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Update in Infectious Diseases: Evidence Published in 2012

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Is there any more dynamic medical specialty than infectious diseases? I don't think so, and I believe the medical literature published in 2012 supports my assertion. Revelations include a paradigm shift in our understanding of the role of asymptomatic bacteriuria, the description of an ehrlichiosis-like illness due to a newly discovered virus, and a sinusitis study based in primary care, office-based practices showing that antibiotic treatment does not improve disease-specific quality of life. This Update reviews clinically based papers that would be interesting and useful to general internists.

Sinusitis

The Usual Patient With Sinusitis Does Not Benefit From Antibiotic Treatment

Garbutt JM, Banister C, Spitznagel E, et al. Amoxicillin for acute rhinosinusitis: a randomized controlled trial. JAMA. 2012;307:685-92. [PMID: 22337680]

Background: One in 5 antibiotic prescriptions for U.S. adults is for treatment of sinusitis. Because antibiotic resistance is driven by use, antimicrobials should be given only in instances when they will be helpful. Expert guidelines advise clinical criteria for sinusitis diagnosis and a narrow-spectrum antibiotic only for patients with moderately severe or severe symptoms.

Findings: This randomized, placebo-controlled trial included 166 adults with uncomplicated, acute rhinosinusitis from 10 community-based, primary care office practices. Sinusitis was diagnosed in those with maxillary pain or tenderness, purulent nasal secretions, and rhinosinusitis symptoms from 7 to no more than 28 days. Treatment consisted of amoxicillin, 500 mg three times daily, versus placebo for 10 days. All patients received a 1-week supply of symptomatic treatments for pain, fever, cough, and nasal congestion. The primary outcome measured was quality of life after 3 days of treatment as assessed by the Sinonasal Outcome Test-16. Study results showed no significant difference between the antibiotic and placebo. At day 3, the time of primary outcome assessment, the quality of life was the same in both groups (37% in the antibiotic group felt better vs. 34% in the placebo group). At day 7, more persons in the antibiotic group reported feeling better (74% vs. 56%), but at day 10, quality of life was the same in both groups (78% vs. 80%).

Cautions: This trial did not stratify patients by severity of illness and evaluated only a single antibiotic. It is possible that subsets of patients with sinusitis might benefit from antibiotic treatment in primary care settings.

Implications: Trials of antibiotics for sinusitis have had inconsistent results. To my knowledge, this is the first trial of antibiotics for sinusitis to assess improvement in disease-specific quality of life as the primary outcome, which is what patients want. In both the antibiotic and placebo groups, sinus symptoms improved over time with no difference at 3 or 10 days. No differences were noted in workdays missed, satisfaction with treatment, rate of relapse, or the amount of additional medical care needed. The usual patient with acute sinusitis should not be given an antibiotic.

Azithromycin Toxicity

Think Twice About Prescribing Azithromycin for Patients With Heart Disease

Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012;366:1881-90. [PMID: 22591294]

Background: The macrolide antibiotics erythromycin and clarithromycin are associated with an increased risk for ventricular arrhythmias and sudden death. The macrolide azithromycin, the most commonly prescribed antibiotic in the United States, was thought to be free of cardiac toxicity, but case reports and adverse event reports collected by the U.S. Food and Drug Administration suggest otherwise.

Findings: The authors hypothesized that patients who took azithromycin would have an increased risk for sudden death compared with persons who did not take antibiotics and those who took other selected antibiotics. This retrospective cohort study of azithromycin use and death included persons aged 30 to 74 years enrolled in the Tennessee Medicaid Program who received azithromycin between 1992 and 2006 and had no life-threatening noncardiovascular illness. Matched control periods during which no study antibiotics were used (4 control periods for each azithromycin prescription) and control groups that took amoxicillin (including amoxicillin–clavulanate), ciprofloxacin, and levofloxacin were also included. Cardiac risk scores were assessed. This large study included 347 795 persons with azithromycin prescriptions, 1 391 180 matched control periods with no antibiotic, 1 348 672 amoxicillin prescriptions, 264 626 ciprofloxacin prescriptions, and 193 906 levofloxacin prescriptions. Azithromycin users mostly were women (77.5%). Azithromycin and

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amoxicillin were mostly used for ear, nose, and throat infections and bronchitis (62% and 63% of prescriptions, respectively).

