ID Week 2016
Bugs Without Borders: View From the Americas

Bacterial and viral pathogens travel the globe passport free whereas human travel is monitored. This perspective from the Americas was provided in a symposium at the annual meeting of the Infectious Diseases Society of America in October 2016 in New Orleans, Louisiana.

The appearance and epidemic spread of the Zika and chikungunya viruses in the Americas, in general, and Venezuela, in particular, should take health authorities by surprise. Both epidemics did occur for good reasons, both epidemics did come as no surprise, according to Jaime Torres, MD, Tropical Medicine Institute, Universidad Central de Venezuela, Caracas. Both of the aforementioned viruses are spread by arthropods, which roam widely. However, for good reasons, both epidemics did take health authorities by surprise.

“This was the first simultaneous occurrence of 3 large viral epidemics transmitted by the same vector. For the first time, a mosquito-borne virus infection has been shown to cause congenital malformations. Zika was the first arbovirus to be sexually transmitted,” said Dr. Torres in his session.

HEALTHCARE-ASSOCIATED INFECTIONS
The Great Debate: Polymyxin B Versus Polymyxin E

By Aileen Ahiskali, PharmD and Krista Gens, PharmD, BCPS-AQ-ID

Analysis of data from a measles epidemic that occurred in California between 1988 and 1990 has revealed the greater-than-anticipated occurrence of subacute sclerosing panencephalitis (SSPE). Analysis of the 17 cases of SSPE suggest the rate could be as high as one in 600, depending on the age of the patients at the time of infection.

The finding, which once again emphasizes the importance of herd immunity, was presented by Kristen Wenddorf, MD, MS, Immunization Branch, (continued on page 22)

Fatal Measles Complication More Frequent Than Previously Thought

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SHEA 2016 Up-and-Coming Prevention Methods for Clostridium difficile

During the 2016 Society for Healthcare Epidemiology of America (SHEA) Spring 2016 conference, which was held in Atlanta, Georgia, from May 18-21, 2016, Con-tagon interviewed Robin Jump, MD, PhD, assistant professor in the Department of Medicine at Case Western Reserve University, regarding Clostridium difficile in the hospital setting and up-and-coming prevention methods.

SHEA 2016 Up-and-Coming Prevention Methods for Clostridium difficile (continued on page 23)

ASM Microbe 2016 New Technologies for Detecting Antimicrobial Susceptibility and Resistance

During the American Society for Microbiology (ASM) Microbe 2016 conference held in Boston from June 16-20, 2016, Contagion interviewed Romney Humphries, PhD, DABMM, section chief of clinical microbiology at the University of California at Los Angeles (UCLA), regarding antimicrobial susceptibility and resistance and new technologies in the field. ASM Microbe 2016 New Technologies for Detecting Antimicrobial Susceptibility and Resistance (continued on page 24)

2016 CDC STD Prevention Conference

CDC Presents Novel Strategies to Improve Screening for STIs

Researchers are taking new approaches to sexually transmitted infection (STI) screening, and lead authors of several studies described their innovations in a mini-plenary on September 21 at the Centers for Disease Control and Prevention’s (CDC) 2016 Sexually Transmitted Disease (STD) Prevention Conference in Atlanta, Georgia.

Tiffany Deihl, MD, described an STD tracking system she and her colleagues at Magee-Womens Hospital in Pittsburgh, Pennsylvania, developed and tested. “STD Tracker,” a database of all nonpregnant women who tested positive for chlamydia or gonorrhea in the clinic, enables gynecology clinic nursing staff to schedule or reschedule follow-up visits for repeat testing. Dr. Deihl and her colleagues reviewed electronic charts to compare the retesting rates before and after they began using the tracker.

2016 CDC STD Prevention Conference CDC Presents Novel Strategies to Improve Screening for STIs (continued on page 21)

ASTMH 2016 West Nile Virus Infections May Prove Deadlier Than Previously Thought

At the American Society of Tropical Medicine & Hygiene (ASTMH) Conference on November 14, 2016, scientists from Baylor College of Medicine and Texas Children’s Hospital presented research indicating that infection with West Nile virus may be linked with a shorter lifespan.

Researchers continue to learn more about West Nile virus and its distressing effects. Principal author on the study, Kristy O. Murray, DVM, PhD, was quoted in a press release as saying, “While we understand the current

ASTMH 2016 West Nile Virus Infections May Prove Deadlier Than Previously Thought (continued on page 25)

Previously Thought

Previously Thought (continued on page 7)
Now is an exciting time to be a business leader in the healthcare. The new year and new administration in the White House have brought the promise of major changes—especially in the healthcare field. 

Contagion™ will be at the forefront of covering changes made by the Trump administration that will impact healthcare, including legislation and executive orders with an indirect impact—such as the recent ban on refugees entering the United States. Although this executive order made no mention of decreased collaboration with global healthcare institutions, major infectious disease societies (eg, American Society of Tropical Medicine and Hygiene, Infectious Diseases Society of America) made public statements that the ban will have a negative effect on public health and that it may, in fact, put the US at greater risk for epidemics and pandemics of infectious diseases. The statements cited that infectious diseases know no borders and the majority of those who travel in and out of the country are not refugees. Perhaps most important is the fear that these societies will lose ongoing surveillance of all diseases and their alliance with the global healthcare community to learn more about how to detect, treat, and prevent these infections in the first place.

In this issue of Contagion™, we focus once again on major areas of infectious disease. On page 5, we highlight a recent innovation by a team of Duke University researchers that enables life-saving postexposure prophylaxis to be administered to infants of HIV-infected mothers in developing countries. Previous attempts to get these drugs to infants in these remote locations resulted in the degradation of the life-saving medications; however, the Duke researchers were able to engineer a mechanism by which the drug can be administered without degradation: through a heat-sealed pouch the size of a ketchup packet.

We also feature a review of the sometimes overlooked role of the pharmacist in HIV stewardship—citing important contributions such as ensuring that patients are taking a complete and appropriate regimen; recommending alternative therapy or dose or formulation adjustments, if necessary; mitigating drug-drug interactions; and modifying drug schedules to optimize absorption (page 7). In HCV/Hepatitis news, we explore research on the use of anticoagulants as a prophylactic measure in patients with advanced liver disease; at present, more research is needed before any clinical guidelines can make this recommendation (page 10). And, finally, the identification of an emerging infectious disease, Powassan virus, is discussed in a Q&A with Holly Frost, MD, a pediatrics physician scientist at the Marshfield Clinic Minocqua Center in Minocqua, Wisconsin (page 19).

