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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Measles From Coast to Coast: Risks, Costs, and Potential Interventions

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: It is expensive to respond to and control measles outbreaks in the United States. Primary outbreak prevention should focus on vaccination of travelers and encouragement of routine vaccine acceptance by those who currently are hesitant to have their children vaccinated.

SOURCE: Rosen JB, Arciuolo RJ, Khawja AM, et al. Public health consequences of a 2013 measles outbreak in New York City. *JAMA Pediatr* 2018; doi: 10.1001/jamapediatrics.2018.1024. [Epub ahead of print].

Measles is no longer endemic in the United States, but outbreaks can occur after the arrival of infective travelers who have contact with unimmunized residents. In March 2013, an unvaccinated adolescent traveled home from the United Kingdom to New York. (In New York, 97% of children aged 19-35 months have received at least one measles vaccine.) A total of 58 people then became infected with measles in two Brooklyn neighborhoods. Contact tracing revealed six generations of spread between eventual cases during the three months after the arrival of the infected index case.

Eight days after seeking medical care in New York from an astute clinician who suspected measles, the patient received confirmation of the diagnosis from measles IgM results, and the state health department was notified. Of the 58 measles patients eventually identified, none had documentation of previous vaccination. Measles patients were 0-32 years of age (median 3 years); 12 (21%) were younger than 12 months of age (the age of the first routine measles vaccination in the United States). All patients were involved with an Orthodox Jewish community; 71% were from eight extended families.

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The health department identified 3,351 exposed contacts of the patients with measles; 66% already had evidence of measles immunity, and an additional 11% had received a single measles vaccine previously. Among at-risk contacts, 114 received measles vaccine within three days of the exposure, and another 77 (those younger than 12 months of age who had not received vaccine within three days of exposure) received immunoglobulin within six days of the exposure. Information about the outbreak was provided to physicians, schools, and daycare providers.

The economic impact of public health services related to the measles outbreak was evaluated. The costs of vaccination, laboratory testing, and personnel time totaled $394,448.

■ COMMENTARY

In resource-limited countries, vaccine-preventable illnesses such as measles are more common in rural populations where individuals are unable to travel and access vaccinations. The opposite seems to be true in the United States, where measles outbreaks usually begin through contact with a returning/arriving traveler and then spread through families who have chosen intentionally not to avail themselves of available vaccinations.

It is important that all international travelers be up to date with measles vaccination. Unfortunately, not all physicians are successfully taking advantage of opportunities to vaccinate travelers.[1] Appropriate immunization of travelers could prevent outbreaks of measles. Then, rapid diagnosis and isolation of infected individuals can help prevent spread to others; the index patient in New York went eight days between a clinical diagnosis and attempts to prevent transmission.

The New York outbreak happened to affect unvaccinated people in an Orthodox Jewish community. In California private schools, high rates (> 20%) of non-medical exemption from vaccination of kindergartners because of "personal beliefs" were seen more frequently in secular and non-Catholic Christian schools than in Jewish, Catholic, and Muslim schools.[2] In fact, only 49% of private kindergartens surveyed in California had 95% coverage of measles vaccination.[2] Under-immunization was more common in the more expensive schools than in schools with lower tuition fees.[2] Thus, affluence actually is associated with less vaccination.

Popular awareness of the problems of non-vaccination can affect behaviors. After a widely publicized 2014-2015 outbreak of measles that spread from a California amusement park to involve 111 patients in eight states and three countries, 38% of physicians reported receiving fewer requests for delayed immunizations than prior to the outbreak.[3]

Pediatricians routinely deal with vaccine-hesitant parents.[4] The American Academy of Pediatrics offers guidance to help overcome vaccine hesitancy.[5]

Even while physicians gain skills working with vaccination-hesitant families, the public health costs of outbreaks, as shown by Rosen and colleagues, are significant. Society uses tangible resources to deal with the consequences of non-vaccination. The societal cost prompts some people to wonder if top-down governmental regulatory intervention also might be helpful.

