Practice-Changing Articles 2014
THE LATEST CLINICAL DEVELOPMENTS THAT WILL AFFECT YOUR PRACTICE

Summaries and commentary from our physician-editors
Dear Reader,

At NEJM Journal Watch, we strive to foster your understanding of medical developments and direct you to the information that is most relevant to your practice. Our 110 NEJM Journal Watch physician-editors regularly survey more than 250 medical journals to identify the most important research and guidelines, and provide the clinical context you need to practice with confidence. We choose the articles with the greatest clinical impact and summarize them, highlighting key points and identifying what’s new. As part of this effort, we carefully appraise our selections and assign a rating of Practice Changing to the articles that will immediately affect how you practice medicine today.

It is increasingly important for clinicians to apply the most effective practice standards and meet quality measures. Therefore, we’ve compiled this collection of the latest, most relevant NEJM Journal Watch Practice-Changing articles to thank you for being part of our clinician community. We hope you enjoy this compilation and find it useful in providing the best and most responsible patient care.

Jonathan N. Adler, MD
Clinical Strategy Editor,
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Delayed or No Antibiotic Prescriptions for Patients with Acute Respiratory Tract Infections

— Paul S. Mueller, MD, MPH, FACP

*Antibiotic use decreased markedly without affecting symptom severity or duration.*

Many patients expect to receive antibiotics for acute respiratory tract infections, and many clinicians prescribe them. In this trial, investigators in the U.K. assessed the effects of no or delayed antibiotic prescriptions on symptom control and antibiotic use in 900 primary care patients (age, ≥3 years) with acute respiratory tract infections. About one third of patients were prescribed antibiotics immediately, and the rest were randomized to one of four delayed-prescription strategies: 1) required to recontact clinicians’ offices by phone to request prescriptions, 2) given post-dated prescriptions, 3) allowed to pick up prescriptions but asked to wait before requesting them, and 4) given prescriptions and asked to wait to use them (patient led). A strategy of no antibiotic prescription was added during the trial. Follow-up was 1 month.

In intent-to-treat analysis, symptom severity and duration of moderately bad symptoms (about 3.5 days) did not differ significantly among the delayed-antibiotic and no-antibiotic groups; antibiotic use also did not differ significantly (range, 26% in the no-prescription group to 39% in the patient-led group). Patient satisfaction (about 85%), belief in antibiotics (about 70%), and reconsultation within 1 month (about 13%) were similar in all groups. In contrast, significantly more patients who were prescribed antibiotics immediately used them (97%) and believed they were effective (93%) yet experienced similar symptom severity and duration as did patients who received delayed or no antibiotics.

**COMMENT**

In this study, strategies of delayed or no antibiotic prescriptions in patients with acute respiratory tract infections resulted in at least 60% fewer patients using antibiotics, with no effects on symptom severity and duration, compared with immediate antibiotic prescription. Obviously, widespread implementation of such strategies would help prevent overuse of antibiotics and emergence of antibiotic resistance.

Dr. Mueller is Associate Editor, NEJM Journal Watch General Medicine, and Chair of the Division of General Internal Medicine and Associate Professor, Mayo Clinic College of Medicine, Rochester, Minnesota.

*Little P et al. Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: Pragmatic, factorial, randomised controlled trial. BMJ* 2014 Mar 5; 348:g1606. (http://dx.doi.org/10.1136/bmj.g1606)
Physical Therapy Is Beneficial in Knee Osteoarthritis
— Jonathan S. Coblyn, MD

Thrice-weekly exercise focused on quadriceps strengthening is a useful adjunct for OA patients.

Patients with knee osteoarthritis (OA) can be offered arthroscopy, medications, physical therapy (PT), or other treatment modalities. However, several randomized trials have suggested that arthroscopic interventions do not benefit most patients with knee OA (NEJM JW Gen Med Sep 16 2008 and NEJM JW Gen Med Jul 16 2002). In another study, PT was as effective as arthroscopy for meniscal tears in patients with OA (NEJM JW Gen Med Mar 28 2013). PT alone alleviates pain for many patients, but the optimal regimen is unknown.

To evaluate various PT regimens for patients with knee OA, researchers evaluated 48 trials in which PT was compared with non-exercise control interventions. The most efficacious PT programs provided aerobic, resistance, or performance exercises but did not mix exercise types. More pain reduction occurred with quadriceps-specific exercises than with other types of exercise. Best results were obtained with supervised, thrice-weekly PT programs with durations of at least 4 weeks.