Sudden cardiac deaths during a 5-day course of treatment occurred in 22 persons receiving azithromycin (65 per 1 million treatment courses), 29 persons receiving amoxicillin (22 per 1 million treatment courses), and 33 persons not receiving an antibiotic (24 per 1 million control periods). An estimated 47 additional cardiovascular deaths per 1 million 5-day courses of therapy occurred in the group that took azithromycin. The risk for death with azithromycin use varied according to the baseline risk score for cardiovascular disease. Among persons in the highest decile of baseline risk, 245 additional cardiovascular deaths occurred per 1 million courses. Compared with those who received amoxicillin, persons who received ciprofloxacin had no increased risk for cardiovascular death. There was a nonsignificant trend toward increased risk for cardiovascular death with levofloxacin use.

Cautions: Patient-specific information is difficult to obtain from a large database study such as this.

Implications: A short course of azithromycin was associated with an increase in cardiovascular deaths; the risk for death was highest in those with underlying heart disease. Although the risk was small, it was greater than with amoxicillin. The increased risk for cardiovascular death did not persist after the therapy ended. Physicians should think twice about prescribing azithromycin for patients with cardiovascular disease. First, they should ask whether the patient needs an antibiotic at all.

Infective Endocarditis

Early Surgery for Left-Sided Endocarditis Accompanied by Severe Valve Dysfunction and Large Vegetation, Even in the Absence of Heart Failure, Saves Lives and Prevents Serious Illness From Stroke

Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med. 2012;366:2466-73. [PMID: 22738096]

Background: Guidelines for managing infective endocarditis advocate early surgery for patients with heart failure, but controversy continues about indications for surgery to prevent embolism. Furthermore, no randomized trial has clarified the indications for and timing of such surgery.

Findings: This study was designed to compare surgery with conventional treatment in patients with left-sided endocarditis and a high risk for embolism according to the hypothesis that early surgery would decrease mortality or embolic events. This prospective, randomized trial at 2 centers enrolled consecutive patients aged 18 to 80 years with native valve endocarditis defined by modified Duke criteria, severe mitral or aortic valve disease, and vegetation larger than 10 mm. All patients had blood cultures and transthoracic echocardiograms within 24 hours of hospitalization. In the intervention group, surgery was done within 48 hours after randomization. The conventional treatment group had surgery only if complications requiring urgent surgery developed during medical treatment, or if symptoms persisted after the end of antibiotic treatment. Participants were followed in the hospital, at regular intervals up to 1 year, and at 6-month intervals until September 2011.

The primary end point was a composite of clinical embolic events or hospital death within 6 weeks of randomization. (Skin lesions or metastatic abscesses were not counted as embolic events.) Only 1 patient in the surgery group had the defined end point compared with 9 patients in the conventional treatment group ($P = 0.03$). At 6 weeks, embolism had not occurred in any patient in the surgery group but did occur in 21% of the conventional treatment group ($P = 0.005$). At 6 months, all-cause mortality did not differ in the 2 groups; however, a composite end point of death from any cause, embolic events, recurrence of endocarditis, or repeated hospitalization due to congestive heart failure was 3% in the early surgery group and 28% in the conventional treatment group ($P = 0.02$).

Cautions: The beneficial results achieved by early surgery applied only to a subset of patients with endocarditis. Those with moderate to severe congestive heart failure, heart block, aortic abscess, penetrating lesions requiring urgent surgery, fungal endocarditis, coexisting major embolic stroke, right-sided vegetations, prosthetic valve, or referral from another institution more than 7 days after diagnosis of endocarditis were excluded from this study. The time from the onset of symptoms until randomization is not clear. Sixty-four percent of participants had streptococcal endocarditis; only 13% had infection due to *Staphylococcus aureus*, a much lower percentage than in most series. Patients with *S. aureus* endocarditis are more likely to need surgery than those with streptococcal infection.

Implications: This important study provides compelling evidence that early surgery prevents death and serious illness from embolism in patients who have left-sided endocarditis associated with large vegetations and severe valvular dysfunction, even in the absence of congestive heart failure and with pathogens less virulent than *S. aureus*. This salutary outcome far outweighs the additional risk of surgery in patients with active infection.

Asymptomatic Bacteriuria and Recurrent Urinary Tract Infections

Don't Screen for or Treat Asymptomatic Bacteriuria in Young Women With Recurrent Urinary Tract Infections

Cai T, Mazzoli S, Mondaini N, et al. The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: to treat or not to treat? Clin Infect Dis. 2012;55:771-7. [PMID: 22677710]

Background: Asymptomatic bacteriuria (AB) is the presence of bacteria in the urine without signs or symptoms of a urinary tract infection (UTI), independent of pyuria. The assumption has been that AB defines a population at risk for subsequent infection and that elimination of bacteriuria will minimize risk for symptomatic UTI; but, the effect of treating AB in young women with recurrent UTIs had not been assessed.