In fact, regulatory changes in California led to more children receiving vaccinations prior to kindergarten. The state of California chose to make vaccine exemption more difficult for families by requiring a healthcare professional signature even for non-medical exemptions to routine pre-school vaccinations. The rate of children starting kindergarten without measles vaccine because of non-medical exemptions dropped from 3.1% in 2013, prior to the new regulations, to 2.3% in 2015, after the new regulation took effect.[6]

It behooves physicians to work with patients and families to foster appropriate, timely immunization. In addition, publicizing personal and societal

consequences resulting from non-vaccination can help transform some vaccine-hesitant families into vaccine advocates. On a larger societal level, legal regulations can improve vaccination and decrease public health expenditures. ■

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ABSTRACT & COMMENTARY

Latent Tuberculosis Treatment With Four Months of Rifampin Compared to Nine Months of Isoniazid

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: In an open-label trial, adults with latent tuberculosis infection were randomized to either four months of treatment with rifampin or nine months of treatment with isoniazid. The four-month rifampin regimen was non-inferior to nine months of isoniazid for prevention of active tuberculosis. It also was associated with a higher treatment completion rate and superior safety.

SOURCE: Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med* 2018;379:440-453.

Adult patients with latent tuberculosis infection (LTBI) from nine countries were assigned randomly to either a four-month regimen of rifampin (RIF) at a dose of 10 mg/kg/day (maximum dose 600 mg) vs. a nine-month regimen of isoniazid (INH) at 5 mg/kg/day (maximum dose 300 mg). Patients considered to be at high risk for development of neuropathy also received vitamin B6.

Of the 3,443 patients randomized to RIF, confirmed active tuberculosis (TB) developed in four patients and clinically diagnosed TB developed in four patients during 7,732 person-years of follow up, compared to development of confirmed active TB in four patients and clinically diagnosed TB in five patients among the 3,416 patients in the INH arm.

Seventy-nine percent of the RIF patients completed their course of treatment compared to 63% of the INH patients. One hundred sixty-two patients (5.8%) in the INH arm and 80 patients (2.8%) in the RIF arm experienced adverse events, with 1.7% of the INH patients experiencing grade 3 or 4 hepatotoxicity and 0.3% of RIF patients experiencing grade 3 or 4 hepatotoxicity.

■ COMMENTARY

This is an important clinical trial, which clearly will change practice in both the developed and developing world. The shorter and better-tolerated RIF regimen proved as effective as INH in preventing development of active TB, and a significantly higher proportion of patients completed their treatment. However, a big limitation of RIF (since it is a potent inducer of many cytochrome P450 isoforms) is the many problematic drug interactions. In view of this, a careful review of all patients' concomitant medications by a clinical pharmacist would seem to be prudent in many cases before initiating RIF. In many of these patients, INH will need to be used instead.

This bit of excellent news comes quickly on the heels of the release of a meta-analysis and CDC recommendations to consider the 12-week regimen of once-weekly INH plus rifapentine (3HP) given by either directly observed therapy or self-administered treatment in persons 2 years of age and older for LTBI.[1] The authors of the CDC meta-analysis reported a 5% drug discontinuation rate (largely due to systemic drug reactions often associated with fever, headache, and myalgias). While rifapentine probably is not quite as potent of a cytochrome P450 inducer as rifampin is, drug interactions are still potentially problematic. ■

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ABSTRACT & COMMENTARY

A Grossly Inadequate Global Response to Chronic Hepatitis B Virus Infection

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

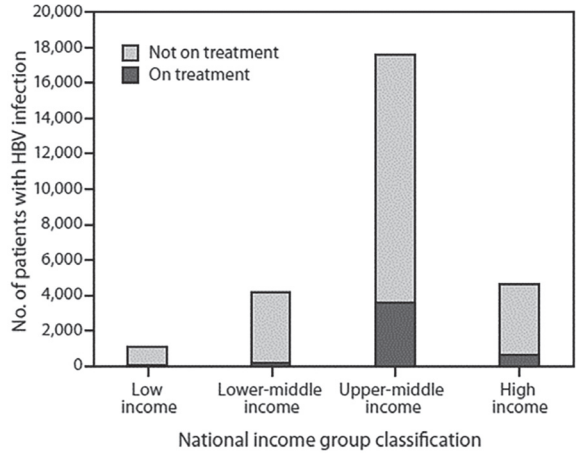
Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Only 1.5% of all individuals in the world with chronic hepatitis B virus infection are receiving treatment.

SOURCE: Hutin Y, Nasrullah M, Easterbrook P, et al. Access to treatment for hepatitis B virus infection — worldwide, 2016. *MMWR Morb Mortal Wkly Rep* 2018;67:773-777.