**COMMENT**

Treating patients with knee osteoarthritis is not standardized. Patients can be offered analgesia, nonsteroidal anti-inflammatory drugs, steroid injections, hyaluronate compounds, arthroscopic interventions, or physical therapy. This study helps clinicians choose among these options. PT clearly helps relieve pain in patients with OA, and perhaps thrice-weekly PT for 4 weeks should be an adjunct treatment for all patients who are not responding to their current therapy.

**Steroids for COPD: Less Is Probably More**

— Patricia Kritek, MD

*Patients with chronic obstructive pulmonary disease exacerbations who require intensive care admission do better with low-dose steroids.*

A 2010 observational study suggested that relatively low-dose oral corticosteroids were as good as — or better than — high-dose parenteral steroids in hospitalized patients with chronic obstructive pulmonary disease (COPD) exacerbations, but intensive care unit (ICU) patients were excluded from that study (NEJM JW Gen Med Jun 24 2010). Whether these results can be extrapolated to patients admitted to ICUs is unclear.

Researchers evaluated 17,239 patients (77% older than 60; 31% tobacco users) with COPD exacerbations who were admitted to ICUs at 473 U.S. hospitals. Nearly one third of patients received noninvasive ventilation; 15% were intubated. Almost all patients received antibiotics and bronchodilators. Methylprednisolone doses were categorized as either high (>240 mg) or low (≤240 mg), based on total methylprednisolone administered on hospital day 1 or 2; 11,083 patients (64%) received high doses.

Patients in the two groups were matched by propensity scoring. After adjusting for unbalanced covariates, the groups had similar in-hospital mortality. Compared with high-dose treatment, low-dose treatment was associated with shorter ICU and hospital lengths of stay, lower hospital costs, and shorter duration of mechanical ventilation. Low-dose patients were less likely to require insulin therapy or develop fungal infections.

**COMMENT**

This study strongly suggests that a moderate dose of steroids is more than adequate to treat ICU patients with severe COPD exacerbations. I would feel comfortable treating such patients with <240 mg of methylprednisolone (i.e., 80 mg to 160 mg), but a randomized trial is necessary to determine optimal dosing and duration of steroids.

Dr. Kritek is Associate Editor, *NEJM Journal Watch General Medicine*, and Associate Professor, Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle.


Abroug F and Krishnan JA. What is the right dose of systemic corticosteroids for intensive care unit patients with chronic obstructive pulmonary disease exacerbations? A question in search of a definitive answer. *Am J Respir Crit Care Med* 2014 May 1; 189:1014. (http://dx.doi.org/10.1164/rccm.201403-0568ED)
Diagnostic Algorithm for Suspected Upper-Extremity Deep Venous Thrombosis

— Jamaluddin Moloo, MD, MPH

Clinical score, d-dimer testing, and ultrasonography identified patients with upper-extremity DVT.

The rate of upper-extremity deep venous thrombosis (DVT) has risen in conjunction with more frequent use of central venous catheters. We have clear algorithms for diagnosing lower-extremity, but not upper-extremity, DVT. In this multicenter study, a diagnostic algorithm was assessed in 406 patients with suspected upper-extremity DVTs. Evaluation included calculating a clinical decision score, d-dimer testing, and ultrasonography. The clinical score consisted of +1 point each for presence of a central venous catheter or lead, localized pain, or unilateral edema and −1 point for a plausible alternate diagnosis. Scores of \( \leq 1 \) implied that upper-extremity DVT was unlikely. Follow-up was 3 months. Upper-extremity DVTs were verified in 103 patients.

Fifty percent of patients (203) were assigned clinical decision scores of 0 or 1 (upper-extremity DVT unlikely); 90 had normal d-dimer tests and did not undergo further testing or treatment — none developed symptomatic DVTs. The 113 low-scoring patients with abnormal d-dimer tests underwent ultrasonography: Ultrasonography was negative in 73 — they did not receive treatment, and none developed symptomatic DVTs. Upper-extremity DVTs were diagnosed in 12 low-scoring patients. In the 203 patients with higher scores, ultrasonography detected no upper-extremity DVTs in 83; those patients underwent d-dimer testing and repeated ultrasonography if d-dimer test were abnormal, with a yield of 3 additional DVT diagnoses. Rates of upper-extremity DVT were significantly lower in patients with scores \( \leq 1 \) than in those with scores >1 (6% vs. 44%).