As we head into this tumultuous time in healthcare, we hope you will look to us as your guide for breaking news and updates on disease-specific information designed to improve patient outcomes. Please follow us online at www.contagionlive.com, on social media (Facebook [@ContagionLive], Twitter [@Contagion_Live], and LinkedIn [:@Contagion_Live]), and sign up for one of our newsletters (contagionlive.com/link/2) to stay informed.

Thanks for reading!
Mike Hennessy, Sr
Chairman and CEO
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Respiratory Syncytial Virus Infection
—What it Means for You

By Laurie Saloman, MS

Respiratory syncytial virus (RSV) was first identified more than 60 years ago and is an incredibly common virus in the Pneumoviridae family that hits both the very young and the very old disproportionately. It consists of two major viral groups: A and B, with A being more common. Just about every child gets infected with RSV, according to research by Edward E. Walsh, MD, a professor of infectious disease at the University of Rochester Medical Center in Rochester, New York. Dr. Walsh says 50% to 70% of newborn babies are infected with RSV during their first winter of life, and those who aren’t almost certainly get it by the age of 2 years, after which further infections are common but less severe.

Twenty percent of all babies with RSV are seen at pediatricians’ offices or emergency departments, and 1% to 2% of all babies are hospitalized (about 100,000 per year) because of it. Deaths from RSV are rare in the United States—about 50 to 100 each year—but in developing nations, the annual death rate ranges from 66,000 to 199,000 and infections account for 3 million hospitalizations for children younger than 5 years.

The virus, which tends to hit colder areas of the United States hardest in the winter, can persist for 16 to 22 weeks in the communities in which it circulates, overlapping with the 6- to 8-week influenza epidemics. In warmer areas, RSV may proliferate during rainy periods. Nasal secretions are the primary mode of contagion; as the virus can linger for hours on hands and surfaces, touching contaminated spots is a reliable way to contract it. Thus, children frequently introduce RSV into the home, infecting both parents and younger siblings.

RSV typically incubates for four to six days, after which nasal congestion, mucus discharge, and fever develop, followed by rapid breathing, coughing, and respiratory distress manifesting as chest retractions and wheezing. This is due to bronchiolitis or inflammation of the smallest airway passages in the lungs. Preterm infants may even stop breathing periodically.

The illness may coexist with pneumonia or influenza. It’s not clear exactly how RSV interacts with these other illnesses, but protection against them may make RSV infection less likely. A 2015 study by epidemiologists found an 18% reduction in RSV hospitalizations in the United States when patients received a pneumococcal vaccine. Other factors that may play a role in more serious cases of RSV include cyanotic heart disease; chronic lung disease; and being born before 29 weeks’ gestation, when the lungs are not fully developed. Despite these risk factors, 70% of infants hospitalized for RSV were full-term at birth without any prior health issues.

Treatment for sick infants consists mainly of administering oxygen in cases where oxygen saturation is below 90%; once infected, there is no treatment to lessen the disease’s severity or duration, however. Prevention is the goal, and certain infants may benefit from preemptive prophylactic treatment. Babies born at less than 29 weeks may benefit from injections of palivizumab (Synagis), a monoclonal antibody therapy, during their first winter of life. Similarly, infants born at less than 32 weeks who have chronic lung disease and needed supplemental oxygen after birth and those with aycnotic congenital heart disease may receive the treatment.

RSV can leave children with lasting health effects. Many will continue to wheeze when they develop other viral infections, up until they are about 7 years old. However, certain babies with severe bronchiolitis are at greater risk of developing asthma later in childhood or in young adulthood, as well as experiencing a reduction in peak airway flow should they become cigarette smokers. It’s also possible that severe RSV in infancy is a risk factor for later development of chronic obstructive pulmonary disease.

Microbes and Hosts Fight to Acquire Essential Metals: This Battle May Lead to New Treatments

By Kristi Rosa

Every time a bacterial infection occurs within an individual, microbes and hosts engage in a persistent battle over precious metals, such as iron, with the host struggling to keep these essential metals away from the microbes, which need them for their survival. During these battles, the hosts and the microbes release a number of molecules and proteins. Researchers, including Elizabeth Nolan, PhD, an associate professor of chemistry at MIT, hope that further analysis of this struggle will help to inform the development of new drugs that can be used in the fight against bacterial infections.

In a recent press release, Dr. Nolan explained, “Understanding how our innate immune system works is important for thinking about the development of new ways to treat infectious diseases.”

Essential metals, such as iron, calcium, magnesium, and zinc assist cells in performing a variety of functions, including “cell respiration, catalyzing chemical reactions, signal transduction, and maintaining the structural integrity of proteins and nucleic acids.” In fact, 30% of cell proteins need assistance from the aforementioned metals. Dr. Nolan, head of the Nolan Lab at MIT, created a research program to focus on how microbes and hosts fight for these essential metals. One of her team’s projects specifically looked at siderophores, which are molecules that bacteria use to extract essential metals from hosts. These siderophores, once released into their environment, adhere to the essential metals and bring them back in to bacterial cells.

The team sought a closer look at this extraction process to see if further understanding could inform potential therapeutic avenues; they intervened on the process by using siderophores to instead bring antibiotics into bacterial cells. By doing this, they found they could avoid killing microbe species that are actually beneficial; by adhering antibiotics to specific siderophores, only certain bacterial strains are targeted, and thus, only harmful microbes are eliminated.

This isn’t the only time that Dr. Nolan and her team used Salmonella siderophores to increase their understanding. In another study, the researchers found a new way to “immunize against microbes that invade the gastrointestinal tract” in mice.
Engineers Tackle Growing Threat of Infectious Diseases

By Brian Dunleavy

Scott Adams, creator of the “Dilbert” comic strip, once said: “Normal people believe that if it ain’t broke, don’t fix it. Engineers believe that if it ain’t broke, it doesn’t have enough features yet.” Although Adams cleverly captures the innovative spirit of engineers (he developed “Dilbert” after working with engineers at the Pacific Bell telephone company in the 1980s and 1990s) even he might not believe how some engineers have applied their unique knowledge and skill sets to solve seemingly intractable problems in infectious diseases.

