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ABSTRACT & COMMENTARY

Mefloquine: Still Effective and Still Safe for Malaria Chemoprophylaxis

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Dr. Fischer reports no financial relationships relevant to this field of study.

SYNOPSIS: Mefloquine is known as an effective agent for malaria chemoprophylaxis. However, concerns about serious adverse effects have limited its use. Now, a careful review of data suggests that fatal outcomes related to mefloquine prophylaxis are very rare.

SOURCE: Tickell-Painter M, et al. Deaths and parasuicides associated with mefloquine chemoprophylaxis: A systematic review. *Travel Med Infect Dis* 2017;20:5-14.

Mefloquine has been available for malaria chemoprophylaxis for three decades. It has been effective and is widely used. However, there is a belief that prophylactic mefloquine can prompt psychosis, suicidal ideation, and death. To better determine if data supported such a belief, an expert investigative group, in conjunction with a Cochrane review of efficacy and safety of mefloquine,[1] systematically reviewed scientific reports about death and suicidal attempts in patients who use preventive mefloquine.

Using rigorous search criteria, 2,521 potentially relevant papers were identified. Of these, 71 papers mentioned mefloquine as a potential link to death and/or suicide attempts; 17 papers reported death and suicide attempt in apparent association with prophylactic mefloquine. These papers were analyzed carefully; some papers did not actually provide data supporting death and/or suicide related to mefloquine, some dealt with treatment doses, some cited other articles which, in fact, did not corroborate the claims, and some did not provide enough information to determine any hint of a causal association between the medication and the outcome. From this extensive literature review, two deaths were linked to what seemed to be idiosyncratic reactions "probably caused by" mefloquine (one with pulmonary fibrosis, one with an exfoliative illness with neutropenia), and there was one suicide attempt

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"possibly caused by" mefloquine. Using a causality framework, there were eight other reports of death deemed "unclassifiable" or "unlikely" related to mefloquine. The investigators thought that it was "striking" that so few deaths could be causally linked to mefloquine. Despite a rigorous search for potential cases, investigators found only three cases that potentially could be linked to mefloquine. These three cases were many fewer than previously cited cases that had not been subjected to such scrutiny.

■ COMMENTARY

There are three main malaria chemoprophylaxis medications — mefloquine, atovaquone-proguanil, and doxycycline. No medication is perfect, and travelers can experience bothersome and life-threatening events no matter which malaria medication they take. Thus, it is helpful to understand existing scientific data to sort through risks and benefits of various antimalarial options when caring for international travelers.

To that end, Tickell-Painter et al have provided a good summary of published data on the possibility of an association between mefloquine and death and/or suicide. Decades ago, when mefloquine was introduced as a chemoprophylactic agent, caution was urged in using the medication in people with cardiac rhythm disturbances, active seizure disorders, and psychiatric difficulties. Bad psychiatric reactions seemed to be more common with larger treatment doses than with smaller weekly preventive doses.

Nonetheless, there was anecdotal concern that even prophylactic dosing could trigger serious psychiatric effects in people without pre-existing psychiatric disorders. These safety concerns led to black box warnings on package inserts, a *New York Times* opinion article about "crazy pills,"[2] and a decrease in the use of mefloquine. How large is the actual risk of serious adverse events with prophylactic mefloquine? Beyond anecdotes and case reports, Tickell-Painter et al provided a helpful systematic review of published safety data. Not surprisingly, but perhaps counter to widely held belief, mefloquine is not associated with statistically significant increased risks of either death or suicide-prone psychiatric reactions. This knowledge could help mefloquine return to a position of accepted use in the prevention of malaria in travelers. Of course, travel itself can be associated with bad outcomes. Sleepless nights on airplanes, jet lag, and culture shock all can yield diminished psychological reserves and might provoke the emergence of symptoms related to underlying anxiety, depression, or psychosis.