In 2016, the World Health Assembly endorsed World Health Organization (WHO) goals for the elimination of hepatitis B virus (HBV) and hepatitis C virus infections by 2030. More specifically, the global goal is a 90% reduction in the incidence and a 65% reduction in mortality. Of the estimated 257 million HBV-infected individuals in 2016, only approximately 27 million (10.5%) had been diagnosed and were aware that they were infected. Furthermore, only 4.5 million (16.7%; 1.5% of all infected individuals) of these were receiving antiviral therapy. The proportion of infected individuals was low across countries' income strata, but, interestingly was highest in upper-middle-income countries (*see Figure*), not in high-income countries. As expected, low-income countries performed the worst.

Figure: Hepatitis B Virus (HBV) Treatment Coverage Among the 27 Million Persons With Diagnosed HBV Infection, by National Income Group — Worldwide, 2016



Source: Centers for Disease Control and Prevention

■ COMMENTARY

Approximately 3.5% of the world's population in 2017 was chronically infected with HBV and almost 900,000 died, mostly from cirrhosis and/or hepatocellular carcinoma. Unfortunately, only approximately 4.5 million (1.8%) of all individuals with HBV in the world were receiving therapy directed against this viral infection.

A prime example of the failure to deal with the problem is exemplified by Africa, which has among the highest rates of chronic HBV infection and the highest mortality from related hepatocellular carcinoma in the world. Despite this, there are no national programs in the entire region, with limited exceptions, such as pilot programs and those associated with HIV activities, that provide testing and treatment services.

The failure to address global HBV infection exists even though the WHO-recommended anti-HBV drugs tenofovir and entecavir are available in most or all countries of the world and that their cost has decreased. Thus, in 2015, the yearly cost of entecavir was as low as $427, while that of WHO-prequalified generic tenofovir in 2016 was only $32.

This dramatic decrease in cost should provide low- and middle-income countries an opportunity for dealing with the problem of chronic HBV infection. This will require the development of national strategies with initial prioritizing of treatment initiation to individuals who have developed cirrhosis already, followed by more expansive use. ■

ABSTRACT & COMMENTARY

Clinicians Prescribe Antibiotics for Excessive Duration in Patients With a Diagnosis of Acute Sinusitis

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Clinicians inappropriately prescribe antibiotics most often to patients with a diagnosis of acute sinusitis for durations much longer than recommended.

SOURCE: King LM, Sanchez GV, Bartoces M, et al. Antibiotic therapy duration in US adults with sinusitis. *JAMA Intern Med* 2018;178: 992-994.

Antibiotic therapy often is prescribed when it is unnecessary (and, therefore, by definition, more likely to be harmful than beneficial). Even when antibiotic therapy is appropriate, it often is administered for durations well beyond the time when its benefit has passed and only negative consequences remain, such as adverse reactions and continued unnecessary risk of selection of antibiotic resistance.

King and colleagues now have determined more precisely the actual practice of front-line clinicians regarding their prescribed duration of antibiotic therapy for patients with a diagnosis of acute sinusitis. The researchers examined the new antibiotic prescriptions for adults in association with a diagnosis of acute sinusitis in the 2016 National Disease and Therapeutic Index (IQVIA). They identified 3,696,976 visits meeting their criteria and found that the median duration of prescribed therapy was 10 days. Approximately two-thirds of antibiotics were prescribed for 10 days or longer.

While azithromycin is administered most often for five days, its unusual pharmacokinetics with very slow elimination from tissues generally is considered to result in approximately 10 days of antibiotic exposure. A re-analysis of the data with removal of azithromycin from consideration found that, for the remaining prescribed antibiotics (80% of the total), an astounding 91.5% of prescriptions were for 10 days or longer. Furthermore, only 7.6% were for seven days, and 0.5% were for five days.

■ COMMENTARY

The most recent Infectious Diseases Society of America guideline published in 2012 recommends that for patients with a diagnosis of uncomplicated acute sinusitis who meet certain criteria (basically, severe or worsening illness or at least 10 days of symptoms), the duration of treatment should be five to seven days. Furthermore, the guideline recommends that macrolides, such as azithromycin, not be used for empiric therapy because of the high rate of resistance among pneumococci.

This study included prescriptions from a broad range of physician practitioners, including family practice, general practice, internal medicine, pediatrics, and emergency medicine. It documents what we already know — that physicians of all types often prescribe antibiotics for durations well in excess of the duration for which maximum benefit is achieved. Implementing antimicrobial stewardship principles in the settings in which these therapies are prescribed is a critical element of the work ahead. ■

ABSTRACT & COMMENTARY

Probiotics for the Primary Prevention of *Clostridium difficile* Infection

By Richard R. Watkins, MD, MS, FACP, FIDSA

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Dr. Watkins reports that he has received research support from Allergan.