One such group, from the lab of Ankur Singh, PhD, at the Sibley School of Mechanical and Aerospace Engineering at Cornell University, partnered with colleagues from Cornell’s Meinig School of Biomedical Engineering and Weill Cornell Medicine to create what they describe as a 3-D modular immune organoid designed to replicate the anatomical structures found within the lymph nodes and mimic the early stages of immune response. According to the team’s study published in a December 2016 issue of ACS Biomaterials: Science and Engineering, the model can be manipulated to recreate the process of immune cell response and reproduce the function of the lymph nodes in immune cell activation. Another study on aspects of the project was published in December 2016 in the journal Nature Protocols.

In a recent interview with Contagion™, Dr. Singh commented on his team’s research: “There is a massive increase in infectious disease outbreaks, including the recent Ebola and ongoing Zika threats,” he said. “We do not fully understand how the human body responds to these rapidly mutating viruses and evolving pathogens. Conventional benchside research and clinical therapeutic development rely on animal sources, and existing 2-D systems do not represent what’s inside your body, which is a dynamic 3-D space that undergoes remodeling post infection. This is a fundamental advance.”

Dr. Singh and his colleagues note that their 3-D organoid model is designed to foster faster replication of B cells in much higher quantities than existing 2-D models. With the organoid, researchers can modify immune organs following infection to tailor and control how immune cells respond, cell-cell interactions, and other functions. Made from a synthetic polyethylene glycol– or semisynthetic gelatin–based platform, the organoid also provides bench researchers with an efficient method for replicating the microenvironment of the germinal center, the structures within lymphoid tissues that develop following B cell activation, in response to infection. To date, the mechanisms underlying this response have not been fully understood; however, the new organoid, will allow researchers to model processes that they have not been able to recreate in vivo until now because it mimics living tissue.

“This is really a neat designer technology, where you can plug-and-play biological signals,” Dr. Singh said. “Tailored immune organoids will [provide] researchers and clinicians the ability to identify factors that have the potential to rapidly boost immunity. We hope this technology will enable rapid, higher-throughput translation of immunotherapeutics.”

Dr. Singh and his colleagues are not done with this organoid just yet. He told Contagion™ that his team is already working to expand the organoid technology to “address the urgent unmet need in the field of infection and autoimmune diseases, transplant rejection, and cancers.”

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How Old Is HIV? University of Oxford Researchers Say Hundreds of Millions of Years

By Sarah Anwar

University of Oxford researchers’ findings, published in Nature Communications, indicate that viruses from the Retroviridae family, which includes HIV and the human T-cell lymphotropic virus, date back to the Paleozoic Era.

To assess the age of retroviruses, the researchers decided to analyze another type of virus whose evolution is more well-known, the foamy virus (FV). These viruses “are characterized by an extremely stable history of co-speciation with their mammalian hosts, at least since the origin of eutherians,” approximately 100 million years ago, and their evolution is therefore, “described in unprecedented detail.”

As such, the researchers gleaned information on 36 foamy-like endogenous retroviruses (FLERVs), identified from the genomes of salamanders, a frog, lobe-finned fish, a shark, and ray-finned fish. Using this information, the researchers developed a model to measure the time-dependency of the evolution of mammalian FV. The model investigated how the total per-lineage substitutions compared to evolutionary timescales by backtracking the mammalian FV’s lineage.

The researchers concluded, “By assuming that viruses infecting modern-day mammals and their ancient vertebrate ancestors share the same [time-dependent rate-phenomenon] dynamics, and based on posterior distribution of the Bayesian Pol phylogeny, the glace of mammalian FVs and lobe-finned fish FLERVs was estimated to be approximately 263 (95% HPD = 195-342) [million years old],” while the age of the entire clade of FVs/FLERVs was estimated to be approximately 455 (95% HPD = 304-684)” million years old. Earlier speculations had estimated retroviruses, such as HIV, to have evolved much more recently than this.

A letter published in Molecular Biology and Evolution discussed a similar study conducted by researchers from the Czech Academy of Science. In this second study, researchers analyzed lentivirus genes from exotic Malayan flying lemurs and estimated that lentivirus “emergence may date as early as 60 [million years ago].” Now, the University of Oxford researchers estimate that these viruses may be hundreds of millions of years old.

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Behavioral Traits Plague HCV Patients Who Achieve SVR but Still Have Higher Mortality
By Carole Ellis

Despite the fact that an increasingly large portion of those infected with hepatitis C successfully achieves a cure for their infection, a sustained viral response (SVR), this population still deals with increased mortality rates. With achievement of SVR, liver damage ceases, liver function improves, and there is a much lower risk of liver-related complications and death—although SVR status does not guarantee that any existing scarring will heal. Patients, however, will retain the hepatitis C antibody for life.

Given the positive prognosis that comes with SVR, it is surprising that SVR patients in a Scottish study still faced mortality rates 1.9 times more frequent than the general population. The researchers who conducted the study noted that about two-thirds of the “excess deaths” could be attributed to either liver cancer or “modifiable characteristics,” such as heavy alcohol and drug use, suggesting that patients with hepatitis C who have been “cured” of the infection could benefit from continued monitoring from health professionals and a direct address of the lifestyle risk factors that may have led to the infection in the first place.

To analyze mortality, the research team followed 1,824 patients who had attained SVR between 1996 and 2011. All patients began and then terminated a course of interferon-based antiviral therapy between January 1996 and December 2010, and all showed compensated liver disease at the time of treatment completion. This meant that although their livers may have been damaged, they were still functional. Patients also showed no HIV or hepatitis B co-infections. The study began nine months after the antiviral treatment stopped in order to fully verify SVR status.

In the 5.2 years of the study, the predominantly male (67%) population experienced 78 deaths, a relatively high number given the median age of 40.7 years. “The number of deaths that would have been expected in our SVR cohort, given general population mortality rates, was 42,” said the team, noting that “significant elevations in mortality” were observed for death due to primary liver cancer and death due to drug-related causes.

The team pinpointed seven distinct causes of death: primary liver cancer; other liver disease; external causes such as accidents, homicide, and suicide; nonliver cancers; diseases of the circulatory system; and “other.” Of the 78 deaths, 18 were due to drug-related causes and nine were caused by primary liver cancer. In younger patients (those under 50), more than half of the deaths were due to drug-related issues, while older patients (those over 50) were more likely to die from liver cancer.