COMMENT

This algorithm for upper-extremity deep venous thromboses — a clinical decision score, a d-dimer test, and ultrasonography — is similar to strategies for diagnosing lower-extremity DVTs. Given that this algorithm is successful and noninvasive, it could become a standard for clinical practice.

Dr. Moloo is Associate Editor, NEJM Journal Watch General Medicine, and Assistant Professor of Medicine, University of Colorado Health Sciences Center, Aurora, Colorado.

More Evidence That Meniscal Tears Might Not Require Surgery

— Jonathan S. Coblyn, MD

_Sham arthroscopy was as effective as arthroscopic repair for meniscal tears without osteoarthritis._

In a recent study, patients with coexisting meniscal tears and osteoarthritis who were treated with physical therapy alone or with arthroscopic repair followed by physical therapy had similar outcomes (NEJM JW Gen Med Mar 28 2013). Now, investigators in Finland have conducted a randomized trial in which nearly 150 patients (age range, 35–65) with knee pain consistent with nontraumatic meniscal tears and no osteoarthritis were assigned to either arthroscopic partial meniscectomy or sham arthroscopy. Patients were followed for 1 year. All patients underwent the same postoperative care, including a graduated exercise program.

During follow-up, both groups showed marked improvements in knee pain–related scores — after exercise and 12 months after surgery — and no significant between-group differences were observed. Of the seven patients who underwent additional surgeries because of persistent symptoms, two were in the meniscectomy group and five were in the sham group, but this difference was not statistically significant.

**COMMENT**

This study adds to growing evidence that patients with nontraumatic meniscal tears (with or without osteoarthritis) probably do not require arthroscopic surgery, at least not initially. Time and physical therapy might yield similar outcomes with much less expense.

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Smoking Cessation Is Associated with Improvements in Mental Health

— Paul S. Mueller, MD, MPH, FAC

The effect size is similar to that of antidepressant treatment.

Many smokers cite relief of psychological symptoms as a reason for continued smoking. However, the relation between smoking and mental health is unclear. In this meta-analysis of 26 prospective, observational studies conducted in various countries worldwide, investigators compared changes in mental health (anxiety, depression, mixed anxiety and depression, quality of life, positive affect, and stress) at ≥6 weeks’ post–smoking cessation with changes after the same amount of time in people who continued to smoke.

After a median follow-up of 6 to 12 months, smoking cessation, compared with continued smoking, was associated with significant decreases in anxiety, depression, mixed anxiety and depression, and stress and significant increases in psychological quality of life and positive affect (all measured via questionnaires). The effect size was similar in participants from general populations and those with physical or psychiatric illnesses.

COMMENT

In this study, smoking cessation was associated with improved mental health outcomes. Although these observational associations do not prove causality, they do challenge widely held beliefs that smoking relieves psychological symptoms and that trying to quit smoking aggravates such symptoms. As the authors note, if the associations are causal, the effect size of smoking cessation is similar to that of drug treatment for depression or generalized anxiety disorder. At least, these results should inspire us to be more proactive in encouraging smoking cessation among patients with anxiety and depression.

Dr. Mueller is Associate Editor, NEJM Journal Watch General Medicine, and Chair of the Division of General Internal Medicine and Associate Professor, Mayo Clinic College of Medicine, Rochester, Minnesota.

Taylor G et al. Change in mental health after smoking cessation: Systematic review and meta-analysis. BMJ 2014 Feb 13; 348:g1151. (http://dx.doi.org/10.1136/bmj.g1151)
Careful Meta-Analyses Cast Doubts on Flu Drugs

— Abigail Zuger, MD

The Cochrane Collaboration again concludes that both oseltamivir and zanamivir are overrated.

Cochrane reviewers have been skeptical about the efficacy of the neuraminidase inhibitors zanamivir (Relenza) and oseltamivir (Tamiflu) for treating patients with influenza (NEJM JW Gen Med Jan 5 2010). However, because much of the proprietary data on these drugs has been unavailable for public review, their conclusions have been tentative. Now, two new Cochrane reviews incorporate thousands of pages of previously unavailable data from the drugs’ manufacturers.