SYNOPSIS: The authors of a before-and-after intervention study and a meta-analysis found that probiotics reduce the incidence of *Clostridium difficile* infection (CDI). The strategy seems to work best in hospital settings where the incidence of CDI is ≥ 5% and for patients receiving two or more antibiotics.

SOURCES: Trick WE, Sokalski SJ, Johnson S, et al. Effectiveness of probiotic for primary prevention of *Clostridium difficile* infection: A single-center before-and-after quality improvement intervention at a tertiary-care medical center. *Infect Control Hosp Epidemiol* 2018;39:765-770.

Johnston BC, Lytvyn L, Lo CK, et al. Microbial preparations (probiotics) for the prevention of *Clostridium difficile* infection in adults and children: An individual patient data meta-analysis of 6,851 participants. *Infect Control Hosp Epidemiol* 2018;39:771-781.

Clostridium difficile infections (CDI) cause significant morbidity, mortality, and cost to the healthcare system. Therefore, finding effective methods to prevent CDI is a laudable goal and an area of active research. One particular method that has gained attention for primary prevention of CDI is the use of probiotics. As part of a quality improvement initiative, Trick et al gave probiotics to patients about to start antibiotic therapy and evaluated the rates of CDI before and after the intervention. In another study, Johnston et al performed a meta-analysis to determine if probiotic prophylaxis reduces the odds of CDI in adults and children.

The before-and-after study was conducted at a single hospital in Chicago and compared 12-month baseline and intervention periods. Patients were excluded from receiving probiotics if they were on neonatal, pediatric, or oncology units. Additional exclusion criteria included receiving only perioperative antibiotics, having leukopenia (white blood cell count < 1,000 cells/mm^3), being a transplant recipient, or being restricted from oral intake, although patients receiving enteral feedings were given a liquid probiotic preparation. The incidence of hospital-onset CDI was the primary outcome. Researchers performed a post-hoc analysis that compared the incidence between the intervention's beginning six months and its final six months. The investigators also conducted a matched case-control study to determine a patient-level analysis. The meta-analysis included randomized controlled trials (RCTs) with children and/or adults who were given antibiotics for any reason along with concomitant probiotics and compared to placebo, alternative prophylaxis, or no treatment (i.e., standard of care). The primary outcome was the diagnosis of CDI, which was defined as diarrhea with *C. difficile* laboratory confirmation, the presence of pseudomembranes with endoscopy, *C. difficile* histological diagnosis, or toxic megacolon diagnosis. The secondary outcome was severe adverse event incidence.

In the first study, there was a decreased incidence of CDI during the second six months of the intervention period compared to the first six months (5.4 vs. 8.6 per 10,000 patient days, respectively; incident rate ratio [IRR], 0.6; 95% confidence interval [CI], 0.4-0.9; $P = 0.009$). However, in the case-control part of the study, logistic regression determined that probiotic receipt did not decrease the risk for CDI (adjusted odds ratio [aOR], 0.95; 95% CI, 0.8-1.2; $P = 0.65$). Missed doses of probiotic were common, but no associating factors were found.

In the meta-analysis, there were 18 studies that reported CDI outcomes. Receiving a probiotic lowered the unadjusted odds of developing CDI (OR, 0.37; 95% CI, 0.25-0.55; $P < 0.0001$). Receiving two or more antibiotics raised the odds for CDI significantly (OR, 2.20; 95% CI, 1.11-4.37; $P = 0.0243$). Factors such as age, sex, hospitalization status, and exposure to high-risk antibiotics (e.g., third- and fourth-generation cephalosporins, lincosamides, and fluoroquinolones) did not increase the odds for CDI significantly. A control group event rate of ≥ 5% had a significant association with CDI

(aOR, 16.33; 95% CI, 7.79-34.26; $P < 0.0001$). For adverse events, there were no major differences between the intervention and control groups (OR, 1.06; 95% CI, 0.89-1.26; $P = 0.536$). No cases of bacteremia or fungemia were associated with probiotics, nor were there any serious adverse events deemed attributable to them. The number needed to treat to prevent one case of CDI was 96.