Although the researchers emphasized that several factors were missing from the study that would provide a complete picture of the issue, they said that they were able to conclude that “health risk behaviors emerged [in the study] as the major modifiable risk factor for mortality in the [SVR] population.” The group recommended a multidisciplinary approach to hepatitis C treatment that not only offers medical treatment, but also addresses lifestyle risk factors. “The SVR time-point may provide a particularly opportune moment to assess what other services and support the patient may be in need of,” they said, adding that the high incidence of liver cancer-related deaths indicates that regular screenings for liver cancer could also improve mortality rates.

“It will be important to repeat this analysis five years hence,” they said, noting that new trends in treatment regimens that include “intensive coaching from clinicians and nursing staff” could positively affect patients’ resolve to make healthier lifestyle decisions after achieving SVR.

New Surgical Mask Designed to Kill Viruses
By Einav Keet

During the severe acute respiratory syndrome (SARS) epidemic in 2003, images of people wearing protective surgical masks became the norm in places that were most affected. Now, a team of researchers has taken on the task of improving these masks so that they can both trap and kill pathogens.

Surgical masks are designed to be worn by healthcare workers over the nose and mouth to provide barrier protection against large respiratory particles and other droplets. They do not filter small particles from the air effectively or prevent these particles from entering around a mask’s edges. Therefore, they not as effective as respirator-style masks at filtering out airborne particles.

In a new study published in Scientific Reports, a team of researchers from the University of Alberta in Edmonton, Canada, released its findings on improvements they made to surgical masks to make them more effective at reducing the risk posed by aerosolized pathogens. “Surgical masks were originally designed to protect the wearer from infectious droplets in clinical settings, but it doesn’t help much to prevent the spread of respiratory diseases, such as SARS or MERS [Middle East respiratory syndrome] or influenza,” explained study author Hyo-Jick Choi, PhD.

Dr. Choi and his team developed a universal, reusable virus deactivation system—a surgical mask with a sodium chloride salt coating along its main fibrous filtration unit. They explained that the salt coating on the fiber surface dissolves once exposed to aerosolized pathogens and recrystallizes during drying, destroying the pathogens. In their study, the researches exposed their mask to influenza virus and found that their design, offering tightly sealed sides, showed remarkably higher filtration efficiency than a conventional mask. They observed that viruses captured on the salt-coated masks showed a more rapid infectivity loss than on untreated mask fibers. Furthermore, the masks were able to deactivate influenza viruses of different subtypes.

“Development of a universally applicable, low-cost, and efficient mechanism for virus negation is regarded as a major challenge in public health against general airborne biological threats,” the authors wrote. “Our salt-coated filter unit can promise the development of a long-term, stable, versatile airborne pathogen negation system, without safety concerns.”

Lifestyle factors need to be considered when treating HCV.
A
though the Centers for Disease Control and Prevention (CDC) recommends that all pregnant women get tested for HIV as early as possible, some are unable to do so. Often, particularly in underdeveloped countries, access to testing and antiretroviral drugs, such as Nevirapine and Zidovudine, is very limited—this puts unborn children at risk of acquiring the infection from their pregnant mothers who are positive for the virus. However, this mother-to-child transmission can be prevented. Students from Duke University’s Developing World Healthcare Technologies Lab have developed a medical device to aid in this effort.

According to the CDC, close to 8,500 HIV-positive women give birth each year, and each day, 1,000 children acquire the virus, the majority as newborns. In total, the United Nations says that mother-to-child transmission in the developing world leads to a 260,000 newly acquired infections in children annually.

Although preventing transmission is possible with the assistance of antiretroviral drugs, these drugs need to be administered within 24 hours of birth—at most, 72 hours—in order to ensure effectiveness. Many clinics in developing areas that have been hit especially hard by the virus—such as sub-Saharan Africa—have these drugs available, but the majority of pregnant women tend to deliver their babies at home. Therefore, their babies face an especially high risk of acquiring the virus during the birthing process or through breastfeeding. Additionally, according to a press release, "Previous attempts to give the medication to newborns using syringes, cups, and spoons were failing because the [antiretroviral] was
According to the CDC, close to 8,500 HIV-positive women give birth each year, and each day, 1,000 children acquire the virus, the majority as newborns.

degrading before it could be administered. Therefore, it became obvious that the problem was related to drug storage and delivery.

In an effort to remedy the issue, Robert Malkin, PhD, a biomedical engineering professor at Duke University, and his team—comprising graduates, undergraduates, and postdoctoral students—invented a packaging device dubbed the “Pratt Pouch,” a “foilized polyethylene pouch,” that would extend the lifespan of the antiretroviral drugs to up to one year. The pouch, which resembles a ketchup packet, is designed to be filled and closed with an electric heat sealer by local pharmacists and then distributed “during antenatal care visits at district hospitals, clinics, and on outreach trips to more rural communities by nurses and healthcare workers,” according to the press release. After distribution, mothers can simply squeeze the contents of the pouch in their newborn’s mouth.

According to Dr. Malkin, it was designed for easy transport and delivery, meaning it is “easy to open without spilling the contents.”

When speaking with Contagion™, Dr. Malkin explained the inspiration behind the design of the pouch: “The pouch was designed after another organization tried to solve the problem for about 7 years. I met the head of that project at the coffee pot of a conference and was intrigued by the problems they had found with their various solutions. I asked an undergraduate to investigate the leading hypotheses for why standard methods don’t work. (Your mom almost certainly gave you liquid medications in a spoon, cup, syringe, or eye dropper—all of those destroy the medication before it can be used.) After many months designing experiments (mostly failed), we were able to determine that leading hypotheses were wrong. Furthermore, once we knew what the problem really was, it was very straightforward to design a solution.”

According to the press release, after the Pratt Pouch was introduced to Zambia, medicinal access to antiretroviral drugs increased from 35% to 92%, which “equates[d] to an almost 10-fold drop in the number of children becoming HIV positive.” The pouch has also proved so successful in Ecuador that Dr. Malkin estimates it will be available throughout the country by 2018.

In comparison with Ecuador, Uganda has been hit harder with the virus. To address this, the Elizabeth Glaser Pediatric AIDS Foundation is administering the pouch in the country and Dr. Malkin hopes they reach at least 40% of mothers living with the virus there.