In a review of 20 randomized, controlled studies of oseltamivir, investigators concluded that the drug reduced mean duration of influenza symptoms in adults by about 17 hours (from 7 days to 6.3 days) and in otherwise healthy children by about 29 hours; the drug had no significant effect on duration of symptoms in children with asthma. Oseltamivir slightly lowered rates of unverified pneumonia among adults (but not among children) but had no effect on hospital admission rates among either adults or children. Because virtually no influenza-related deaths occurred among study participants, the drug’s effect on mortality could not be addressed. In prophylaxis studies, the drug lowered the incidence of symptomatic influenza by 55% during 42 days of follow-up. Adverse effects included nausea and vomiting.

In a review of 26 studies of the inhaled medication zanamivir, researchers concluded that the drug reduced mean duration of symptoms by about 14 hours in adults (from 6.6 days to 6 days) and had no significant effect on duration of symptoms in children. Zanamivir did not prevent pneumonia, otitis media, or sinusitis among either adults or children. The studies did not report hospital admission rates. In prophylaxis studies, zanamivir lowered risk for symptomatic influenza in adults and children by about 60% during roughly 1 month of follow-up. No adverse effects were associated with the drug.

COMMENT

These two long, meticulously documented analyses deliver a consistent message: The neuraminidase inhibitors oseltamivir and zanamivir are modestly effective in preventing symptomatic influenza and minimally effective in treating it. Data regarding the much-hyped oseltamivir are particularly damning. In the words of the researchers, “these findings provide reason to question the stockpiling of oseltamivir, its inclusion on the WHO list of essential drugs, and its use in clinical practice as an anti-influenza drug.”

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Jefferson T et al. Oseltamivir for influenza in adults and children: Systematic review of clinical study reports and summary of regulatory comments. BMJ 2014 Apr 9; 348:g2545. (http://dx.doi.org/10.1136/bmj.g2545)

Heneghan CJ et al. Zanamivir for influenza in adults and children: Systematic review of clinical study reports and summary of regulatory comments. BMJ 2014 Apr 9; 348:g2547. (http://dx.doi.org/10.1136/bmj.g2547)
Recommended Childhood and Adolescent Immunization Schedule for 2014

— Deborah Lehman, MD

The CDC Advisory Committee on Immunization Practices has released its new immunization schedule.

The 2014 recommended pediatric immunization schedule is again presented as a single schedule for children and adolescents from birth through 18 years of age. A second table shows recommendations for catch-up immunizations. Extensive footnotes contain key clarifications of previous recommendations, including the following:

- **Tetanus, diphtheria, and acellular pertussis (Tdap) vaccine**: This is recommended as a single lifetime dose during adolescence; however, pregnant adolescents should receive one dose of vaccine with each pregnancy irrespective of time since last dose.

- **Haemophilus influenzae type b (Hib) vaccine**: Incompletely vaccinated children aged 12 to 59 months who are at high risk for invasive Hib disease should receive two doses 8 weeks apart. This includes children with asplenia or HIV infection and chemotherapy recipients.

- **Pneumococcal vaccination in high-risk children**: Administer the complete PCV13 series before administering PPSV23, with PPSV23 administered at least 8 weeks after completion of the PCV13 series. Children for whom PPSV23 is indicated and for whom a booster after age 5 years is recommended are identified.

- **Human papillomavirus virus vaccine intervals**: Administer the third dose >12 weeks after the second dose and >24 weeks after the first dose.

- **Quadrivalent conjugate meningococcal vaccine**: Children who should receive Meneveo starting at age 2 months include those with sickle cell disease or complement deficiency and travelers to endemic areas.

**COMMENT**

The updated schedule does not contain any dramatic changes but does clarify previous recommendations and adds trade names for many vaccines. Health care providers need to be aware of the updated schedules and know how to access them. New parent-friendly vaccine schedules also are available at http://www.cdc.gov/vaccines/schedules/index.html.

