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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Antibiotics and Adverse Events: Doctors, Do No Harm

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

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

SYNOPSIS: A retrospective study found that among 1,488 hospitalized patients who received an antibiotic, 298 (20%) experienced at least one antibiotic-associated adverse drug event. Furthermore, 287 (19%) of the antibiotic regimens were not clinically indicated, and 56 (20%) of these were associated with an adverse drug event.

SOURCE: Tamma PD, Avdic E, Li DX, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Intern Med* 2017;177:1308-1315.

Antibiotics have saved countless lives and momentously improved human health since their use in clinical practice began more than 70 years ago. Yet these miracle drugs have downsides, including adverse drug events (ADEs), organ toxicities, and promotion of antimicrobial-resistant pathogens. ADEs associated with antibiotics include allergic reactions, which can range from mild (e.g., rash or pruritus) to life-threatening (e.g., anaphylaxis), as well as the development of *Clostridium difficile* infection (CDI). Tamma et al sought to determine the incidence of antibiotic-associated ADEs in a cohort of adult inpatients at Johns Hopkins Hospital.

The study was a retrospective analysis that included all patients 18 years of age and older admitted to the general medical service and who received antibiotics for at least 24 hours between September 2013 and June 2014. Patients were excluded if they received antibiotics for prophylaxis, inhaled or topical antibiotics, anti-tuberculosis antibiotics, and

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Infectious Disease [ALERT]

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antibiotics for noninfectious indications. Both inpatient and outpatient medical records were reviewed to obtain follow-up data about ADEs. The investigators followed the patients' clinical course for ADEs up to 90 days after the first day of antibiotic administration for the development of CDI and multidrug-resistant organism (MDRO) infections and up to 30 days for other ADEs (e.g., tendinitis, gastrointestinal, renal, hepatic, dermatologic, cardiac, neurologic, or hematologic toxicities). At least two infectious disease physicians or pharmacists decided on the association between the antibiotic received and the subsequent ADE.

Of 5,579 patients admitted to the medical service during the study interval, 1,488 (27%) received antibiotics for at least 24 hours and were included in the analysis. There were a total of 324 unique ADEs, and 298 (20%) of the patients experienced at least one antibiotic-associated ADE. The most frequently prescribed antibiotics were third-generation cephalosporins (607 [41%] of regimens), parenteral vancomycin (544 [37%] of regimens), and cefepime (414 [28%]) of regimens. Every additional 10 days of antibiotic therapy conferred a 3% increased risk of an ADE. There were 236 (73%) ADEs that occurred during the hospitalization, while 88 (27%) occurred after discharge, which included 11 cases of CDI and 44 MDRO infections.

The researchers determined that 287 (19%) of the prescribed antibiotic courses were not clinically indicated, such as treating asymptomatic bacteriuria or noninfectious respiratory conditions like exacerbations of congestive heart failure. Notably, of the nonindicated regimens, 20% were associated with an ADE. The most common ADEs were gastrointestinal, renal, and hematologic abnormalities. Aminoglycosides, trimethoprim-sulfamethoxazole, and parenteral vancomycin were the most frequent agents associated with renal injury. Two patients experienced QTc prolongation; one had received azithromycin and the other had received ciprofloxacin. Seven patients who received cefepime developed neurological side effects, including encephalopathy and seizures.

The rate of CDI was 3.9 (95% confidence interval [CI], 3.0-5.2) per 10,000 person-days for patients receiving antibiotics, which corresponded to 54 (4%) of the study patients. The antibiotics most commonly associated with CDI were third-generation cephalosporins (present in 52% of regimens preceding CDI), cefepime (present in 48% of regimens preceding CDI), and fluoroquinolones (present in 35% of regimens preceding CDI). Finally, 314 (97%) of the 324 ADEs were considered significant by the investigators, who defined this as resulting in a new hospitalization (n = 10), prolonged hospitalization (n = 77), additional office or emergency department visits (n = 29), and additional testing (n = 198). No deaths occurred as a result of an ADE.