Mefloquine produces some side effects, even if not life-threatening ones. Sleep disturbances (insomnia, vivid dreams) are seen in up to 20% of travelers taking prophylactic mefloquine. Cardiac rhythm disturbances, active seizure disorders, and known psychiatric disorders remain contraindications to mefloquine use. Mefloquine is readily available in pill form, but the crushed pills taste unpleasant; children don't always enjoy taking mefloquine. Despite all this, mefloquine still is very effective in preventing malaria. The oral dose is 5 mg/kg/dose up to an adult dose of 250 mg taken weekly starting one to two weeks prior to travel and continuing through four weeks after leaving the malarial area.

Doxycycline and atovaquone-proguanil also are reasonable chemoprophylactic options, but each requires daily use. Doxycycline can stain developing teeth, so it is not suggested for use prior to 8 years of age. Vaginal yeast infections and photosensitivity skin reactions also limit the use of doxycycline for a minority of travelers. Atovaquone-proguanil produces only rare bothersome side effects.

Each of these medications should be started a day prior to arrival in the malarial area and then continued until after leaving the area of risk for malaria (28 days after leaving for doxycycline, seven days after leaving for atovaquone-proguanil). The cost of doxycycline has gone up in recent years. The cost per pill of atovaquone-proguanil is higher than that of the other agents; a trip of > 10 days usually makes mefloquine less costly than atovaquone-proguanil.

A recent Cochrane review, also led by Dr. Tickell-Painter, highlighted relative risks of bothersome adverse effects of various antimalarial prophylactic medications as determined in studies involving hundreds of thousands of subjects.[1] While mefloquine was very effective in preventing malaria, side effects were reported.[1] Compared to atovaquone-proguanil, mefloquine was

associated with abnormal dreams (relative risk [RR], 2.04), insomnia (RR, 4.42), anxiety (RR, 6.12), and depressed mood (RR, 5.78). Nausea and dizziness also were more common with mefloquine.

Overall, 6% of travelers opted to discontinue mefloquine use, while only 2% of atovaquone-proguanil users opted to discontinue treatment. Mefloquine and doxycycline carried similar rates of discontinuation and serious adverse effects; while mefloquine was associated with more abnormal dreams, insomnia, anxiety, and depression than doxycycline, doxycycline was associated with more dyspepsia, photosensitivity, vomiting, and vaginal candidiasis.[1] Physicians providing pre-travel consultation often need to help travelers balance potential adverse reactions with the varying costs of the medications. Emerging data suggest that primaquine is another reasonable option for chemoprophylaxis of malaria, especially in areas in which *Plasmodium vivax* and *Plasmodium ovale* are common.[3] However, glucose-6-phosphate dehydrogenase deficiency should be ruled out before initiating treatment with primaquine.[3] Most travelers who are diagnosed with malaria in the United States (about 2,000 per year) were traveling to visit friends and relatives and did not take appropriate chemoprophylaxis.[4] Choosing a medication during a pre-travel consultation is important, but it is even more important to try to ensure that all travelers to areas with risk of malaria receive appropriate pre-travel counsel and interventions. Travelers visiting friends and relatives are at particular risk compared to those who travel strictly for business or tourism.[4,5,6] There is wide variation in travel medicine practice,[7] and it behooves all physicians seeing travelers to stay current with evidence-based recommendations. There also are regional and temporal variations in the management of malaria risk in travelers. Realizing that the actual risk of malaria is very low (< 1% per month) in typical business and tourist travelers, European travel medicine specialists increasingly have used standby treatment (providing a curative dosing regimen to have available for use when symptoms develop and a rapid malaria test is positive) instead of providing widespread chemoprophylaxis.[8] Malaria continues to be a problem for international travelers. Travelers should seek pre-travel consultation, and physicians should choose antimalarial chemoprophylactic regimens wisely. ■

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BRIEF REPORT

Hospital Ice Machines Contaminated With Bacteria

By Carol A. Kemper, MD, FACP

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Dr. Kemper reports no financial relationships relevant to this field of study.

SOURCE: Kanwar A, et al. Hiding in plain sight: Contaminated ice machines are a potential source for dissemination of gram-negative bacteria and *Candida* species in healthcare facilities. *Infect Control Hosp Epidemiol* 2018; Jan. 31: doi: 10.1017/ice.2017.321. [Epub ahead of print].