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Sentinel Lymph Node Biopsies for Thin Melanomas

— Hensin Tsao, MD, PhD

*SLNB should be considered in patients with thin melanomas and Breslow thickness >0.75 mm, Clark level IV, or ulceration.*

Surgeons commonly recommend sentinel lymph node biopsy (SLNB) for tumors ≥1 mm in thickness. Some thin melanomas have poor outcomes, recurring as many as 10 years after initial diagnosis, with melanoma-related death in some. The American Joint Committee on Cancer staging manual recommends SLNB for patients with “thin IB” tumors (i.e., lesions less than 1 mm thick but with such adverse prognostic indicators as ulceration and high mitotic rate). The prognostic utility of SLNB in individuals with thin IB tumors is not currently clear. These investigators conducted a large, multi-institutional study to determine factors predictive of SLN metastasis in thin melanomas.

Retrospective review of an international database identified 1250 patients with a thin melanoma (primary tumor thickness <1 mm) and SLNB performed between 1994 and 2012. Breslow thickness, Clark level, ulceration, regression status, and mitotic rate were evaluated. Sixty-five patients had a positive SLNB. The clinically useful predictors for a positive sentinel node in thin melanoma were Breslow thickness >0.75 mm, Clark level IV, and ulceration. Neither mitotic rate ≥1/mm² nor absence of regression predicted SLN disease in any of the multivariable models. Median follow-up was 2.6 years. Among the 65 positive SLN patients, 4 melanoma-related deaths occurred (6.2%). In the negative SLNB group, there were 19 melanoma-related deaths (2.0%).

**COMMENT**

This study, one of the largest evaluating sentinel lymph node biopsy of thin melanomas, is important because most patients present with thin melanomas, a substantial fraction of which fall into the thin IB category. The risk for death in these cases was quite low, and, as one would expect, risk for nodal disease increased with increasing thickness. The 91% overall 5-year survival rate in patients with positive SLN was lower than in patients with uninvolved nodes, but oddly, relapse-free survival rates did not differ statistically between groups. Based on these results, I conclude that SLNB should be considered in patients with thin melanomas and coexisting adverse features of Breslow thickness >0.75 mm, Clark level IV, and ulceration. It is imperative to let patients know that even with positive nodes, the outcome is not nearly as grim as it might be for thicker tumors. With longer follow-up, it is possible that survival rates will drop over time and that positive versus negative node curves will further diverge.

Dr. Tsao is Editor-in-Chief, NEJM Journal Watch Dermatology, and Professor of Dermatology, Harvard Medical School; Clinical Director, MGH Melanoma & Pigmented Lesion Center; Director, MGH Melanoma Genetics Program.

Age-Specific Cutoffs for d-Dimer to Rule Out Pulmonary Embolus
— Daniel J. Pallin, MD, MPH

Using the patient’s age to determine the “normal” d-dimer threshold reduced computed tomography scanning without loss of sensitivity.

Measurement of plasma d-dimer allows pulmonary embolus (PE) to be ruled out when clinical suspicion is low or moderate, but interpretation is complicated by the fact that d-dimer levels rise normally with age. In a multicenter European study, investigators prospectively evaluated the accuracy of an age-adjusted d-dimer cutoff in 2898 patients with low or moderate clinical probability for PE.

For patients aged 50 and older, a d-dimer result was considered negative if it was less than age ×10; for younger patients, the cutoff was fixed at 500 µg/mL. Patients with a positive result underwent computed tomographic pulmonary angiography (CT-PA). All patients were followed for 3 months. The use of the age-adjusted cutoff resulted in a 12% absolute increase and a 41% relative increase in the proportion of negative d-dimer results. Of 331 patients 50 and older with d-dimer levels between 500 µg/mL and their age-adjusted cutoff, only one (0.3%) was found to have PE during follow-up.

COMMENT
This important study shows that customizing the cutoff for “normal” according to the patient’s age can reduce the number of patients requiring CT-PA without sacrificing sensitivity. This study should prompt discussion with laboratory medicine personnel to change the reporting of d-dimer to reflect age-adjusted values.

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Are Dietary FODMAPs a Cause of Irritable Bowel Syndrome?

— Allan S. Brett, MD

In a randomized trial, IBS symptoms improved with a diet low in these short-chain carbohydrates.

The idea that dietary constituents called FODMAPs (Fermentable Oligo-, Di-, Monosaccharides, and Polyols) might be responsible for some cases of irritable bowel syndrome (IBS) is gaining traction. FODMAPs are poorly absorbed, short-chain carbohydrates that include fructose, lactose, fructans (found in wheat), galactans, and polyol sweeteners.