When speaking of the implications of the pouch, Dr. Malkin told Contagion™, “If the project in Uganda is successful, I feel that many neighboring countries can immediately adopt the solution on a country-wide scale. This is because Uganda is developing the capacity to make sufficient pouches for their own country and beyond.”

The Pratt Pouch is now commercially available through Maternova (maternova.net/collections/frontpage/products/pratt-pouch-for-home-based-hiv-prevention-in-neonates).
A Pharmacist’s Role in HIV Antiretroviral Stewardship in the Hospital

Pharmacists Play an Important Role in Advancing Patient Care and Supporting the Continuum of Care for Patients with HIV.

BY BETTY VU, PHARMD AND DREW HALBUR, BSPHARM, BCACP, AAHIVP

Nationally, over 1.2 million Americans are living with HIV, of which 13% are unaware of their infection.1 The management of HIV infection has drastically changed over the last 10 years with the development and enhancement of more than 14 antiretroviral medications, including better formulations and various combination pills approved by the Food and Drug Administration.2 Since entering the decade of enhanced formulations of antiretrovirals and the initiation of pre-exposure prophylaxis in 2014, there has been both a significant reduction in HIV-related illnesses and an increase in proportion of patients with viral suppression—with a more than 19% decline in new HIV diagnoses over the last decade.3

Other significant factors that have contributed to this positive impact include early initiation of antiretroviral therapy (ART) and the use of this therapy for reducing the risk of HIV transmission. Both the START and TEMPRANO studies were landmark randomized controlled trials published in 2015 that provide the highest level of evidence to support the use of early initiation of ART, regardless of CD4 cell count, for benefit in boosting immune recovery and preventing clinical events.4,5 The treatment-as-prevention model is a method studied in the HIV Prevention Trials Network (HPTN 052) study that demonstrated a reduction of sexual transmission of HIV among heterosexual couples, with full viral suppression from ART.6

The Department of Health and Human Services (DHHS) recommends triple combination therapy for treating HIV, with dual nucleoside reverse transcriptase inhibitors and either an integrase strand transfer inhibitor or protease inhibitor in combination with a pharmacokinetic enhancer agent (ie, ritonavir or cobicistat) for HIV treatment-naïve patients.7 These regimens are often complex and have clinically significant drug-drug interactions; without appropriate monitoring, there is a high risk for medication errors and unwanted adverse effects, especially in those with multiple comorbidities. The incidence of medication errors related to antiretroviral agents in hospitalized patients has ranged between 21% and 72%.8-10 Errors were observed in all major antiretroviral therapies.
The management of HIV infection has drastically changed over the last 10 years with the development and enhancement of more than 14 antiretroviral medications.

Antiretroviral drug classes and include medication omission, inappropriate scheduling of drug administration, drug interactions, and incorrect dosing.

Pharmacists play vital roles in optimizing HIV treatment outcomes in multiple ways and in all medical settings, such as ensuring patients are taking a complete and appropriate regimen, recommending alternative therapy, dose or formulation adjustments, mitigating drug-drug interactions, and modifying drug schedules to optimize absorption. In order to improve the quality of care in HIV-infected patients, more institutions are partaking in several forms of ART stewardship, often composed of a team led by pharmacists specialized in infectious diseases and/or HIV.

Pharmacist-Led Antiretroviral Stewardships

The development and implementation of pharmacist-led antiretroviral stewardships have been seen in numerous published studies across the country. Current literature reports a profound impact on improving safety in HIV patients through pharmacist interventions via medication error prevention and daily monitoring. Retrospective studies have seen rates of antiretroviral stewardship interventions for medication errors related to antiretrovirals increase from 16% to 52%. Various methods of stewardship interventions have been utilized, including prescriber and pharmacist education, customized order entry sets, and prospective audit and review. The impact of these methods is discussed below:

- **Prescriber and pharmacist education** can assist prescribers in appropriate selection and dosing of antiretrovirals. Zucker and colleagues’ study saw modest reduction in medication errors (from 45% to 36%) with provider education and order sets in an urban medical center setting.

- **Customized order entry sets** can also facilitate correct prescribing of antiretrovirals and preventing potential drug-drug interactions or improper timing of administration. Another study performed by Guo and colleagues saw error rates reduced by 35% overall, primarily in incorrect doses and drug interactions by over 40%.

- **Prospective audit and review** seem to show a significant reduction in these studies. In the previously mentioned Zucker study, prospective audit reduced errors to 12%. Other studies saw rates of pharmacist interventions on drug interactions increase from 43% to 95%, and medication error rates decrease from 50% to 34%.

Given these results, pharmacists with specialized training and knowledge in HIV are in a unique position to lead stewardship initiatives to significantly reduce medication errors related to ART in numerous ways. In the hospital, there are many opportunities for pharmacist intervention and improving patient safety, including identifying drug-drug interactions. Common inpatient medications such as proton pump inhibitors and statins may have clinically significant and unfavorable consequences. In addition, pharmacists can verify appropriate and complete ART regimens, the accurate route of administration, adjustments for renal and hepatic function, and indications for opportunistic infections associated with HIV/AIDS. Similarly, these interventions can be replicated in the outpatient setting, however, reported data are limited.

Challenges of Pharmacist-Led Antiretroviral Stewardships

Pharmacists, as part of antiretroviral stewardship teams, may face such barriers around therapeutic interchange of newer formulations, such as Genvoya and Descovy, with formulary antiretrovirals or interchange between routes of administration for formulations without alternatives. At times, barriers may lead to a temporary hold on medication administration, which may cause concern for virologic failure. In HIV-treated patients with hepatitis B co-infection, abrupt discontinuation of ART can also lead to an acute flare of hepatitis B. Consequently, in antiretroviral-experienced patients with viral resistance, treatment regimens may become more complex, requiring use of older antiretroviral agents, which have greater potential for drug-drug interactions and toxicity. At this time, further guidance is needed to determine the appropriate process of therapeutic interchange within hospital formularies.

Cascade of Care

Beyond poor engagement in HIV treatment, providers and HIV-infected individuals may face obstacles when disruption occurs along the HIV care continuum, also known as the Cascade of Care. This model—defined in 2011 by Edward M. Gardner, MD, and colleagues—outlines five sequential steps of HIV medical intervention including: diagnosis, linkage to care, retention in care, acquisition of ART, and achievement of viral suppression. Frequently, HIV-infected patients who face psychosocial or economic barriers are at risk of lost to care. Pharmacists, as part of antiretroviral stewardships, can assist with strengthening the continuum of HIV care by ensuring linkage to care after hospital discharge or outpatient.