■ COMMENTARY

These two studies add to the evidence for using probiotics to help reduce the risk for CDI. The meta-analysis found probiotics to be very safe for most patients when used for CDI prevention. In the study by Trick et al, a single episode of *Lactobacillus* bacteremia was documented. A follow-up analysis determined the strain that caused the bacteremia was not part of the three-strain probiotic capsule the patient received. Yet, the authors of a recent study found that data about the harms of agents that modify the gut microbiome (i.e., probiotics, prebiotics, and synbiotics) are lacking in many RCTs and that a definitive recommendation about their safety cannot be made.[1] Therefore, it seems prudent to recommend withholding probiotics in some circumstances, such as immunocompromised patients. There also has been a reported case of a patient with a central line who developed *Lactobacillus* bacteremia from the strain in the probiotic capsule.[2]

The main results of the study by Trick et al are somewhat difficult to interpret because of the delayed impact observed during the intervention period. The authors noted that a similar delay has been seen in previous studies and may be attributable to changes in the environmental burden of *C. difficile* spores over time. They also speculated that the reason no protective effect was found for probiotics in the case-control study was due to unmeasured confounding factors that increased the risk for CDI among the case patients.

The meta-analysis provides some insight regarding the populations that may benefit from probiotics, including settings with CDI incidence ≥ 5% and for patients receiving two or more antibiotics. Pragmatically, this means the greatest benefit is for populations with moderate to high baseline risk.

An interesting finding was that receipt of a "high-risk antibiotic" was not an independent risk factor for CDI. This suggests there should be less focus on these drugs and more on other interventions for reducing the incidence of CDI, such as shortening antibiotic durations, improving hand hygiene, and performing better environmental cleaning. ■

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ABSTRACT & COMMENTARY

Inappropriate Outpatient Antibiotic Prescribing: The Need to Target Urgent Care Centers

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Urgent care centers, which are part of a growth industry, are responsible for a large proportion of antibiotic prescriptions, including inappropriate prescriptions for acute respiratory diagnoses.

SOURCE: Palms DL, Hicks LA, Bartoces M, et al. Comparison of antibiotic prescribing in retail clinics, urgent care centers, emergency departments, and traditional ambulatory care settings in the United States. *JAMA Intern* Med 2018 Jul 16; doi: 10.1001/jamainternmed.2018.1632. [Epub ahead of print].

Palms and colleagues retrospectively analyzed differences in antimicrobial prescribing in urgent care centers, retail clinics, and emergency departments (EDs) in the United States, using the

2014 Truven Health MarketScan Commercial Claims and Encounters Database. This database contains claims data on persons < 65 years of age who have employer-sponsored health insurance. The database included 2.7 million urgent care visits, 58,206 retail clinic visits, 4.8 million ED visits, and more than 10 million medical office visits. The frequencies of antibiotic prescriptions were 39.0%, 36.4%, 13.8%, and 7.1%, respectively. Antibiotic prescribing for "antibiotic-inappropriate" acute respiratory diagnoses also was highest in urgent care centers (45.7%), with EDs coming in second (24.6%), followed by medical offices (17.0%) and retail clinics (14.4%).

■ COMMENTARY

As the authors noted, these data suggest that prior estimates that at least 30% of antibiotics prescribed in physician's offices and EDs were unnecessary provides an underestimate of all outpatient prescribing, given the outsize contribution to unnecessary prescribing in urgent care centers.

These data demonstrate the need to implement outpatient antimicrobial stewardship and that, in addition to the usually considered sites, this effort should target urgent care centers. Addressing this is "urgently" critical given the remarkable growth in what has become an $18 billion industry. Urgent care centers, where the leading diagnostic category is acute respiratory infections, had a 1,725% increase in claims from 2007 to 2016 (compared to only 229% in EDs).[1] ■

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ABSTRACT & COMMENTARY

Eosinophilic Meningitis Caused by *Angiostrongylus cantonensis* in the United States

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Excluding Hawaii, eosinophilic meningitis due to the rat lungworm rarely is encountered in the United States. Ordinarily, the infection is acquired in Asia and the South Pacific, but it also may be acquired in the southern United States.

SOURCE: Liu EW, Schwartz BS, Hysmith ND, et al. Rat lungworm infection associated with central nervous system disease — Eight U.S. states, January 2011-January 2017. *MMWR Morb Mortal Wkly Rep* 2018;67:825-828.

Most cases of infection with *Angiostrongylus cantonensis*, the rat lungworm, are acquired in Asia and the Pacific Islands, including Hawaii. Although the infection usually is asymptomatic, migration of the larvae can lead to serious complications, especially if they reach the central nervous system. Infections occasionally are diagnosed in the continental United States. Liu and colleagues reviewed 12 such cases with eosinophilic meningitis due to infection with this parasite, with the etiology determined by polymerase chain reaction (PCR).