Kanwar et al conducted a point prevalence survey of all ice machines in five different hospitals and two nursing homes in their area. Protocols for cleaning and disinfecting machines on either a weekly or monthly basis were in place at each facility, although none of the facilities performed surveillance cultures

or molecular methods to monitor cleaning. First, machines were inspected visually for debris, and swab cultures were obtained from both the ice and water chutes. Water samples of 100 mL were collected for culture. Swabs for culture were obtained from 64 machines (3-16 samples per facility).

Visual inspection revealed that 98% of machines contained stagnant water in the pan; 38% contained melting ice in the pan, 34% contained dripping water, even when the water spout was not in use, and 27% exhibited visible water sprayed on the surrounding countertops or floor. Many of the machines showed visible soiling, food, or slime layers.

Gram-negative bacilli and/or *Candida* organisms were cultured from 100% of the drain pans, 72% of the pan grills, and 52% of the chutes. Swab cultures from 94% of the pans yielded > 100 colonies of gram-negative bacilli, including *Enterobacteriaceae* (60%), *Pseudomonas* spp. (26%), *Serratia* spp. (6%), *Stenotrophomonas maltophilia* (4%), and *Acinetobacter* spp. (3%). Of these, 7.7% were carbapenem resistant. All cultures of water and ice were negative. Five of the machines were tested again following cleaning and disinfection with a hydrogen peroxide disinfectant, and all cultures were negative.

Hospital staff were observed using the ice machine on 20 occasions. Staff touched the ice and/or water spouts in nine of 20 episodes, and falling ice touched hands (as it fell into the pan) in 10 of 20 episodes. Cultures of hands frequently yielded gram negatives and yeast. This study provides a plausible explanation for contamination of ice machines in hospital units. Even if machines are cleaned and disinfected successfully on a regular basis, they may become contaminated quickly by the hands of staff, touching either spouts or falling ice, with contamination of biofilm. Two quick remedies may be to require staff to cleanse their hands with alcohol hand gel prior to using an ice machine, and to direct housekeeping personnel to perform more frequent machine cleaning. Improvement in the design for these machines also may help. For example, deeper pans may help reduce splashes and sprays of water, and different types of spouts or chutes that cannot be touched readily by personnel would reduce cross-contamination. ■

ABSTRACT & COMMENTARY

Pre-existing Health Determines Quality of Life, Physical Symptoms After ICU Discharge

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Dr. Tran reports no financial relationships relevant to this field of study.

SYNOPSIS: The authors of this nested cohort study within a randomized, controlled trial of ICU survivors requiring > 48 hours of mechanical ventilation found that pre-existing comorbidity was the main determinant of long-term health-related quality of life.

SOURCE: Griffith DM, et al. Determinants of health-related quality of life after ICU: Importance of patient demographics, previous comorbidity, and severity of illness. *Crit Care Med* 2018 Jan 2. doi: 10.1097/CCM.0000000000002952. [Epub ahead of print].

Because their earlier study (RECOVER) failed to show that an intensive post-ICU, multidisciplinary rehabilitation program improved physical recovery and health-related quality of life (HRQoL),[1] Griffith et al hypothesized that pre-ICU health factors may be more important for this failure, thereby explaining why some patients may be refractory to this particular intervention.

This was a cohort study nested within the RECOVER randomized, controlled trial, which enrolled 240 adult ICU survivors who required > 48 hours of continuous mechanical ventilation. The authors aimed to describe the cohort trajectory of HRQoL between three and 12 months and explore the factors associated with HRQoL and patient-reported symptoms at six and 12 months post-ICU discharge. HRQoL was assessed via the Medical Outcomes Study Short Form-12 Version 2 (SF12v2), which included the Physical Component Score (PCS; range, 0-100) and Mental Component Score (MCS; range, 0-100), with higher scores better.