■ COMMENTARY

The most important and alarming findings in the study by Tamma et al were that 27% of patients admitted to the medical service at Johns Hopkins Hospital received an antibiotic for at least 24 hours and 20% of them developed an antibiotic-associated ADE. While the specific ADEs were not novel and have been well described (e.g., nephrotoxicity from aminoglycosides and vancomycin), what is interesting is that the study provides quantitative data that can be used to estimate the risk of ADEs from antibiotics. That 19% of the prescribed antibiotic regimens were not necessary and were associated with a significant number of ADEs underscores the need for vigilant antibiotic stewardship. One of the key roles for antibiotic stewardship programs must be to educate all healthcare providers that antibiotics carry significant risk for ADEs. The same holds true when physicians discuss antibiotics with patients, especially when the decision has been made to stop or withhold antibiotics when they are not indicated.

There were a few limitations to the study. First, the patients had been referred to a large tertiary academic medical center and therefore tended to be sicker and have more underlying

comorbidities than patients at other institutions. This likely made them more susceptible to antibiotic ADEs. Second, the hospital had an antibiotic stewardship program that was active during the study period, which probably caused a reduction in antibiotic-associated ADEs. Thus, the incidence of ADEs in institutions without an antibiotic stewardship program might be higher than the 20% rate reported by Tamma et al. Finally, accurate estimates of some infrequently prescribed antibiotics (e.g., tigecycline, ceftaroline, penicillin) could not be calculated.

Antibiotic-associated ADEs are common and have significant consequences, including higher healthcare costs, longer length of stay, and harmful toxicities. Therefore, using antibiotics judiciously must be an essential goal for all conscientious physicians. The prophetic advice of Hippocrates to "do no harm" remains as relevant today as it was in 400 B.C. ■

ABSTRACT & COMMENTARY

Mice, Mutations, and Microcephaly: The Evolving Pathogenesis of Congenital Zika Syndrome

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Approximately five years ago, a single gene mutation altered Zika virus, making it able to target neuronal progenitor cells and cause what we now know as congenital Zika syndrome with microcephaly and ocular abnormalities.

SOURCE: Yuan L, Huang XY, Liu ZY, et al. A single mutation in the prM protein of the Zika virus contributes to fetal microcephaly. *Science* 10.1126/science.aam7120. [Epub ahead of print.]

For 60 years since its discovery in a Ugandan forest, Zika virus seemed "just" to cause infrequent mild infections. During outbreaks on Pacific islands during the past decade, congenital brain malformations of offspring of women infected during pregnancy became prevalent. This led to a public health emergency as the virus spread to the Americas.

There are two strains of Zika virus circulating: the Asian strain in the Pacific and Americas and the African strain elsewhere. The Zika virus includes genomic RNA that encodes for both non-structural and structural proteins, including the prM structural protein.

Yuan and colleagues wondered why a relatively quiescent virus suddenly emerged during recent years as a cause of severe brain malformations. Thus, they undertook experiments involving cultured cells and living mice.

Intracerebral injection of contemporary (from 2015 and 2016) strains of Zika virus into newborn mice was associated with motor weakness, hind limb paralysis, and 100% mortality. Similar injection of a 2010 Zika strain was associated with only 17% mortality. Thus, it seems that currently circulating Zika strains are more virulent in the central nervous system than were strains circulating seven years ago.

The researchers then employed a mouse embryonic microcephaly model. They injected the virus into fetal mouse brains at a point in gestation corresponding to what would be the second trimester of a human pregnancy. The 2016 Zika virus strain led to cortical thinning and marked microcephaly; the 2010 Zika strain was associated with notably less severe findings. Each virus strain targeted neuronal progenitor cells, but the 2016 strain showed significantly enhanced replication in the brain as compared to the 2010 strain.

In a related experiment using cultured mouse neuronal progenitor cells, the 2016 strain caused more apoptosis with more loss of both mature and immature brain cells than did the 2010 strain. The proliferation and distribution of neuronal progenitor cells also was more greatly reduced by the 2016 strain than by the 2010 strain. Thus, the 2016 strain was shown to be more virulent to the mouse brain

and to cause more significant microcephaly than did the older 2010 strain.

Yuan and colleagues then sought to identify genetic determinants of varying virulence. Several amino acid substitutions were identified in contemporary strains as compared to older ancestral strains. Specific genetic changes were determined to have occurred at different time points and then to have been maintained in the circulating virus. One mutation and resultant amino acid substitution in particular (S139N) was associated with the most neuronal virulence. And, genetically manipulating a reverse S139N change in an otherwise unaltered 2016 virus reduced the mortality of infection in neonatal mice. With the amino acid substitution, there was enhanced viral replication and increased cell death compared to infection with virus lacking that substitution.