In this randomized, crossover trial from Australia, 30 patients who met IBS criteria and 8 healthy controls consumed either a low-FODMAP diet (prepared by the researchers) or a “typical Australian diet” for 3 weeks, followed by the opposite diet for another 3 weeks; the two diet periods were separated by a 3-week washout. Patients were blinded to diet constituents.

At baseline, the mean symptom score for IBS patients was 36 (on a 100-point scale); mean scores declined to 23 during the low-FODMAP period and increased to 45 during the typical-diet period — a highly significant difference \( (P<0.001) \). Regardless of IBS subtype, patients were more satisfied with stool consistency during the low FODMAP diet. In controls, symptom scores were low at baseline and did not change during either diet period.

**COMMENT**

This is the first randomized trial to provide high-quality evidence that FODMAPs contribute to irritable bowel symptoms. One potential confounding dietary constituent is gluten, because a low-FODMAP diet (which eliminates wheat, rye, and barley because of their fructan content) is also low in gluten; however, in a recent study by the same research group, FODMAPs — and not gluten — likely were responsible for gastrointestinal symptoms in nonceliac patients with perceived gluten sensitivity (NEJM JW Gen Med Sep 19 2013). Information on low-FODMAP diets ([http://www.med.monash.edu/cecs/gastro/fodmap](http://www.med.monash.edu/cecs/gastro/fodmap)) is available from this research team’s institution and from other sources (e.g., Stanford University [http://fodmapliving.com/the-science/stanford-university-low-fodmap-diet]). Clinicians should consider recommending a low-FODMAP diet to IBS patients with abdominal bloating, flatus, and diarrhea.

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Fecal DNA Testing Comes of Age
— Douglas K. Rex, MD

A combined fecal DNA assay and immunochemical test is established as the most sensitive, noninvasive, nonimaging screening test for colorectal cancer and precancerous polyps.

As the technology of fecal DNA testing has advanced, its sensitivity for colorectal cancer has increased. The latest iteration is a combination assay that includes molecular tests for KRAS mutations, aberrant NDRG4 and BMP3 methylation, β-actin, and an immunoassay for hemoglobin (i.e., a fecal immunochemical test, or FIT). Now, investigators have assessed its performance compared with FIT in detecting colorectal cancer in patients undergoing screening colonoscopy.

Of 9989 patients evaluated, 65 (0.7%) had colorectal cancer (60 with stages I–III), and 757 (7.6%) had advanced precancerous lesions (advanced conventional adenomas or large (≥1 cm) sessile serrated polyps). The sensitivity of the fecal DNA assay was 92.3% for cancer overall and 93.3% for stage I to III cancers, compared with 73.8% and 73.3% for FIT, respectively. Among the 757 individuals with advanced precancerous lesions, the sensitivity was 42.4% overall, 69.2% for high-grade dysplasia, and 42.4% for large sessile serrated polyps, compared with 23.8%, 46.2%, and 5.1% for FIT, respectively. The specificity of FIT was better compared with the fecal DNA assay in the population with normal colonoscopies or nonadvanced adenomas (94.9% vs. 86.6%) and in the population with normal colonoscopies (96.4% vs. 89.8%).

COMMENT

These findings establish the combined fecal DNA assay and fecal immunochemical test as the most sensitive noninvasive, nonimaging test for colorectal cancer and precancerous polyps. For the first time, FIT is established as having essentially no value for the detection of serrated lesions, whereas DNA testing appears partly effective and promising. Although the fecal DNA assay is now established as superior to FIT in a single-use setting, the program sensitivity of each test remains uncertain. Because fecal DNA testing has traditionally been more costly than FIT and is likely to remain so, relative program sensitivity and cost-effectiveness will be of considerable interest. Selecting the optimal interval for the DNA assay will be a challenge, but recommendations of 3 to 5 years are likely. The lower specificity of the assay will be criticized and may challenge colonoscopy resources in some areas. Also, the positive-predictive value for cancer and advanced adenomas will be low, raising questions as to whether patients with false-positive tests should undergo repeat colonoscopy and imaging to detect extracolonic malignancy. Despite these limitations, the sensitivities described for this noninvasive assay are remarkable, and the story of fecal DNA testing has been one of consistent technological advancement.

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Ondansetron Works for Diarrhea-Predominant Irritable Bowel Syndrome

— Douglas K. Rex, MD

This 5-HT3 receptor antagonist improved stool consistency and symptoms, with a low frequency of severe constipation.