The authors predefined a minimum clinical important difference (MCID) in PCS and MCS as greater than ± 5 points. Patient-reported symptoms of appetite, fatigue, pain, joint stiffness, and breathlessness were measured on a visual analogue scale ranging from 0 (no symptoms at all) to 10 (worst symptoms

imaginable). Overall, mean PCS and MCS were reduced compared to population norms, with mean PCS increasing by a statistically significant, but small (less than the MCID), amount between three and 12 months (mean difference, 2.3; 95% confidence interval [CI], 0.6-3.9; *P* = 0.006); the mean MCS did not change over that same time. Of the 147 patients who had complete PCS and MCS data at three and 12 months, 94 demonstrated no significant clinical improvement in PCS and 101 exhibited no significant clinical improvement in MCS. In the multivariable analysis, higher pre-existing comorbidity burden was associated with worse PCS (beta, -1.56; 95% CI, -2.44 to -0.68; *P* = 0.001) and MCS (beta, -1.45; 95% CI, -2.37 to -0.53; *P* = 0.002) at six months in addition to 12 months; critical illness-related variables were not associated with either PCS or MCS at either point.

As the number of pre-ICU comorbidities increased, both PCS and MCS tended to be lower after discharge and exhibited a flatter trajectory, reflecting lack of improvement. A higher pre-ICU comorbidity count also was associated with worse patient-reported symptom scores.

■ COMMENTARY

This secondary analysis of the RECOVER trial is a helpful addition to our growing understanding of the complex interplay between pre-existing disease and acute critical illness in ICU survivors. Although the RECOVER cohort experienced notably severe critical care stays (APACHE II mean score, 20 [standard deviation {SD}, 8], mean ventilation days 12 [SD, 11], 74% required vasopressors, 27% required renal replacement therapy), pre-ICU comorbidity count was associated most strongly with post-ICU HRQoL and persistent symptoms. These findings support previous studies that have found strong associations between pre-hospital comorbid conditions and 30-day readmissions after hospitalization for sepsis.[2-5]

Based on these data, a pre-ICU health trajectory is highly significant in determining the post-discharge course, not only regarding healthcare use, but also HRQoL and patient-perceived symptoms. This carries important implications for future intervention studies seeking to improve HRQoL or functional recovery. Patients with more comorbid conditions at baseline may experience limited to no improvement and may mask significant effects in other patient subpopulations if not defined appropriately at the outset. This patient population also may require additional resources and/or different interventions to demonstrate improved outcomes. In an age of personalized medicine regarding genetics, biomarkers, and drug response, we should not be surprised that a one-size-fits-all approach to post-ICU care will not suffice. ■

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PHARMACOLOGY UPDATE

Tildrakizumab-asmn Injection (Ilumya)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

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Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a second interleukin-23 (IL-23) inhibitor for the treatment of adults with moderate-to-severe plaque psoriasis who are eligible for systemic therapy or phototherapy.

Tildrakizumab-asmn is a humanized IgG1/k antibody that binds to the p19 subunit of IL-23, similar to guselkumab, a human IgG1/k antibody. Tildrakizumab-asmn is marketed as Ilumya.

INDICATIONS

Tildrakizumab-asmn is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[1]

DOSAGE

The recommended dose is 100 mg given subcutaneously at weeks 0, 4, and every 12 weeks thereafter.[1]

Ilumya is available as 100 mg/mL single-dose prefilled syringes.

POTENTIAL ADVANTAGES

The mean elimination half-life of tildrakizumab-asmn is approximately 23 days, which allows dosing every 12 weeks.

In contrast, guselkumab has a mean half-life of 15-18 days and is dosed every eight weeks.

POTENTIAL DISADVANTAGES

The most frequently reported adverse reactions were infections (14%), injection site reactions (3%), and diarrhea (2%).[1] Corresponding placebo rates were 12%, 2%, and 1%, respectively. Approximately 2.5% of subjects developed neutralizing antibodies. Cases of angioedema and urticaria have been reported.