[Thus, it seems that currently circulating Zika strains are more virulent in the central nervous system than were strains circulating seven years ago.]

The investigators then studied the impact of the altered virus (with S139N substitution) in the embryonic microcephaly model. Infection with the mutant virus was associated with more severe microcephaly, more cortical thinning, more robust infection of neuronal progenitor cells, and more cell death in the cortical plate.

Thus, a single mutation could cause a specific amino acid substitution (S139N) in the Zika virus. This mutation first emerged in early 2013 and has persisted since. The cell data, mouse results, and clinical experience all are consistent in showing that this newly evolved Zika strain is associated with aggressive and destructive pathology in developing central nervous systems (and, it seems from clinical experience, with changes leading to Guillain-Barré syndrome). Studies in related dengue viruses suggest that this specific amino acid substitution is part of the prM protein that affects the timing of fusion of viral particles to infected cells.

■ COMMENTARY

Yuan and colleagues in China seem to have completed a circle of understanding of Zika infections. Clinical observations were consistent with a change in manifestations of Zika infection with both more virulent infections and more congenital brain malformations in recent years. In cellular and animal studies, the researchers showed virus-specific changes over time that correlate directly with clinical observations. And they identified a mutant gene and its altered protein, showing that the mutation was linked with neuropathology, that the absence of mutation was associated with less neuronal pathology, and that the protein plausibly is associated with the resulting pathologic changes. This translational science has linked the cycle from epidemiology to clinical presentations to genetics and to proteomics, and it has prompted a helpful understanding of the history of Zika infection.

The clinical characterization of congenital Zika syndrome is progressing. Although devastating when it occurs, microcephaly is identified only in a small minority of offspring of Zika-infected women.[1] In addition, there are reports of twin pregnancies in which only one of the twins develops microcephaly.[2] Clearly, there is more to learn about the pathogenesis of congenital infection with Zika virus.

Recently, the ocular findings of congenital Zika infection were characterized in embryonically infected humans.[3] Zika antigen was found in iris, retina, choroid, and optic nerve tissue. The eyes manifested pupillary membranes with altered anterior chamber angles, thinning of retinal pigment epithelium, and choroidal inflammation. One can easily speculate that the affinity of current Zika strains for neuronal progenitor cells is what made the virus so harmful to developing retinal and optic nerve cells. ■

REFERENCES

1. Coelho AVC, Crovella S. Microcephaly prevalence in infants born to Zika virus-infected women: A systematic review and meta-analysis. *Int J Mol Sci* 2017;18:pii E1714.
2. Linden VV, Linden HV, Leal MC, et al. Discordant clinical outcomes of congenital ZIka virus infection in twin pregnancies. *Arg Neuropsiquiatr* 2017;75:381-386.
3. Fernandez MP, Parra Saad E, Ospina Martinez M, et al. Ocular histopathologic features of congenital Zika syndrome. *JAMA Ophthalmol* doi:10.1001/jamaophthalmol.2017.3595. [Epub ahead of print.]

ABSTRACT & COMMENTARY

Immunohistochemistry and Diagnosis of Viral Diseases

By Dean L. Winslow, MD

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

SYNOPSIS: Researchers reviewed five years of cases at an academic medical center's pathology department for the use of immunohistochemistry to detect CMV, HSV-1, HSV-2, varicella zoster virus, adenovirus, or polyomavirus. Of 957 cases, 134 were positive. Viral cytopathic effect (CPE) was present on hematoxylin and eosin staining in 75% of the IHC+ cases. No changes in clinical care occurred in any of the IHC+ cases in which viral CPE was absent.

SOURCE: Solomon IH, Hornick JL, Laga AC. Immunohistochemistry is rarely justified for the diagnosis of viral infections. *Am J Clin Pathol* 2017;147:96-104.