Ondansetron is a 5-hydroxytryptamine 3 receptor antagonist (5-HT3RA) used for the treatment of nausea and vomiting. 5-HT3RAs also cause constipation, and one of these agents, alosetron, is approved for the treatment of diarrhea-predominant irritable bowel syndrome (IBS-D).

To assess the efficacy of ondansetron in treating IBS-D, investigators randomized 120 patients to receive ondansetron (one to two 4-mg pills, two to three times daily, as titrated by the patient) or placebo for 5 weeks in a double-blind, crossover study.

After completing 5 weeks of treatment with ondansetron or placebo, patients underwent a 2–3 week washout period, followed by 5 weeks of the alternate treatment. The primary endpoint was average stool consistency during the last 2 weeks of treatment, as documented with the Bristol Stool Form score. Transit time was measured in the last week of each treatment.

Compared with placebo, ondansetron use resulted in the following:

- Greater improvement in stool consistency, fewer days with fecal urgency, less urgency, fewer bowel movements, and less bloating
- A greater decrease in the IBS symptom severity score (83 vs. 37; \( P=0.001 \)) but no difference in pain score
- A higher rate of reported adequate relief (65% vs. 14%)
- A higher rate of constipation (9% vs. 2%), resulting in 2% of patients dropping out of the study
- Longer transit time (10 hours longer than with placebo)

**COMMENT**

These findings support the use of ondansetron as a new agent in the armamentarium for treating diarrhea-predominant irritable bowel syndrome.

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A Next-Generation Monoclonal Antibody for Chronic Lymphocytic Leukemia
— Michael E. Williams, MD, ScM

In CLL patients with coexisting illness, the type-2 anti-CD20 antibody obinutuzumab was superior to rituximab when each was combined with chemotherapy.

Rituximab (R) has been an integral component of chronic lymphocytic leukemia (CLL) therapy for the past 15 years, usually in combination with cytotoxic chemotherapy agents. In preclinical studies, the type-2 humanized monoclonal antibody obinutuzumab (Ob) demonstrated improved antibody-dependent cellular cytotoxicity and direct tumor cell death versus R. To evaluate Ob versus R in CLL patients with comorbidities, investigators conducted an industry-sponsored, phase III, multinational, randomized, three-arm trial involving 781 patients (median age, 73) with previously untreated CLL and serious coexisting illness (81% with >3 conditions; median Cumulative Illness Rating Scale score, 8).

Patients were randomized 1:2:2 to chlorambucil (C; 0.5 mg/kg orally on days 1 and 15 of each 4-week cycle for 6 cycles), C plus R (375 mg/m² on day 1 of cycle 1 and 500 mg/m² on day 1 of cycles 2–6), or C plus Ob (1 gm intravenously on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2–6).

Results were as follows:
• Median progression-free survival (PFS; the primary endpoint) was significantly higher with C+Ob than with C alone (26.7 vs. 11.1 months; hazard ratio, 0.18; *P* <0.001), with C+R than with C alone (16.3 vs. 11.1 months; HR, 0.44; *P* <0.001), and with C+Ob than with C+R (HR, 0.39; *P* <0.001).
• Overall response rates, complete remission rates, and molecular responses were significantly higher with C+Ob than with C alone or C+R.
• The benefits were observed in all CLL subsets except patients with del(17p).
• Overall survival was significantly longer with C+Ob than with C alone.
• More adverse events were observed with C+Ob, and more patients discontinued treatment with C+Ob due to adverse events, than with C alone or with C+R. The most common toxicity was grade 3 or 4 infusion reactions in 20% of patients with the first Ob infusion.

**COMMENT**

The high responses and improved outcomes for obinutuzumab in this trial led the FDA, on November 1, 2013, to approve the use of Ob in combination with chlorambucil for patients with previously untreated chronic lymphocytic leukemia. The enhanced mechanisms of action of this glycoengineered antibody may contribute to its increased activity in CLL, as the associated low CD20 density and impaired immune mechanisms may limit response to type-1 antibodies such as rituximab. Precautions include careful management of first-infusion reactions and monitoring for tumor lysis syndrome.
Bevacizumab for Advanced Cervical Cancer

— Susana Campos, MD, MPH

*Adding bevacizumab to chemotherapy significantly improved overall survival.*

Several cytotoxic regimens are often employed in the management of patients with advanced cervical cancer. Regrettably, advanced cervical cancer does not have a sustained response to chemotherapy. Bevacizumab has single-agent activity in heavily pretreated, recurrent cervical carcinoma (*J Clin Oncol* 2009; 27:1069).