COMMENTS

The pathogenesis of psoriasis involves numerous proinflammatory cytokines, including tumor necrosis factor alpha and interleukins 12 (IL-12), 17A (IL-17A), and IL-23. Tildrakizumab-asmn binds to IL-23 and inhibits its interaction with the IL-23 receptor, thereby inhibiting the release of proinflammatory cytokines and chemokines.[1]

The efficacy and safety of tildrakizumab-asmn 100 mg compared to placebo were evaluated in two randomized, double-blind, placebo-controlled, 12-week trials.[1,2] Subjects registered a Physician Global Assessment (PGA) score of ≥ 3 on a 5-point scale, Psoriasis Area Severity Index (PASI) score ≥ 12, and a minimum body surface area (BSA) involvement of 10%. At baseline, subjects demonstrated a median PASI of 17.8 and a BSA of 27%.

Thirty-three percent of subjects scored 4 or 5 on the PGA scale. A total of 309 subjects were randomized to tildrakizumab-asmn in study 1 (reSURFACE 1) and 307 in study 2 (reSURFACE 2). Correspondingly, 154 and 156 were randomized to placebo, respectively.

The co-primary endpoints were the proportion of subjects who achieved at least a 75% reduction in PASI (PASI 75) and the proportion of subjects with PGA scores of 0 or 1 and at least a two-point improvement.

PASI 75 results at 12 weeks were 64% vs. 6% in study 1 and 61% vs. 6% in study 2. PGA of 0 or 1 were 58% in study 1 and 55% in study 2 vs. 7% and 4% for placebo, respectively. In an active arm of study 1, a PGA score of 0 or 1 of 48% was achieved for etanercept.[2] In study 1, 74% were responders at week 28. These responders were further randomized to continue tildrakizumab-asmn or placebo to week 64, at which time 84% maintained PASI 75 compared to 22% for placebo.[1]

CLINICAL IMPLICATIONS

Psoriasis is a chronic inflammatory autoimmune disease primarily affecting the skin. In some patients, joints are involved (psoriatic arthritis). Generally, topical therapy is effective for mild-to-moderate disease. For moderate-to-severe disease, treatment options include phototherapy, conventional systemic agents (e.g., methotrexate, acitretin), and biologics.

Numerous biologics targeting the various proinflammatory cytokines are available. Tildrakizumab-asmn is the second drug (after guselkumab) that solely targets IL-23, while ustekinumab targets both IL-12 and IL-23. There are no direct comparisons between tildrakizumab-asmn and guselkumab; however, a systematic review and meta-analysis suggested similar efficacy.[3]

In an indirect comparison of the two IL-23 inhibitors in their clinical trials, a higher proportion of subjects on guselkumab achieved PASI 75 and a PGA score of 0 or 1 compared to tildrakizumab-asmn, suggesting greater efficacy.[4] A similar analysis found ixekizumab (IL-17 inhibitor) as the most effective biologic, followed by secukinumab, brodalumab, and guselkumab.[5]

Tildrakizumab-asmn is a new biologic for the treatment of psoriasis but may not offer any clear therapeutic advantage over existing agents. The cost for tildrakizumab-asmn was not available at the time of this review. ■

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Clinical Briefs

By Louis Kuritzky, MD

Obstructive Sleep Apnea: Oral Appliances

SOURCE: Hamoda MM, et al. *Chest* 2018;153:544-553.

Continuous positive airway pressure (CPAP) has been the traditional recommended intervention for obstructive sleep apnea for more than three decades. Unfortunately, limitations on the ultimate application of CPAP to treat obstructive sleep apnea include expense and (for many) poor tolerability. Among the alternative interventions are oral appliances, typically divided into two categories: tools that stabilize the tongue in a forward position, and tools that stabilize the mandible in a forward position. The recently FDA-approved device that employs an electrical current to activate oropharyngeal musculature with improved tongue muscular tone is not included in this review.

Using technical metrics for success, such as degree of improvement of the apnea-hypopnea index, CPAP has been shown to outperform oral appliances. On the other hand, patient-centered outcomes (sleepiness, quality of life, and driving performance) have been found to be equally well-improved by oral appliances as CPAP. Perhaps the most important bottom line is that many patients find compliance with CPAP difficult, and the limited data on oral devices suggest significantly greater compliance with them than with CPAP.