Researchers studied 1,636 viral immunohistochemistry (IHC) stains ordered on 1,099 specimens from 957 cases over a five-year period at an academic center. Three pathologists who were blinded to the results of IHC reviewed the corresponding hematoxylin and eosin (H&E) stained slides. From all specimens, a total of 134 of 1,636 (8.2%) were positive by IHC. Specimens lacking definitive cytomegalovirus (CMV) viral cytopathic effect (CPE) on H&E included 15 (31%) of 49 gastrointestinal specimens, one placenta specimen, two lung specimens, and one buccal mucosal specimen. HSV-1/HSV-2 and varicella zoster virus CPE-negative specimens were seen in three cervical/vaginal and three central nervous system specimens. No cases of adenovirus IHC+ sections were found, which also lacked viral CPE on H&E. Five of 22 (23%) kidney and bladder cases that were IHC+ for polyomavirus lacked distinctive viral CPE. A representative review of 36 cases reported as negative for viral CPE with or without +IHC were confirmed as negative. All cases reported as showing viral CPE were confirmed as positive. Focusing on IHC+/H&E- discrepant cases of CMV infection, all had only rare or single IHC+ cells observed. This discrepancy resulted in either no treatment or continued treatment in a patient with known established CMV infection.

■ COMMENTARY

Immunohistochemistry commonly is requested on biopsy specimens obtained from patients who are suspected of having viral infection. While occasionally one sees specimens that are positive by IHC but negative for CPE, this is almost always in cases in which only single or rare IHC+ cells are seen. In addition, in this case series, of the 33 cases from all of the viral infections studied in which IHC was positive without definitive CPE, none resulted in significant change in clinical care.

This paper was interesting because I've now encountered several gastroenterologists who aggressively look for concomitant CMV infection in patients with inflammatory bowel disease flares and insist on treating for CMV either before or while giving corticosteroids for the inflammatory bowel disease flare. The study typically cited to justify this practice showed that five of eight patients with even isolated IHC+ cells exhibited worsening symptoms, which seemed to improve with antiviral therapy.[1] However, none of the cases in which CMV IHC was positive and viral CPE was negative resulted in a change of treatment. Interestingly, only two of eight patients in the case series had inflammatory bowel disease. One of these patients seemed to improve on valganciclovir, and the other patient with Crohn's colitis improved without receiving antivirals. Clearly, using antivirals to treat CMV in the setting of inflammatory bowel disease flares is something that should be subjected to a randomized, controlled trial.

In summary, it seems that it is rarely helpful to perform IHC for viral pathogens on biopsy specimens in the absence of viral CPE on H&E examination. ■

REFERENCE

1. Yan Z, Wang L, Dennis J, et al. Clinical significance of isolated cytomegalovirus-infected gastrointestinal cells. *Int J Surg Pathol* 2014;22:492-498.

ABSTRACT & COMMENTARY

Treatment of Pulmonary *Mycobacterium avium* Infection: Failure Is Common

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Current treatment regimens for pulmonary *Mycobacterium avium* infection leave a great deal to be desired.

SOURCES: Kwak N, Park J, Kim E, et al. Treatment outcomes of *Mycobacterium avium* complex lung disease: A systematic review and meta-analysis. *Clin Infect Dis* 2017 Jun 3. doi: 10.1093/cid/cix517. [Epub ahead of print.]

Pan SW, Shu CC, Feng JY, et al. Microbiological persistence in patients with *Mycobacterium avium* complex lung disease: The predictors and the impact on radiographic progression. *Clin Infect Dis* 2017;65:927-934.

The studies reviewed here confirm that currently used regimens for the treatment of patients with pulmonary infection due to organisms of the *Mycobacterium avium* complex (MAC) are frequently unsuccessful.

Kwak and colleagues at the Seoul National University College of Medicine conducted a meta-analysis of 16 studies, including 1,462 patients. All were observational cohort studies, six of which were prospective, two with randomization (albeit lacking blinding of outcome assessment), and eight were retrospective. The median duration of treatment in the studies ranged from 12.0 to 28.4 months.

Treatment success, defined as sustained sputum culture negativity for 12 months while on treatment, was achieved in 60.0% (95% confidence interval [CI], 55.1-64.8%). Of note is that the success rate of macrolide recipients was significantly lower among patients in the two randomized trials (43.2%; 95% CI, 35.6-50.8%) compared to those in the other observational studies (61.9%; 95% CI, 59.3-73.1%). Seven studies reported results in patients who did not receive a macrolide as part of their therapy, and their treatment success was 53.6% (95% CI, 38.0-69.3%). The most frequently reported adverse event was hearing loss.

Pan et al retrospectively reviewed 126 patients with pulmonary MAC infection, 111 of whom received no chemotherapy for their disease during at least the initial year of their care. Of the 126 patients, 60% failed to convert their sputum at 12 months. Failure of conversion was associated with radiographic progression, which occurred in 54%. Those who did convert had a significantly lower risk of radiographic progression. Both lack of conversion and radiographic progression were worse in the 15 patients who did not receive treatment. Low body mass index (BMI), nodular bronchiectatic radiographic pattern, and markedly positive smears were independent predictors of microbiological persistence.