The Cascade of Care has become such a significant model that former President Barack Obama prioritized efforts in addressing this model through executive order of the HIV Care Continuum Initiative in 2013. This step in implementation of the national HIV/AIDS strategy focuses efforts on increasing the proportion of patients in each stage of the continuum by increasing access to HIV testing, care, and treatment.

Within institutional care of HIV-infected patients, one major stage of the Cascade of Care that is affected is initiation of ART during hospitalization, particularly in those with late entry into medical care when concomitantly diagnosed with HIV/AIDS and opportunistic infection or active seroconversion. Pharmacists involved with...
the care of these individuals play an important role as patient advocates by facilitating appropriate and timely initiation of ART where added benefit has been previously seen. Additionally, appropriate transition into outpatient care is a key intervention to ensure patients are linked with and engaged in care with health care providers, including pharmacists with special training in HIV ART. This ultimately leads to viral suppression and optimized HIV treatment outcomes.

FUTURE DIRECTIONS
There is still much left to be done even with the great progress that has been made over the recent years with the reduction in HIV diagnoses and improved viral suppression. The medication error rate in ART regimens reported in hospitalized patients is alarming, but it is also a great opportunity for pharmacists to optimize and improve the medication use process, as the results of published studies have already demonstrated. Further direction with impact of ART stewardship in the ambulatory setting and with guidance on appropriate therapeutic interchange within hospital formularies are needed. With a variety of methods to reduce medication errors, such as use of computerized order entry sets, provider education, and prospective feedback, pharmacists can continue to work to make an impact in advancing HIV patient care and supporting the continuum of care.

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References available online at ContagionLive.com.
Historically, patients with liver cirrhosis have been thought to be “auto-anticoagulated,” naturally protected against venous thrombotic disease. This concept has since been debunked and replaced with the understanding that advanced fibrosis promotes anti-coagulant and pro-thrombotic states. Specifically, liver cirrhosis leads to decreased synthesis of the majority of clotting factors, thereby increasing the risk of bleeding in patients with advanced liver disease. However, patients with fibrosis have decreased levels of anticoagulation factors, such as protein C and antithrombin, which promote a pro-thrombotic state. This seemingly contradictory phenomenon places patients with cirrhosis and healthcare providers in a challenging position: should physicians administer prophylactic anticoagulant drugs to patients with cirrhosis? On the one hand, the risk of bleeding increases with the use of anticoagulant drugs; however, without these drugs, patients could be at risk for developing venous thrombotic disease.

In an article in press for publication in *Journal of Hepatology*, Mark Thursz, MD, professor of hepatology from Imperial College in London, and colleagues, attempt to address this difficult question. They introduce the issue of prophylactic anticoagulation by presenting a case study of a man in his late 50s who suffers from chronic hepatitis C with liver cirrhosis. After multiple hospital visits, the patient was admitted to the emergency department complaining of painful swelling in his left leg, which testing later revealed to be a blood clot in his left femoral vein. During previous hospital admissions, physicians opted not to administer prophylactic anticoagulant drugs due to concerns about bleeding. Sadly, the patient suffered a heart attack and died. The cause of death: pulmonary embolism. Dr. Thursz and his colleagues argue that the reasons cited by the physicians against
prophylaxis did not make a strong enough case and that the patient could have benefited from anticoagulant drug therapy. They use this case study to pose a series of questions that seek to address the risk of development of thrombosis in patients who suffer from chronic liver disease and whether or not prophylactic anticoagulant drugs should be administered to them.

Before determining if anticoagulant drugs should be administered, it is imperative to assess if there is a real need for such measures in patients with cirrhosis. To examine the correlation between cirrhosis and thrombotic disease, Dr. Thursz and his colleagues cite a Danish study comprising 100,000 patients diagnosed with venous thromboembolism. In this study, patients with liver cirrhosis were shown to be 1.7 times more likely to develop thrombosis compared with the general public. The authors also discussed the risk of developing portal vein thrombosis (PVT), but concluded that in those with chronic liver disease, the magnitude of the risk of developing PVT is unclear.

Although patients with cirrhosis seem to be at a higher risk of developing thrombotic disease, current clinical guidelines do not make any recommendations to physicians for the use of anti-coagulants as a prophylactic measure. Therefore, before any changes to clinical guidelines can be made, prospective studies are needed to examine whether patients with cirrhosis could benefit from prophylaxis, and if so, what an ideal drug regimen would look like. Until such studies are conducted, the benefits and disadvantages for each patient need to be assessed on a case-by-case basis, with the ultimate tough decision falling into the hands of the attending physician.

An additional wrench in the works is the issue of accurately assessing anticoagulation status in patients, a critical parameter to consider before administering anticoagulant drugs. Currently, the international normalized ratio (INR), a prothrombin time test, is utilized, where a high INR indicates slow clotting blood and a lower INR means the patient’s blood is clotting faster than normal. Current clinical guidelines support aiming for an INR of 2.0 or 3.0. However, no studies have been conducted to determine if this is a sound approach to monitoring patients with cirrhosis. Overall, more studies are needed to evaluate optimal dosing regimens, as mentioned previously, and to determine a more effective way to assess anticoagulation status.

To return to the original case study, prophylactic anticoagulation was not administered to the patient due to concerns about the risk of bleeding. It is natural to have such trepidations about the safety of such a measure and to question if anticoagulation therapy can be safely and effectively used in patients with cirrhosis without significantly heightening their risk of bleeding. Dr. Thursz and his colleagues concluded, “With careful screening and management of varices, there does not seem to a significantly increased risk of bleeding, implying that patients may be safely anticoagulated either in the setting of prophylaxis or therapeutic treatment.”

In summation, although evidence suggests that patients with advanced liver disease could stand to benefit from anticoagulation as a prophylactic measure, much research is still needed before clinical guidelines can make this recommendation. In the future, studies are needed to determine the ideal dosing regimens for anticoagulation therapy and an effective and accurate way to assess anticoagulation status.

References available online at ContagionLive.com.