Aside from efficacy and tolerability, cost may be the ultimate deal maker (or breaker). Mandibular advancement devices that may be created at home by the patient cost as little as $30. While dental experts may offer more complex, sophisticated oral appliances, success attained with simple do-it-yourself home kits is quite appealing for many. Fortunately, the diversity of treatment options currently available should stimulate optimism that the consequences of obstructive sleep apnea can be improved successfully in most patients. ■

Influenza Increases Rate of Myocardial Infarction

SOURCE: Kwong JC, et al. *N Engl J Med* 2018;378:345-353.

It is obvious that influenza is an important cause of morbidity and mortality. Exploration of the causes of death related to influenza is a bit more complicated. Reporting on influenza epidemics usually includes the single broad category "influenza and pneumonia," since that category tracks directly with incident cases of influenza each year.

But even with that clarification, the proportion of patients who succumb to influenza pneumonia vs. those who incur bacterial pneumonia (typically Staph) subsequent to pneumonia vs. all other incident pneumonias that occur concomitantly with flu season is not readily discernible. The association between cardiovascular event rates and influenza has been recognized since the 1930s, but few direct studies of rates of myocardial infarction in patients with acute influenza have been performed.

To that end, Kwong et al reported that in a study of subjects with laboratory-confirmed influenza (n = 19,045), myocardial infarction rates were six-fold higher in the "risk interval" (i.e., seven days after influenza identification) than in the "control interval" (i.e., one year immediately before and after the risk interval). Although other viral infections, such as respiratory syncytial virus, also were associated with increased risk for myocardial infarction, of the viruses studied, influenza incurred the greatest relative risk increase. ■

Promising News About Zika Vaccine

SOURCE: Modjarrad K, et al. *Lancet* 2018;391:563-571.

Zika virus infection during pregnancy can cause microcephaly and other serious neurologic defects. Protection from infection with Zika virus has been demonstrated in animal studies using a formalin-inactivated Zika virus vaccine derived from a 2015 Puerto Rican virus strain, similar to the 2015 Brazilian Zika virus strain. In preclinical trials in mice and nonhuman primates, two doses of vaccine (day 1 and day 29) produced high antibody levels within two weeks after the second dose.

Modjarrad et al reported on the first study in humans, using an aluminum hydroxide adjuvant Zika virus vaccine. Zika seronegative adults (n = 67) were randomized to Zika vaccine or placebo. Intramuscular vaccine was administered on day 1 and day 29. Efficacy was determined by the percent seroconversion (i.e., attainment of a microneutralization titre of ≥ 1:10).

By day 57, seroconversion had occurred in 92% of vaccine recipients. Tolerability of the vaccine was good, with only mild-moderate adverse events reported. These results compare well with trials of Japanese encephalitis virus and yellow fever virus that have used the same seroconversion status as a surrogate for protection from infection. Clinicians look forward to confirmation of vaccine efficacy in a large population. ■

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CME QUESTIONS

1. **Malaria chemoprophylaxis with mefloquine is not associated with which of the following?**
   a. Abnormal dreams
   b. Insomnia
   c. Anxiety
   d. Death by suicide

2. **In the study by Griffith et al, which factor was associated most strongly with health-related quality of life after an ICU stay involving mechanical ventilation for at least 48 hours?**
   a. Duration of heavy sedation in the ICU
   b. Number of acute organ failures developing during ICU stay
   c. Discharge from ICU to a long-term acute care facility or skilled nursing facility
   d. Number of pre-existing comorbid conditions

3. **Based on the study of Griffith et al, which of the following statements is true?**
   a. Most patients demonstrated no clinically significant improvement in physical or mental performance scores between three and 12 months after ICU discharge.
   b. Critical illness-related variables were significantly associated with physical and mental performance scores at six months, but not 12 months, post-discharge.
   c. As the number of pre-existing comorbid conditions increased, there was a steeper improvement in mental, but not physical, scores at 12 months post-ICU discharge.
   d. Age was most strongly associated with patient-reported symptoms at 12 months post-ICU discharge.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Non-opioid vs. Opioid Medications for Chronic Back, Knee, or Hip Pain

Patient, Provider, and Practice Matter in Inappropriate Antibiotic Prescribing