■ COMMENTARY

The recommended initial treatment of MAC infection of the lungs consists of a multidrug regimen with clarithromycin or azithromycin (which I prefer because of its tolerability and more limited drug-drug interactions), together with ethambutol and a rifamycin. For mild to moderate bronchiectatic disease, the regimen (with appropriate dosing) can be given thrice weekly, while for fibrocavitary or severe disease, it should be taken daily. Some clinicians recommend that the initial portion of the therapeutic course include streptomycin or amikacin, but this, of course, complicates the regimen because of the need for parenteral administration and risk of toxicity. Furthermore, the benefit of this approach may be questioned. While susceptibility testing is performed routinely, the only one with results that are predictive of therapeutic outcome is clarithromycin (which also predicts azithromycin susceptibility).

Whatever the treatment, the results are frequently less than stellar. In a metanalysis, Pasipanodya et al found that the pooled incidence ratio for sustained sputum conversion for regimens that included a macrolide antibiotic was 0.54 (95% CI, 0.45-0.63), while it was 0.38 (0.25-0.52) for a macrolide-free regimen.[1] The mean rate of sputum conversion associated with

prolongation of therapy beyond 12 months was only 22% (95% CI, 1-44%).

Among the conclusions that can be reached from the results of these and other studies regarding pulmonary MAC disease is that treatment, especially in the absence of administration of a macrolide, frequently fails to eradicate the organism. Furthermore, persistence of MAC in respiratory secretions, with or without treatment, is associated with radiographic progression.

While one could consider current regimens for the treatment of pulmonary MAC to be frequently, at best, minimally ineffective, lack of treatment appears to be worse. Thus, Park and colleagues examined the radiographic changes by computerized tomography of 40 untreated patients, with the nodular bronchiectatic form of MAC pulmonary infection over a mean of 6.2 years.[2] Most were minimally symptomatic. Significant worsening occurred in 39 (97.5%) of the patients. ■

REFERENCES

1. Pasipanodya JG, Ogbonna D, Deshpande D, et al. Meta-analyses and the evidence base for microbial outcomes in the treatment of pulmonary *Mycobacterium avium*-intracellulare complex disease. *J Antimicrob Chemother* 2017;72(suppl_2):i3-i19.
2. Park TY, Chong S, Jung JW, et al. Natural course of the nodular bronchiectatic form of *Mycobacterium avium* complex lung disease: Long-term radiologic change without treatment. *PLoS One* 2017;12:e0185774.

ABSTRACT & COMMENTARY

How Many Personnel Are Required for Antimicrobial Stewardship? More Than You Have at Your Hospital

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: A work group in the Veterans Administration determined that the necessary staffing of antimicrobial stewardship programs dealing with inpatients (including long-term care) is 1.0 clinical pharmacy specialist with infectious disease knowledge and 0.25 physician (preferably trained in infectious disease) per 100 occupied beds. Needs for outpatient stewardship, which is now mandated, were not included in the assessment.

SOURCE: Echevarria K, Groppi J, Kelly AA, et al. Development and application of an objective staffing calculator for antimicrobial stewardship programs in the Veterans Health Administration. *Am J Health Syst Pharm* 2017; doi: 10.2146/ajhp160825. [Epub ahead of print.]

Hospitals in the United States now are required to have antimicrobial stewardship programs (ASP). The CDC has listed extensive activities that such programs should implement. These activities require sufficient personnel to fulfill them in an appropriate manner. But the question remains: How many personnel are required to fulfill the activities to assure the patient safety improvements that accrue from their full implementation? A formal process within the Veterans Administration, which like the rest of the U.S. healthcare system requires stewardship programs, was developed and executed with the aim of determining the number of personnel required for this purpose.

To this end, a Tools and Resources Work Group was assigned the task of developing and validating a calculator capable of estimating, in full-time equivalents (FTE), the necessary number of clinical pharmacy specialists and physicians. The work group collaborated with the Clinical Pharmacy Practice Office to develop the calculator. They developed a list of stewardship activities for hospitalized or long-term care patients related to both patient care and management functions and assigned a time value to each activity.