IN OTHER HCV NEWS

Liver Disease Severity and Treatment Costs Dependent on Patient’s HCV Genotype

A recent study funded by Bristol-Myers Squibb and published in Current Medical Research and Opinion, suggests that liver disease severity and treatment costs for people with hepatitis C (HCV) vary depending on a patient’s genotype.

In the retrospective study, US-based researchers collected data on patient demographic and clinical characteristics provided in healthcare claims from a large US health plan. All of the patients had at least 18 months of continuous pharmacy and medical insurance. Potential participants were excluded if their age, sex, geographic region, and health insurance were unknown.

Approximately 64% of the patients were male with an average age of around 50.6 years. Out of the more than 10,000 patients included in the review, 79.1% had genotype 1, 12.8% had genotype 2, and 8.1% had genotype 3.

The study found that patients with genotype 3 had the highest percentage of liver-related comorbidities and advanced liver disease. These patients were about one-third times more likely to have advanced liver disease than patients with genotype 1 of the virus. The highest rates of steatosis, liver transplant, and hepatocellular carcinoma (the most common form of liver cancer) were also found to be among patients with genotype 3.

“These findings support the notion that genotype 3 variant of the virus imparts a unique pathophysiology throughout the disease course,” the authors said, noting that the findings were similar to those from previous studies.

Those with genotype 1 took the hardest financial hit with the highest all-cause costs, while patients with genotype 2 had the lowest costs and lower healthcare resource utilization.

One limitation of the study is that results may not generally represent other patients outside the insurance plans from which data was analyzed, the authors noted.

— Contagion™ Editorial Staff

Samar Mahmoud graduated from Drew University in 2011 with a BA in biochemistry and molecular biology. After two years of working in industry as a quality control technician for a blood bank, she went back to school and graduated from Montclair State University in 2016 with a MS in pharmaceutical biochemistry. She is currently pursuing her PhD in molecular and cellular biology at the University of Massachusetts at Amherst.
Decongestants and Hypertension: Dangerous Together
Pharmacists Can Play an Important Role in Managing the Use of These Medications in Patients, Particularly Those With High Blood Pressure.

BY CLARENCE D. MOORE, PHARMD, BCPS

Nearly 33% of adults in the United States have the typically symptomless disease known as hypertension.1 When healthcare providers treat these individuals, caution should be exercised, as several medications are contraindicated. For example, because decongestants—which are frequently used to manage nasal congestion—can increase blood pressure (BP), their use is a concern in patients with hypertension.

Nasal congestion is a typical symptom of the common cold, occurring when nasal and adjacent tissues and blood vessels become swollen with excess fluid.2 This symptom has been described as the most bothersome by adults with allergies.2,3 Individuals with nasal congestion are encouraged to drink plenty of fluids to thin mucus and promote nasal drainage, in addition to getting plenty of rest and limiting activities.4 OTC medications are often used to manage symptoms; however, they do not shorten the duration of illness and only offer temporary relief.

Individuals with hypertension should be made aware that decongestants can elevate their BP. Various medical guidelines characterize hypertension in adults as a systolic BP of 140 mm Hg or higher or a diastolic BP of 90 mm Hg or higher.5 Hypertension is treated by using various methods to decrease BP to a predetermined target. The American Heart Association warns all individuals with hypertension, including those being treated for it, to read the labels on all OTC medications prior to use.6

DECONGESTANTS
Nasal decongestants are vasoconstrictors that belong to the pharmacologic class “sympathomimetic amines.” They exert their primary action by activating alpha-adrenergic receptors on blood vessels of the nasal mucosa. This results in vasoconstriction, which decreases blood flow through the nasal mucosa and shrinks tissue.7 Decongestants are available in multiple formulations with varying degrees of systemic effects, including potential elevation of BP.

Oral Decongestants
The decongestants pseudoephedrine and phenylephrine may offer mild relief from nasal congestion associated with the common cold.4 These medications are administered alone or in combination with antihistamines, which minimize other symptoms associated with the common cold.

Pseudoephedrine is a common ingredient in more than 135 medications and has proved effective in treating nasal congestion. Although a 2005 meta-analysis that showed the drug significantly increased systolic BP (0.99

*Previously published in Pharmacy Times November 2016 issue.


Antihistamines can be used in combination with decongestants; however, they should not be used in small children.

**The Pharmacist’s Role**

With their training in OTC medications, pharmacists can play a major role in managing decongestion in their patients. Because no product can be recommended to provide safe and effective relief of congestion in all patients with hypertension, pharmacists’ medication knowledge, coupled with their keen ability to obtain valuable information from patients, can ensure optimal drug selection for individuals with hypertension.

References are available online. at ContagionLive.com.

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mm Hg) and heart rate (2.83 beats/min), the results revealed no effect on diastolic BP. Higher BP increases were associated with higher doses and immediate-release formulations of pseudoephedrine. ⁹ Studies comparing phenylephrine with placebo showed no significant improvement in measures of nasal congestion. There is a lack of data on phenylephrine’s effect on BP.

Phenylephrine and pseudoephedrine have been described as safe and effective for treating nasal congestion. ³ However, as a result of the Combat Methamphetamine Epidemic Act of 2005, pseudoephedrine products are kept behind the pharmacy counter and have certain restrictions regarding their purchase.

**Topical Decongestants**

Naphazoline, oxymetazoline, and phenylephrine are commonly used topical decongestants. Although these agents are expected to promote local activity, the FDA requires their instructions to contain a warning for individuals with high BP; however, the data on the connection between their use and hypertension are sparse. Unlike other topical decongestants, propylhexedrine is a topical OTC decongestant that is not required to carry a warning against unsupervised use in patients with hypertension. ¹⁰ The use of topical nasal decongestants for more than 5 days is associated with the development of rhinitis medicamentosa, also known as “rebound rhinitis,” which can lead to user dependency. ¹¹

**Alternatives**

A 2003 Cochrane review concluded that monotherapy with antihistamines does not alleviate nasal congestion to a clinically significant degree. In that review, first-generation antihistamines were found to have greater adverse effects than placebo, but neither first- nor second-generation antihistamines increased BP. Antihistamines can be used in combination with decongestants; however, they should not be used in small children. ⁸

Saline has been used to relieve congestion and is thought to thin mucus in the sinus cavities. Increasing humidity in the environment of patients with nasal congestion may also provide relief; therefore, the use of humidifiers is recommended. A third solution, nasal strips may help open the nostrils and improve breathing in patients with congestion. ¹³

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Respiratory Infections

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and that carry the potential for substantial side effects: polymyxins.