The implicated sources of infection included raw vegetables, snails, and slugs. One individual had a history of geophagia. Six of the patients, all from southern states, denied any travel outside the continental United States.

Patients most often presented with subjective fever, weakness, headache, numbness, and/or tingling sensations. Among the findings on examination were cranial nerve deficits, nuchal rigidity, and focal weakness. Initial testing detected peripheral eosinophilia in 10 patients, and all 12 had cerebrospinal fluid (CSF) pleocytosis. CSF eosinophilia was absent on initial examination in only two patients, but was present on subsequent examination in both. Brain abnormalities were seen on MRI in eight of the 11 patients who underwent this examination, and spinal cord abnormalities were observed in five of six patients; one patient had optic nerve abnormalities.

Eleven patients received corticosteroids and seven received albendazole. Eleven of 12 patients improved (although it must be noted that whether this resulted from the therapeutic intervention is unknown), but four had continuing focal neurological abnormalities and one developed seizures five months later.

■ COMMENTARY

The only thing unusual about this report is that six of the 12 cases apparently were autochthonously acquired within the continental United States. The authors noted that *A. cantonensis* infection has been detected in snails (both native and exotic species) in Florida and Louisiana, and in rat species in these two states as well as in Oklahoma. Infections of opossums and nine-banded armadillos, among other vertebrates, also have been observed.

Despite the rarity of occurrence, these findings indicate that clinicians must keep in mind the possibility of infection with this parasite as a cause of eosinophilic meningitis, including among patients without a history of travel outside the continental United States. As an aside, there are other causes of eosinophilic meningitis that may be acquired within the United States, such as neurocysticercosis and coccidioidomycosis. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Risk Behavior and *Toxoplasma*

SOURCE: Johnson SK, Fitza MA, Lerner DA, et al. Risky business: Linking *Toxoplasma gondii* infection and entrepreneurship behaviors across individuals and countries. *Proc Biol Sci* 2018;285(1883).

Recent studies purport various links between the human biome and latent infections. These range from viruses to parasites, to everything from overall human health and well-being, academic performance, atopy and asthma, to host immunity and even to attractiveness to the opposite sex.

The authors of this study examined the relationship between latent infection with *Toxoplasma gondii* and an interest in business and other entrepreneurial behaviors. Other studies have suggested a negative correlation between the prevalence of *T. gondii* infection and avoidance risk behavior — meaning that people who generally are risk takers are more likely to have serologic evidence of latent *T. gondii* infection. Why this may be the case is not at all clear. Is this, in fact, some variant of the tall height/large feet "causality," or is there something to the emotional and psychological nature of people who are more likely to take risks and, therefore, are more willing to start a business along with a risk of parasitic infection? Or does latent infection with certain parasitic infections influence behavior through hormonal or neurological changes?

The researchers performed two studies: The first examined 1,495 students at a large university within the United States, comparing *T. gondii* IgG antibodies (detected via indirect competition saliva-based immunoenzyme assay [ELISA]) and their major areas of study (i.e., business-oriented majors vs. non-business majors), including such areas of study as marketing, finance, and accounting. Of these students, 22% tested positive for *T. gondii* IgG antibodies. While controlling for sex and grade point average, the researchers found that positive antibody status significantly correlated with majoring in business-related fields ($P < 0.005$). Among 1,293 students with either positive or negative results (excluding those with indeterminate results), 31% of business majors compared with 22% of non-business majors tested positive for *T. gondii* IgG antibody. Further, those students with interest in establishing their own business or demonstrating management and entrepreneurial tendencies were 1.7 times more likely to have *T. gondii* antibodies compared to those in other business areas.

A second study was conducted with 197 individuals attending entrepreneurial events who offered to provide a saliva sample and answer a brief questionnaire. Once again, the presence of *T. gondii* antibody positively predicted an interest in business and entrepreneurship. Antibody-positive individuals were 1.8 times more likely to have started a business successfully than those who tested negative.

The authors admitted that any relationship between behavior and parasitic infection probably is complex and influenced by myriad unknown variables. Could this be as simple as people who love business also travel abroad more frequently, have a tendency to eat more undercooked red meat, or love to hunt elk or deer and make their own sausage? A direct effect of parasitic infection seems less likely than a behavioral link.

Embolic Risk and Vegetation Size

SOURCE: Mohananey D, Mohadjer A, Pettersson G, et al. Association of vegetation size with embolic risk in patients with infective endocarditis. A systematic review and meta-analysis. *JAMA Intern Med* 2018;178:502-510.