For validation, 12 facilities with average daily census ranging from 72 to 418 completed the staffing calculator over one five-day work week. Six of the sites were large, complex facilities, while the other six were of moderate or low complexity. None of the facilities had more than

1.0 pharmacist at the time of evaluation.

The median need based on the calculator and the observed activities was 1.1 pharmacist FTE per 100 occupied beds (IQR, 1.0-1.47). Patient care activities accounted for 70% of the FTE requirement, while program management activities accounted for 30%. The majority of the time spent on patient care activities involved audit and feedback.

The final recommendations were that to provide a strong ASP, an FTE investment was needed of 1.0 pharmacist, ideally with ASP or infectious disease experience, per 100 occupied beds. They also recommended 0.25 physician per 100 occupied beds, ideally with a physician with infectious disease training.

■ COMMENTARY

Antimicrobial resistance has been acknowledged as a global public health crisis, analogous in a number of respects to the problem of climate change. In the United States, critical access and acute care hospitals are required to address this issue via the vehicle of antimicrobial stewardship programs. Unfortunately, many hospital administrators primarily look upon such programs as a financial burden and fail to provide the necessary support. Determining the number of needed personnel by benchmarking against other institutions is not of value since it only indicates the inadequacies of staffing at many or most hospitals, not the number to robustly fulfill the requirements of optimizing patient care while working to slow the emergence of antimicrobial resistance and, thus, assuring safety and sustainability.

The approach taken by this working group within the VA system has determined that proper staffing of a hospital ASP requires one FTE pharmacist with ID knowledge for every 100 occupied beds and 0.25 physician, preferably ID trained, per 100 occupied beds. It should be noted that half the hospitals included in this analysis were of only moderate to low complexity. It also should be noted that the analysis did not include stewardship in outpatient facilities, something which now is required in the rest of the U.S. healthcare system for all hospital-affiliated (as determined by tax identification number) outpatient settings. Now is the time for funding to catch up with the critical need. ■

ABSTRACT & COMMENTARY

Chikungunya Locally Acquired in Italy and France

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: An outbreak of autochthonously acquired chikungunya infection has affected 298 individuals as of early October 2017, while a small outbreak also has occurred in southeastern France.

SOURCE: European Centre for Disease Prevention and Control. Clusters of autochthonous chikungunya cases in Italy. First Update. 9 October 2017. Available at: https://ecdc.europa.eu/sites/portal/files/documents/RRA-chikungunya-Italy-update-9-Oct-2017.pdf. Accessed Oct. 13, 2017.

On Sept. 7, Italian public health authorities reported the identification of three locally acquired cases of chikungunya virus infection in Anzio, a seaside town approximately 60 km south of Rome and the site of a famous World War II battle. A week later, six cases from within Rome itself were reported. Cases continued to occur in nearby areas as well as from the more distant Calabria region, the "toe of the Italian boot." As of Oct. 4, the total number of reported cases was 298. Further investigation suggested that autochthonous transmission actually had started in June and perhaps earlier.

Meanwhile, on Aug. 11, France reported an outbreak of chikungunya in the commune of Cannet-des-Maures, in the Provence-Alpes-Cote d'Azur region in the southeastern part of the country. Two clusters of additional cases were reported, reaching a total of 17 cases as of Oct. 3.

The viruses causing infection in Italy and France are distinct. The virus detected in Anzio belongs to the East/Central/South African (ECSA) lineage with homology to strains recovered in India and Pakistan in 2016. Of note is that it does not carry the E1-A226V mutation previously reported to facilitate transmission by *Aedes albopictus*, the tiger mosquito, which was introduced in Italy prior to the only previous outbreak of autochthonous cases in 2007, with the infection first introduced by a traveler from India. That outbreak accounted for 205 cases and one death, all in the province of Ravenna. The French virus, in contrast, belongs to a sublineage of ECSA that is known to include virus from central Africa and does contain the E1-A226V mutation. France experienced small outbreaks of locally acquired cases in 2010 and 2014, with two and 11 cases, respectively.

