed; if it is negative, a D-dimer test is obtained to confirm the absence of a UEDVT. Inconclusive results on compression ultrasound were managed with repeat ultrasound and, if necessary, venography. Patients who were classified as having no UEDVT after completing the algorithm had clinical follow-up for 3 months [*Ann Intern Med* 2014 Apr 1;160(7):451].

A total of 406 patients (mean age 56 years) with suspected UEDVT were enrolled, and 390 patients (96%) had a full workup according to the algorithm. UEDVT was diagnosed by compression ultrasound (done when indicated by the algorithm) in 25%. During clinical follow-up of patients without UEDVT according to the algorithm, UEDVT was subsequently diagnosed in 1.2% of 84 patients initially classified as likely UEDVT (including 12 protocol violations) but in none of 162 patients initially classified as unlikely UEDVT (level 1 [likely reliable] evidence).

An algorithmic approach to diagnosing lower extremity DVT using a clinical prediction rule, D-dimer testing, and compression ultrasound where indicated has previously been described [*J Thromb Haemost* 2009 Dec;7(12):2035]. These new findings extend the use of a similar diagnostic algorithm to patients with clinical suspicion of UEDVT. Like the previous algorithm, this new algorithm benefits from being relatively simple, quick, and noninvasive. In addition, the similarity of this new diagnostic strategy to an established algorithm may help facilitate its implementation into clinical practice.

Elastic Compression Stockings May Not Decrease Risk of Postthrombotic Syndrome After First-Time Proximal Deep Vein Thrombosis

The American College of Chest Physicians currently recommends wearing compression stockings with 30-40 mmHg pressure at the ankle for 2 years to reduce the risk of developing postthrombotic syndrome. However, the data supporting this recommendation are inconsistent and come from small randomized trials without blinding. A new double-blind randomized trial compared compression stockings to sham stockings (without therapeutic compression) in 806 patients with proximal deep vein thrombosis (DVT) [*Lancet* 2014 Mar 8;383(9920):880].

Patients (mean age 55 years) with first-time symptomatic proximal DVT were randomized to elastic compression stockings with ankle pressure 30-40 mmHg vs sham stockings with ankle pressure <5 mmHg. They were instructed to wear their assigned stockings daily during waking hours for 2 years. Postthrombotic syndrome was assessed using Ginsberg criteria (leg pain and swelling for ≥ 1 month). The development of postthrombotic syndrome was assessed every 6 months.

The overall proportion of patients adhering to use of stockings ≥ 3 days/week was 86.4% at 1 month (83.8% with compression vs 89.1% with sham) and 55.6% at 2 years (56.1% with compression vs 54.8% with sham). The cumulative incidence of postthrombotic syndrome was 14.2% with elastic compression stockings vs 12.7% with sham stockings (not significant). No significant between-group differences were found in postthrombotic syndrome severity, frequency of ipsilateral leg ulcers, or quality of life scores (level 2 [mid-level] evidence).

The findings of this new trial do not support routine use of compression stockings following acute DVT for prevention of postthrombotic syndrome. These new results are not consistent with previous findings, although this is the largest trial to date to evaluate

compression stockings and the only one thus far to have a blinded assessment using a sham stocking as a comparator. The adherence to compression stockings in this trial is reported to be lower than those observed in previous trials, although differences in methods used to measure adherence make any direct comparisons difficult. In addition, stockings may lose their elasticity after about 3 months, so the decision to replace stockings every 6 months in this new trial may have resulted in suboptimal therapeutic compression.

ONCOLOGY

Anastrozole May Decrease Risk of Breast Cancer in High-Risk Postmenopausal Women

Breast cancer is the most common type of cancer affecting women, with more than 230,000 new cases estimated in the United States in 2013 [*CA Cancer J Clin* 2013 Jan;63(1):11]. The United States Preventive Services Task Force recommends that women at increased risk of breast cancer and low risk for adverse medication effects be offered tamoxifen 20 mg daily for 5 years or raloxifene 60 mg daily for 3-4 years to reduce their risk of breast cancer. This recommendation is partially based on a recent systematic review of 7 randomized trials showing that tamoxifen or raloxifene may reduce the incidence of invasive breast cancer by 7-9 cases per 1,000 women over 5 years compared with placebo [*Ann Intern Med* 2013 Apr 16;158(8):604]. In addition, the MAP.3 trial recently showed that the aromatase inhibitor exemestane may reduce the incidence of invasive breast cancer among high-risk postmenopausal women [*N Engl J Med* 2011 Jun 23;364(25):2381].

A randomized trial compared anastrozole to placebo in 3,864 postmenopausal women aged 40-70 years at high risk of breast cancer [*Lancet* 2014 Mar 22;383(9922):1041]. Women were randomized to anastrozole 1 mg orally once daily vs placebo. At baseline, 47% of women were receiving hormone replacement therapy. All women had mammograms at least once every 2 years during median 5 years of follow-up. The 5-year adherence rate was 70% overall and was slightly lower with anastrozole vs placebo (68% vs 72%, $P=0.0047$).

The incidence of breast cancer (either invasive cancer or noninvasive ductal carcinoma in situ) was 2% with anastrozole vs 4% with placebo ($P<0.0001$, number needed to treat [NNT] 50). Similarly, anastrozole was associated with a lower rate of invasive estrogen receptor-positive cancer (1% vs 2%, $P=0.001$, NNT 100) and ductal carcinoma in situ in (0.3% vs 1%, $P=0.009$, NNT 143), but no differences were found in invasive estrogen receptor-negative cancer (1% in each group) or mortality (1% in each group). The rate of non–breast cancer was 2% with anastrozole vs 4% with placebo ($P=0.005$, NNT 50). Hot flushes or night sweats occurred in 57% with anastrozole vs 49% with placebo ($P<0.0001$, number needed to harm [NNH] 12). Treatment discontinuation because of adverse events occurred in 20% with anastrozole vs 15% with placebo (no *P* value reported) (level 2 [mid-level] evidence).

This trial demonstrates that anastrozole is associated with modest reductions in the incidence of breast cancer among high-risk postmenopausal women. These results add another option in addition to selective estrogen receptor modulators tamoxifen and raloxifene and the aromatase inhibitor exemestane for prevention of breast cancer. However, none of these trials has yet shown a benefit for preventive therapy in breast cancer-related mortality or all-cause mortality. Consequently, the decision to offer such therapies for reducing the incidence of breast cancer in high-risk postmenopausal women must be carefully balanced by the potential for increased adverse events.

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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