Findings: This study evaluated the effect of AB treatment on UTI rates in young women with recurrent UTIs. Women attending a sexually transmitted disease center for recurrent UTIs were screened. Investigators included sexually active women aged 18 to 40 years who had a UTI in the previous year but at least 1 month before enrollment, were currently asymptomatic, and had clinically significant bacteriuria (defined as 10^5 colony-forming units/mL of a single uropathogen in 2 consecutive collections of midstream urine).

Persons were randomly assigned to group A (330 untreated women who received treatment only if they had a UTI) and group B (369 women who were treated with an antimicrobial on the basis of susceptibility). Follow-up with cultures occurred at 3, 6, and 12 months. Symptomatic UTIs developed at 3 months in 3.5% of group A and 8.8% of group B, at 6 months in 7.6% of group A and 29.7% of group B, and at 1 year in 14.7% of group A and 73.1% group B. Treatment of AB due to *Enterococcus faecalis* was associated with the development of multidrug-resistant *Escherichia coli*.

Cautions: The study sample attended a sexually transmitted disease clinic and had a history of several antibiotic courses for recurrent UTIs; most participants had more than 3 UTIs per year. There was no control group of healthy young women. One would very much like to see this study replicated.

Implications: This study creates a paradigm shift in our thoughts about AB in nonpregnant women. In healthy, sexually active young women with recurrent UTIs, the treatment of AB increases the risk for subsequent infection and is associated with the development of resistant organisms. Physicians should not screen for or treat AB in young women with recurrent UTIs.

HIV Prevention

In HIV Discordant Heterosexual Couples, Adherence by the Seronegative Partner to Daily Preexposure Prophylaxis Reduces HIV Acquisition

Baeten JM, Donnell D, Ndase P, et al; Partners PrEP Study Team. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367:399-410. [PMID: 22784037]

Background: Infection prevention strategies are essential to impact the global HIV epidemic. Antiretroviral prophylaxis is a potential HIV prevention strategy for uninfected persons. It can be given either as postexposure prophylaxis after high-risk exposure or as preexposure prophylaxis for those who have ongoing HIV exposure, such as an HIV-seronegative person in a relationship with an infected partner (a serodiscordant couple).

Findings: A randomized trial of antiretrovirals for preexposure prophylaxis was conducted among HIV-1–discordant couples in Kenya and Uganda. At enrollment, the seropositive partner was not eligible for treatment, according to national guidelines, and the median CD4 count was 495 cells/mm^3 (range, 375 to 662 cells/mm^3). The seronegative partner (men in 62% of couples) was assigned to 1 of the following 3 daily regimens: tenofovir ($n = 1584$), tenofovir and emtricitabine ($n = 1579$), or placebo ($n = 1584$). Participants were followed monthly up to 36 months. Eighty-two HIV infections occurred in 17 participants in the tenofovir group, 13 in the tenofovir-emtricitabine group, and 52 in the placebo group. The relative reduction of HIV infection in treatment groups was 67% to 75% ($P < 0.001$); protective effects were not significantly different in the 2 treatment group. Eight of those treated were found to have been infected at baseline; antiretroviral resistance developed in 2 of these.

Cautions: These positive results are much better than those cited in similar preexposure prophylaxis studies. This salutary effect was almost certainly caused by many efforts to ensure adherence to preexposure prophylaxis synergistically combined with efforts to reduce ongoing risk. Study patients had monthly visits where they had HIV and pregnancy testing, received 30 days' worth of medications, received adherence counseling, and had their medications from the previous month collected. In addition, participants had counseling before and after testing, risk-reduction counseling, screening for and treatment of sexually transmitted infections, free condoms with training, referrals for male circumcision, and postexposure prophylaxis. Ninety-seven percent of the study medication was taken, and condom use increased. Prescribing preexposure prophylaxis without efforts to maximize adherence is not likely to result in the excellent results reported in this study.

Implications: In heterosexual, HIV discordant couples, oral prophylaxis with daily tenofovir or tenofovir combined with emtricitabine protects against HIV transmission in both women and men. Preexposure prophylaxis can reduce HIV acquisition in heterosexual persons and may be a useful approach to HIV prevention in certain settings. High adherence is essential.

New Pathogen Discovered

A New Virus, Likely Tickborne, Produces an Ehrlichiosis-like Illness

McMullan LK, Folk SM, Kelly AJ, et al. A new phlebovirus associated with severe febrile illness in Missouri. N Engl J Med. 2012;367:834-41. [PMID: 22931317]

Background: Phleboviruses are single-stranded, RNA viruses belonging to the Bunyaviridae family. The *Phlebovirus* genus contains more than 70 distinct members that are variously transmitted by sand flies (the cause of "3-day fever"), mosquitoes (the cause of Rift Valley Fever), or ticks.