■ COMMENTARY

Aedes albopictus maintains activity throughout the year in tropical and subtropical regions, peaking in summer and autumn. Furthermore, there is evidence that cold adaptation of this aggressive mosquito is occurring in central Italy. It breeds in both natural and man-made collections of water. An outdoor mosquito (although apparently also adapting to indoor environments), it bites throughout the day, with peak activity in the early morning and late afternoon. The E1-A226V envelope mutation detected in the virus in France increases the transmissibility of the virus by *Aedes albopictus*. One can hope that its absence in the virus causing the current infections in Italy will limit transmissibility, ameliorating the outbreak. The major vector of chikungunya virus in the world is not *Aedes albopictus*, but *Aedes aegypti*, which is present in Europe, albeit limited to date to the Black Sea region and Madeira. Both of these mosquitoes are present in areas of the United States, and local transmission of chikungunya has occurred in Florida, as well as in Puerto Rico and the U.S. Virgin Islands. As many have suggested, many people in the United States as well as residents and travelers to Europe may encounter this virus.

Just to add to the woes in Italy, the CDC just reported that four cases of locally acquired malaria due to *Plasmodium falciparum* have occurred in migrant workers in Ginosa (which is in the "instep" of the Italian boot).[1] The isolated nature of the outbreak, however, would appear to represent little threat outside that community. ■

REFERENCE

1. Centers for Disease Control and Prevention. Malaria outbreak in Ginosa, Italy. Available at: https://www.cdc.gov/malaria/new_info/2017/Italy_2017.html. Accessed Oct. 13, 2017.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Travelers Unaware of the Need for Pre-travel Vaccinations

SOURCE: Hyle EP, Rao SR, Jentes ES, et al. Missed opportunities for measles, mumps, rubella vaccination among departing U.S. adult travelers receiving pre-travel health consultations. *Ann Intern Med* 2017;167: 77-84.

Outbreaks of measles continue to occur in the United States, mostly because of imported cases. More than half of these occur as the result of inadequately vaccinated returning U.S. travelers who acquire measles infection abroad. And the problem is not limited to those returning to the United States. This column recently commented that, on any given day, only 86% of persons at Disneyland have received MMR vaccine — far below the threshold for herd protection in the event of an outbreak. The recent measles outbreak at Disneyland in Anaheim, CA, in 2014-2015 resulted in 125 measles infections, 110 of which occurred in Californians. Nearly half (45%) were unvaccinated, most for non-medical exemption.

These authors surveyed 54,100 departing U.S. adult travelers for measles immunity and eligibility for MMR between 2009 and 2014. Travelers were evaluated at one of 24 sites with Global TravEpiNet (GTEN), which is a consortium of travel clinics, 14 of which are based at academic centers and 10 at primary care practices, public health facilities, or pharmacies. Travelers born before 1957 were considered immune and excluded from analysis (n = 13,290 adults). Of those remaining, the median age was 33 years (range, 26 to 44 years). The most common travel destinations included Africa (35%) or Central or South America (28%), and the median duration of planned travel was two weeks.

Most travelers born after 1957 were deemed to be measles-immune (84%), based on a history of receiving two doses of measles vaccine (73%), serologic testing (10%), and/or a history of measles infection (3%), and/or provider judgment (18%). Only a small number (0.3%) were ineligible for vaccination for medical reasons. The remaining 16% were eligible for MMR.

MMR was offered to anyone eligible for vaccination; 53% did not receive MMR during their visit. The most common reason was patient refusal (48%). In 28% of cases, vaccination was not provided based on provider decision — 94% of the time because the provider thought the vaccine was unnecessary and 6% of the time because of insufficient time before travel. "Health system barriers" were listed as the reason for non-vaccination in 24% of cases, largely due to referral to an outside provider.

For the 1,698 travelers who refused the vaccine, three-fourths indicated they were "not concerned about illness," 20% were concerned about vaccine safety, and a small percentage (6%) were concerned about vaccine cost.

Many travelers remain unaware of the risks of illness abroad and the need for good travel advice and immunization. Too often, I've argued with patients who weigh the imagined risk of illness against the inconvenience and expense of vaccination, and lost the argument. This survey also demonstrates that at least one-fourth of missed MMR vaccine was the result of provider decision, suggesting that travel clinic providers would benefit from additional education about the benefits and need for MMR vaccination in eligible travelers.

Fecal Microbiota Testing

SOURCES: Saey TH. Here's the poop on getting your gut microbiome analyzed. *Science News*, June 17, 2014; Rabin RC. Can I test the health of my gut microbiota? *New York Times*, July 7, 2017.