In studies of infective endocarditis (IE), researchers have observed an increased risk of embolic events with echocardiographic evidence of larger vegetations, although it is recognized that certain bacteria have a propensity for early and more frequent embolism. As a result, consideration of surgical options, in addition to medical therapy, has been recommended for aortic or mitral valve vegetations greater than 10 mm in size.

To better assess the effect of vegetation size on embolic risk, Mohananey et al performed a meta-analysis involving available observational studies of randomized clinical trials of endocarditis and embolic risk. Only those studies based on two-dimensional transthoracic or transesophageal echocardiography in which vegetation size was measured and clearly specified and an odds ratio (OR) of embolic risk was determined were included in the analysis. Studies of IE involving prosthetic valves or cardiac devices were excluded unless they also included cases of IE involving native valves.

A total of 21 unique studies published from 1983 to 2016 were identified, encompassing a total of 6,646 patients with IE, for which vegetation size was clearly specified in 5,116. Using Mantel-Haenszel statistical testing (which gives weight to the individual ORs based on the weight of the study), the overall OR of an embolic event for those with valve vegetation size 10 mm or greater was 2.28 compared to those with vegetation size 10 mm or less ($P < 0.001$; range of OR varied from 0.19-15.22). In addition, investigators observed an increase in all-cause mortality for those with vegetation size greater than 10 mm compared to those with smaller vegetations (OR 1.63; $P = 0.009$).

Multiple subgroup analyses were performed. When studies performed from 1983 to 1999 were pooled, an increased risk of embolic events with vegetation size greater than 10 mm was observed but did not meet statistical significance. However, in those studies published from 2000 to 2016, a statistically significant increased risk of an embolic event was observed for larger vegetations. The authors suggested this may be the result of improvements in echocardiography, leading to more accurate identification and measurement of smaller vegetations. They also examined studies based on the use of Duke or modified Duke criteria compared to those that did not, and found similar results. Further, using various vegetation size cut-offs from 5 mm to 15 mm, the authors found the odds of an embolic event using a cut-off of 5 mm was similar to that observed using a cut-off of 10 mm.

While it is recognized that certain bacterial pathogens, such as *Staphylococcus aureus* and the HACEK organisms, are more likely to cause "more friable" vegetations with an increased risk of embolism, there were insufficient microbiologic data to include in the analysis. Their analysis of the percentage of *S. aureus* infection among the studies analyzed did not show a clear trend. In addition, while the authors attempted to focus their analysis on native valve IE, 14 of the 21 studies in the analysis included some number of prosthetic valves, ranging from 2% to 30% of reported cases. A subgroup analysis suggested these cases did not significantly affect the overall results.

Recertification: Is There a Better Way?

SOURCES: Gray B, Vandergrift J, Landon B, et al. Associations between American Board of Internal Medicine maintenance of certification status and performance on a set of healthcare effectiveness data and information set (HEDIS) process measures. *Ann Intern Med* 2018;169:97-105.

Goldman L. Maintenance of certification: Glass not entirely empty? *Ann Intern Med* 2018;169:124-125.

The American Board of Internal Medicine (ABIM) has taken heat lately for its stringent certification requirements that go well beyond what is required for state licensure or hospital privileges — as well they should. In short, there is no good evidence that Maintenance of Certification (MOC) status and the requirements of a rigorous closed-book examination independently correlate with better physician performance. MOC is time-consuming, detracts from and disrupts usual clinical practice, soaks up valuable remaining family time, and imposes a burden on colleagues — and it's expensive. Fulfilling MOC requirements for a general internist is estimated to cost $17,000 per physician every 10 years, at a time when many physicians are shuttering their practices because of lower reimbursements, increasing regulation, and increased costs. And who benefits from this expense? The very organization that requires it — and there are no alternative certifying options. Simply signing up for the ABIM MOC program costs $2,600, which does not include the cost to attain the actual required MOC credits. Further, the ABIM seems to have a lock on what satisfies MOC credit. I was stunned to learn that only a fraction of the CME credit earned attending IDWeek 2016 qualified for MOC.