Findings: In 2009, 2 men from northwestern Missouri were independently hospitalized 5 to 7 days after tick bites with fever, fatigue, diarrhea, leukopenia, thrombocytopenia, and increased aminotransferase levels. They were thought to have ehrlichiosis and were treated with doxycycline without clear response. Studies for *Ehrlichia* and *Anaplasma* species were negative. Both men were hospitalized for about 2 weeks and recovered in about 6 weeks. Blood was collected from each man on the second hospital day, and separated leukocytes were inoculated onto cell lines for virus isolation. Electron microscopy showed enveloped particles averaging 86 nm in diameter, typical of viruses in the Bunyaviridae family. RNA was extracted from infected cell cultures, and complementary DNA products were sequenced and analyzed. Genome sequences were found to be similar to those of the genus *Phlebovirus*. Similarity of genes indicated that both men were infected with the same *Phlebovirus* strain, but differences between isolates suggested independent infection. The authors called this virus the "Heartland Virus." Both patients had high IgG antibody titers to the virus 2 years after their illnesses.

Cautions: It has yet to be proved that the infection vector is a tick. The disease incidence, geographic range, and variety of clinical manifestations caused by this new virus all need to be elucidated.

Implications: Until now, the only tickborne *Phlebovirus* known to cause human disease was identified recently in China as the cause of severe fever with thrombocytopenia syndrome (SFTS). On phylogenetic analysis, the "Heartland Virus" clusters with the SFTS virus but is distinct from it. A new viral cause of human illness has been identified. It is likely transmitted by ticks and has a clinical syndrome similar to ehrlichiosis (for example, fever, leukopenia, thrombocytopenia, and increased aminotransferase levels). Consider this virus when a patient with suspected ehrlichiosis does not respond within a few days of doxycycline treatment.

Lyme Disease

Second Episodes of Early-Stage Lyme Disease Represent Reinfection and Should Be Treated Like the First

Nadelman RB, Hanincová K, Mukherjee P, et al. Differentiation of reinfection from relapse in recurrent Lyme disease. N Engl J Med. 2012;367:1883-90. [PMID: 23150958]

Background: Erythema migrans, the most common clinical manifestation of Lyme disease, may recur after appropriate antimicrobial treatment. Controversy exists about whether such recurrences represent reinfection or relapse. The outer-surface protein C (ospC) of *Borrelia burgdorferi* is expressed in early infection. Nineteen distinct *ospC* genotypes are associated with Lyme disease in the United States.

Findings: *Borrelia burgdorferi* was isolated from cultures of blood or skin biopsies in 17 patients from the lower Hudson Valley region of New York who had initial and second episodes of erythema migrans. The *ospC* genotypes were measured in patients with 2 or more consecutive, culture-confirmed (such as blood or skin biopsies) episodes of erythema migrans. Further analysis included identification of the 16S-23S ribosomal RNA intergenic spacer type, multilocus sequence type, or both. Patients were treated with standard antibiotics at each episode of erythema migrans with subsequent resolution of skin lesions. The median age at the first episode was 47 years (range, 27 to 80 years). Second episodes occurred 1 to 15 years later (median, 4 years). Twenty-seven percent of patients recalled a tick bite within 30 days before the appearance of a skin lesion.

Twenty-two paired episodes were identified in 17 patients. None of the skin or blood cultures grew more than 1 *ospC* genotype, and none of the paired consecutive episodes was due to the same genotype; the strains were distinct. Clinical evidence also suggested reinfection rather than relapse: The intervals between the first and second episodes were quite long, second episodes occurred at body sites other than those seen with the first episode, and recurrent erythema migrans lesions often had a central punctum suggesting a recent arthropod bite. Epidemiologic findings also supported reinfection rather than relapse. All second episodes occurred from April through August, months when the nymphal ticks that transmit infection are active. One would expect relapses to occur throughout the year.

Cautions: Symptoms and signs of early Lyme disease may transiently improve and then worsen in patients who receive a suboptimal antibiotic, such as cephalexin.

Implications: Recurrent episodes of erythema migrans in appropriately treated patients are due to reinfection, not relapse, and do not represent "chronic Lyme disease" as claimed by some. Treatment of second episodes of erythema migrans should be the same as for first episodes and should not be longer.