Now, investigators have used a 2×2 factorial design to evaluate the effectiveness of bevacizumab in conjunction with either a nonplatinum doublet (topotecan and paclitaxel) or a platinum doublet (cisplatin and paclitaxel) in 452 patients with metastatic, recurrent, or persistent cervical cancer. Most patients had recurrent disease (72%) and had previously received platinum-based chemoradiotherapy (>70%).

At a median follow-up of 20.8 months, the combined data for both chemotherapy regimens showed that overall survival (the primary endpoint) was superior with bevacizumab plus chemotherapy versus chemotherapy alone (17.0 vs. 13.3 months; hazard ratio, 0.71; *P*=0.004); the response rate was also higher with bevacizumab (48% vs. 36%; *P*=0.008). Incidence of grade 2 or higher hypertension, thromboembolic events, and gastrointestinal or genitourinary events was higher with bevacizumab. The survival benefit of bevacizumab was not associated with a significant reduction in health-related quality of life (QOL), as measured by three validated QOL instruments. Mortality was similar between the groups receiving the two regimens of chemotherapy alone.

**COMMENT**

Bevacizumab is the first biological therapeutic agent to have a clinically meaningful impact in cervical cancer. Given the economic burden of such novel agents, understanding which patients might benefit most from treatment is of the utmost importance. This trial included patients with squamous cell, adenocarcinoma, and other histologic subtypes. Whether patients with adenocarcinoma achieve the same degree of benefit as those with a squamous histology remains uncertain. In addition to identifying predictive and prognostic biomarkers, finding an antiangiogenic signature that can predict response to bevacizumab should be a focus of future studies. It is important to note that research continues to identify other actionable molecular aberrations that drive the tumorigenesis of cervical cancer, such as mutations in the PI3K pathway.

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Statin Benefits Secondary Progressive MS
— Robert T. Naismith, MD

A phase II trial in secondary progressive multiple sclerosis demonstrated reduction in brain atrophy.

HMG-CoA reductase inhibitors are postulated to have immunomodulatory effects that appear to be independent of their effect on cholesterol. A benefit has been suggested in early multiple sclerosis (MS) based on reduction of magnetic resonance imaging brain lesions (NEJM JW Neurol May 22 2012). In this multicenter, double-blind study, investigators randomized 140 participants with secondary progressive (SP) MS to 80 mg of simvastatin or placebo daily for 2 years. Participants were 18 to 65 years old, had active progression over the preceding 2 years, and had difficulties ambulating but were not wheelchair bound (Expanded Disability Status Scale [EDSS] score range, 4.0–6.5).

Whole brain atrophy (the primary endpoint) was 43% slower annually in simvastatin recipients than in placebo recipients. The simvastatin group also had small clinical improvements over placebo on the EDSS and a patient-reported MS impact scale at 24 months.

COMMENT
These findings show that simvastatin reduced the primary outcome of brain atrophy in secondary progressive multiple sclerosis patients and yielded benefits on several key clinical endpoints. Whereas many progressive MS trials seek a young and less disabled cohort, this study, remarkably, recruited patients with MS duration of more than 20 years, median disability of requiring a cane to ambulate 100 meters (EDSS 6.0), and median age of 51.

The results provide encouragement to proceed to a larger phase III study, but since simvastatin is already in widespread use for other conditions, patients may inquire about trying it for their MS. Participants were off disease-modifying therapy for at least 6 months, which raises the issue of whether to discontinue disease-modifying therapies or add simvastatin. A controversy remains as to whether statins negate the effects of interferon-beta. High-dose statins were well tolerated in this study but do necessitate ongoing monitoring with occasional safety issues.

It would be premature to make a recommendation to switch all patients with SPMS to simvastatin. The study findings must be confirmed, and we need to understand the clinical implications of brain atrophy reduction in this patient population. However, with the lack of effective therapies in SPMS, we face a dilemma of whether to try simvastatin in select patients, with appropriate counseling and monitoring. Some clinicians may decide to prescribe simvastatin to their SPMS patients, while others may wait for confirmatory trials.

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