The authors of a recent *Annals* article attempted to confirm whether MOC status correlates with any meaningful clinical measure of performance as a general internist. The investigators examined older internists who initially certified in 1991 and who provided care to Medicare patients between 2005 and 2012. These were grouped by MOC status and how often they met current standards for hemoglobin A1c testing, annual lipid-cholesterol screening, and three other diabetes standards of care. After multiple adjustments to their model, between those physicians who maintained certification and those who did not, the authors successfully confirmed that MOC status correlated with small but measurable differences in these five Healthcare Effectiveness Data and Information Set (HEDIS) standards. By way of example, MOC physicians more frequently provided annual lipid-cholesterol measurements than non-MOC physicians (83.1% vs. 80.5%; confidence interval [CI], 0.6-4.1; $P = 0.008$). Biennial mammography also was performed more often in patients of MOC physicians than of non-MOC physicians (79.4% vs. 77.4%; $P = 0.032$). Comparing MOC vs. non-MOC physician results, hemoglobin A1c testing was obtained in 58.4% vs. 54.4% of their patients.

Requirements for accreditation should not be based on such meager differences in outcomes. As the authors of an accompanying editorial pointed out, these small differences could be explained by a myriad of cofactors. Any small confounder with a relative risk of 1.2 could easily explain away these differences — anything from the type of computer system to which physicians have access to the patient group they serve. Our computer system includes best practice alerts for hemoglobin A1c; I don't even have to think about it, I just click the button. Does this make me a better physician?

What was not clearly explained in this article was that rates below 50% for hemoglobin A1c testing warrant a grade of F according to HEDIS standards, suggesting that MOC certification might raise up some physicians from an F to an F+ or D-. The authors of an accompanying editorial suggested that any certification that lets you, as the consumer, know that a physician has a slightly better F than his colleague down the road is not really meaningful.

Since the ABIM is holding physicians accountable, let's make the ABIM accountable. If there are requirements, let's make them meaningful and cost-effective.

Now that a year has passed since I was forced to recertify in infectious disease (and I am not spitting as many nails), I will share my own experience. Shortly before my 59th birthday, I was informed by my employer that I was "out of compliance" with board certification. I initially certified in infectious disease in 1991, just months after the cut-off for non-requirement, but was under the misapprehension that further recertification was not required. I recertified voluntarily in 2005 because I thought it would be fun and interesting. It turns out my new employer, who had purchased our group, apparently required current subspecialty certification. Worse, I was informed that if I did not sign up for MOC immediately and pass the exam, I would lose my job. (I could continue to work per diem with no benefits or healthcare.) During my 27 years of experience, I have written this column for 22 of those, have maintained state licensure and CME credit, and I am a fellow of the American College of Physicians and the Infectious Diseases Society of America (IDSA).

I cleared my schedule, spent every weekend from February to April studying, took two weeks of vacation — and I memorized. I went over and over material, I completed several of the IDSA modules (which I thought were good), I tried to review old textbooks (which were out of date), and, finally, at a colleague's suggestion, I signed up for an online ID review course (which cost $1,100). And I memorized. The sheer amount of material you have to remember is daunting — material that I usually know where to reach for when needed.

The examination was brutal: 10 hours locked in a room, walled up in a cubbyhole; allowed only three breaks totaling no more than 1.5 hours (not even a bathroom break). The questions were dizzyingly difficult and tricky. I barely finished one of the sections in time. Of course, throughout, I knew if I didn't pass, I was going to lose my job. I admit, I was traumatized for weeks. Of course, I passed. That's not the point.

Did I gain anything from the experience, other than keeping my job? In all honesty, I enjoyed indulging in the long hours of study. I loved the slide shows and images of diseases, bugs, and worms. I loved listening to Dr. John Bennett (such a treat!) and other experts speak. I admit, I filled in some gaps in my knowledge, especially about newer antibiotics and HIV medications. However, I could have accomplished the same result by completing a one-week board review course and an open book exam, with far less anxiety, time, and expense. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Factors associated with increased risk for measles in the United States include which of the following?

a. Affluence

b. International travel

c. Lack of vaccine-favoring laws

d. All of the above

2. Which of the following is correct regarding global chronic hepatitis B virus infections in 2016?

a. Fewer than 1 million people are infected.

b. Ninety percent of global hepatitis B virus infections have had laboratory diagnosis.

c. Only 16.7% of those diagnosed and 1.5% of the total number of infected patients were receiving treatment.

d. The prices of the World Health Organization-recommended drugs for treatment of chronic hepatitis B virus infection, entecavir and tenofovir, recently have increased dramatically.

3. At which of the following outpatient sites are patients most likely to receive antibiotic prescriptions for acute respiratory diagnoses for which antibiotics are not indicated?

a. Urgent care centers

b. Emergency departments

c. Medical offices

d. Retail clinics

CME OBJECTIVES

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

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.