Iatrogenic Epidemic of Fungal Meningitis

Improved Regulatory Control of Compounding Pharmacies Is Needed to Prevent Tragic Epidemics

Lyons JL, Gireesh ED, Trivedi JB, et al. Fatal *Exserohilum* meningitis and central nervous system vasculitis after cervical epidural methylprednisolone injection [Letter]. Ann Intern Med. 2012;157:835-6. [PMID: 23277893]

Kerkering TM, Grifasi ML, Baffoe-Bonnie AW, et al. Early clinical observations in prospectively followed patients with fungal meningi-

tis related to contaminated epidural steroid injections. Ann Intern Med. 2013;158:154-61. [PMID: 23183583]

Kainer MA, Reagan DR, Nguyen DB, et al; Tennessee Fungal Meningitis Investigation Team. Fungal infections associated with contaminated methylprednisolone in Tennessee. N Engl J Med. 2012; 367:2194-203. [PMID: 23131029]

Outterson K. Regulating compounding pharmacies after NECC. N Engl J Med. 2012;367:1969-72. [PMID: 23134357]

Perfect JR. Iatrogenic fungal meningitis: tragedy repeated [Editorial]. Ann Intern Med. 2012;157:825-6. [PMID: 23080380]

Shoham S, Marr KA. Treatment of iatrogenic fungal infections: a black mold defines a new gray zone in medicine. Ann Intern Med. 2013;158:208-10. [PMID: 23147215]

Background: Between 21 May and 26 September 2012, approximately 14 000 patients received spinal epidural or joint injections with contaminated methylprednisolone acetate from a single compounding pharmacy, resulting in a multistate outbreak of invasive fungal infections.

Findings: On 18 September 2012, a clinician reported to the Tennessee Department of Health a case of fungal meningitis in an immunocompetent adult after an epidural steroid injection, prompting an epidemiologic investigation. Two days later, active surveillance identified 2 more cases, and the Centers for Disease Control and Prevention was notified. By mid-November, 490 cases of invasive infection had been documented in 19 states, resulting in 34 deaths. The causal agent is an environmental mold, *Exserohilum rostratum*. (Curiously, the index case was due to an *Aspergillus* species.) Diagnosed infections included neutrophilic meningitis, with or without complicating stroke, epidural abscess, the cauda equina syndrome, osteomyelitis, and peripheral joint infection. Cerebrospinal fluid leukocyte counts ranged from 6 to 15 000 cells/mL. In some culture-negative instances, polymerase chain reaction was used to identify the causal fungus. Headache or pain at injection sites were common presenting symptoms. The time from the last injection to illness was mostly 1 to 4 weeks, but it was much longer in some patients. Voriconazole seems to be the most useful drug, but drug levels need to be followed. The duration of effective treatment remains unknown. Lumbar puncture is recommended for patients who were injected with 1 of the known contaminated lots and who develop headache or local pain; they should start treatment if the cerebrospinal fluid leukocyte count is greater than 5 cells/mL. Prophylaxis for asymptomatic injection recipients is not recommended.

Pharmaceutical compounding refers to the combining, mixing, or altering of ingredients of a drug by a licensed pharmacist to produce a product tailored to an individual patient's needs as prescribed by a licensed medical practitioner. Estimates are that 0.25% to 2% of U.S. prescriptions are for compounded products. These drugs are not reviewed and approved by the U.S. Food and Drug Administration. Their quality, safety, and efficacy have not been established. Individual states license pharmacies and have primary responsibility for the oversight of compounding pharmacies.

A similar outbreak has occurred before. In 2002, the Centers for Disease Control and Prevention confirmed 5 cases of *Exophiala* (a mold different from *Exserohilum*, the cause of the current outbreak) meningitis or arthritis due to contaminated, injectable, preservative-free methylprednisolone acetate prepared by a compounding pharmacy (1).

Subsequently, it was learned that fungi grow aggressively in an environment of concentrated corticosteroids. We learned that compounding of preservative-free steroids requires meticulous sterility to prevent fungal contamination.

Cautions: Some individuals with adverse outcomes may have been missed in the investigation because of the difficulty in establishing the diagnosis. At the time of this writing, the full extent of the multistate outbreak of fungal meningitis and other infections has yet to be defined. Contamination of other compounded products from the implicated company has been found to be caused by organisms that include bacteria as well as fungal species other than *Exserohilum*. Other infections may yet be identified.

Implications: States do not generally have the resources to oversee compounding pharmacies. These pharmacies have become a national drug manufacturing industry with interstate activity. Federal regulation, perhaps by the U.S. Food and Drug Administration, will probably be necessary to see that this epidemic is not repeated.

In addition, no quality evidence supports the use of epidural steroid injections to treat back or neck pain (2). Physicians considering the use of epidural steroid injections or compounded products should remember the principal directive of primum non nocere—first, do no harm.

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