Just Google "gut microbiota testing" and see the array of possible "gut report" kits out there for purchase. Send in a sample and pay a fee — usually $100 or more — and you will receive a profile of your gut microbiome, with lots of detailed information and colorful graphics on the dominant species populating your gut. Your fecal microbiota will be compared to the "normal" profiles of other Americans or people in other parts of the world, vegetarians, or those who follow different diets. The problem is that little is known about the typical genomic profile of the gut or what is "normal." There's obviously tremendous diversity, even in healthy people. Researchers have determined that persons with diabetes or inflammatory bowel disease — or people who have received recent antibacterial therapy — may have very different microbiota profiles. Unfortunately, no one really knows what these differences mean in terms of your overall health.

Different methodologies also may offer differing results. Saey submitted stool samples to two companies for testing and received wildly different results.

Increasingly, we are seeing outfits that offer molecular testing of blood, stool, or other specimens, but with little credibility or science behind it. And yet, patients looking for an explanation for their symptoms or an illness will latch on to anything. A young Stanford graduate student who felt "fuzzy-headed" for more than a year recently spent $1,000 on specialized "molecular" testing of his blood and stool, only to be disappointed when I explained the results were basically uninterpretable.

Newer Guidelines for Influenza Testing This Season

SOURCES: California Department of Public Health. Testing and treatment for patients hospitalized with suspected influenza. Oct. 2, 2017; Merckx J, Wali R, Schiller I, et al. Diagnostic accuracy of novel and traditional rapid tests for influenza infection compared with reverse transcriptase polymerase chain reaction: A systematic review and meta-analysis. *Ann Intern Med* 2017;167:394-409.

As we approach flu season, I like to remind providers that rapid influenza diagnostic tests are imperfect — and before ordering a rapid flu test,

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consider the likelihood of a positive result. Do they plan to treat the patient or the test result?

Merckx and associates performed a meta-analysis of more than 162 diagnostic studies, comparing the diagnostic accuracy and sensitivity of rapid influenza diagnostic tests (RIDTs) with immunoassays (DIAs) and nucleic acid amplification tests (NAATs) in children and adults with influenza-like illness (ILI). The overall results confirm what we already know: RIDTs are helpful in providing a rapid result for many patients, but false-negative results are common. Pooled sensitivities for detecting Influenza A using RIDTs were 54%, compared with 80% for DIAs and 91.6% for NAATs. Pooled sensitivities for detecting Influenza B were similar: Using RIDTs they were 53%, compared with 77% for DIAs and 95% for NAATs. Pooled sensitivities generally were higher in pediatric patients compared with adults.

Keep in mind that false negatives are common when flu is more frequent in your community — and false positives are more common when flu is less frequent.

The California Department of Public Health and Centers for Disease Control and Prevention have recommended that, regardless of the results of prior rapid influenza testing, empiric therapy with a neuraminidase inhibitor should be administered promptly to patients hospitalized with ILI or suspected influenza, and not necessarily discontinued simply because an RIDT result may be negative. NAAT testing or RT-PCR testing should be performed in all suspect cases, and many hospitals have an RT-PCR panel for respiratory virus, which can be helpful. Although treatment has shown the greatest benefit when initiated within 48 hours of onset of illness, evidence supports the administration of antiviral therapy when begun later than 48 hours in those hospitalized with severe flu. ■

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CME QUESTIONS

1. Neurologic manifestations of congenital Zika infection are due to:

a. direct influence of the virus on neuronal progenitor cells.

b. lymphocyte-mediated inflammatory changes in the meninges.

c. accelerated replication of glial cells.

d. altered cerebral blood flow in infected fetuses.

2. Which of the following is the best single answer regarding the findings of Tamma and colleagues about adverse effects of antibiotic therapy at Johns Hopkins Hospital?

a. Of those who received an antibiotic, 20% experienced at least one adverse event.

b. There was no clinical indication for antibiotic therapy in 19% of those given an antibiotic.

c. Cephalosporins were the class of antibiotics most frequently associated with the development of *Clostridium difficile* infection.

d. All of the above are correct.

3. Which of the following is correct?

a. The major vector of chikungunya virus infection in the recent outbreaks in Italy and France is *Aedes aegypti*.

b. The 2017 outbreaks of chikungunya infection in Italy and France represent the first ever autochthonously acquired cases of this disease in Europe.

c. The mosquito that has been the vector of chikungunya in Italy and France bites throughout the day, peaking in activity in early morning and late afternoon.

d. Chikungunya virus cannot be transmitted by the tiger mosquito.

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.