To further complicate matters, there is an intriguing debate developing within the infectious diseases arena: the use of polymyxin B versus polymyxin E (colistin). Colistin has been called into question as a drug of choice for multi-drug resistant (MDR) infections, while a recent spotlight on polymyxin B is bringing it back onto the MDR treatment stage. Colistin’s historically unattractive properties have incentivized providers to reevaluate other potential options, reopening the door for polymyxin B with its potentially more appealing profile. Many clinicians are aware of colistin’s nephrotoxicity and the ambiguity surrounding dosing, particularly in renal insufficiency, but most are largely unfamiliar with polymyxin B. We start the debate by delineating the benefits of polymyxin B and follow it up with an explanation of why hospitals continue to use colistin.

**TEAM POLYMYSXIN B**

Although structurally similar to colistin, polymyxin B offers multiple pharmacokinetic advantages in the treatment of systemic infections. Polymyxin B achieves therapeutic concentrations rapidly, provides more predictable serum concentrations, does not require renal dose adjustments and may not require a loading dose. In comparison, colistin’s peak serum concentration may not be reached for up to 7 hours, serum concentrations are unpredictable due to significant interpatient variability, renal dose adjustments must be considered, and a loading dose is required.

What accounts for these prominent differences in two structurally similar drugs? Colistin is administered as an inactive prodrug, colistimethate (CMS), while polymyxin B is already in its active form. In patients with moderate to good renal function, studies suggest only 20% to 25% of CMS is converted to its active form, with the majority of the dose being renally excreted prior to conversion.1 Because of this, larger doses of CMS are required to achieve therapeutic systemic colistin concentrations. Polymyxin B is mainly eliminated via nonrenal pathways, accounting for little interpatient variability across a wide range of creatinine clearance, whereas CMS clearance is variable even at a given creatinine clearance (eg, two patients with the same creatinine clearance will clear CMS at different rates). Although nephrotoxicity has been a point of contention, recent studies have found lower rates of nephrotoxicity with polymyxin B compared with colistin.2 The need for higher doses and extensive renal excretion of CMS leading to increased renal exposure have been offered as the rationale for this difference.
A recent study assessing the pharmacokinetic differences on bacterial killing and resistance emergence in *Acinetobacter baumanii* found that rapid attainment of target concentrations was critical for polymyxin-induced bacterial killing.\(^4\) The gradual rise in colistin concentrations lead to faster development of polymyxin resistance, contributing to little bacterial killing over the treatment period. Conversely, polymyxin B demonstrated good early bacterial killing, which the authors attributed to rapid attainment of bactericidal concentrations that overtook the onset of polymyxin resistance. However, resistance eventually developed following treatment with either agent, despite significant differences in the magnitude of bacterial killing. This supports the importance of using both polymyxins only in combination with additional antibiotics and (almost) never as monotherapy.

**TEAM POLYMYXIN E**

Although polymyxin B can seem like a very appealing alternative, little literature is available detailing the pharmacokinetics of polymyxin B, and there is a dearth of information regarding its pharmacodynamic properties. What we do know from five clinical trials comparing colistin and polymyxin B treatment is there is no difference in mortality.\(^5-9\) In addition, there are particular diseases states where colistin is likely preferred. Colistin is readily converted to its active form in urine and therefore reaches superior urinary concentrations compared with polymyxin B.\(^1\) Less than 1% of polymyxin B is recoverable in urine.\(^9\) Another benefit of colistin is its ability to be administered via inhalation. Inhalational colistin is currently recommended by the Infectious Diseases Society of America for treatment of hospital acquired- and ventilator associated pneumonia with multi-drug resistant infections.\(^11\) Finally, admixtures of polymyxin B require a considerable amount of solution volume, which may make colistin more appealing for those that cannot handle the extra fluid. Depending on patient weight, volumes of 500 to 1000 mL per dose (typically given twice daily) are not uncommon.

Although dosing of colistin is ambiguous at best and an unfortunate amount of interpatient variability exists, a considerable quantity of recent literature has been published to help clarify this issue. A recent study determined that a steady-state concentration of 2 mg/L should meet our targets.\(^12\) This study also identified that concentrations greater than 2 mg/L lead to increased incidence and severity of acute kidney injury.\(^12\) In addition, studies have suggested no benefit to more aggressive dosing,\(^13\) so in the future, it may be possible for us to be able to optimize colistin dosing. Whereas appropriate dosing, especially in renal insufficiency, is still a considerable barrier and a reason why many contemplate polymyxin B, recent literature has at least been able to guide us in the direction of using a 5-mg/kg loading dose and to strongly consider using ideal body weight.\(^14\) In addition, a potential scoring system is available to help identify patients most at risk for nephrotoxicity, which may help us customize our dosing in high-risk patients.\(^15\)

**CONCLUSION**

As rampant antibiotic resistance continues to diminish our treatment options, we are more frequently forced to utilize the broadest spectrum and more toxic antibiotics. Recent reports from China documented the emergence of plasmid-mediated colistin resistance (MCR-1).\(^16\) and as of November 30, 2016, there have been human isolates of MCR-1 gene-containing organisms in Connecticut, Maryland, New Jersey, New York, and Pennsylvania.\(^17\) Animal isolates have also been found in Illinois and South Carolina.\(^17\) Optimization of antimicrobial therapy is the fundamental premise in slowing the unavoidable propagation of resistance. Thus, it is imperative to use and dose our polymyxins appropriately. Polymyxin B discernably wins the nephrotoxicity battle and is not a prodrug; administering its active form enables reliable dosing regardless of renal dysfunction and rapid achievement of therapeutic concentrations. However, despite polymyxin B’s multiple benefits, colistin certainly should not be disregarded. Superior urinary concentrations and the ability to administer via inhalation are undoubtedly some of colistin’s strong points. Additionally, more literature has been published that is enabling us to better understand how to appropriately and safely dose colistin.

So, which polymyxin do we choose? As with all clinical conundrums, there is no easy answer and the intellectual debate rages on. Thankfully, new literature on these old drugs continues to be published, and we will undoubtedly further our understanding of these unique antibiotics in the coming years.

A quick breakdown of the pros vs cons of the two polymyxins appears at the end of this article (see Table). \(^\text{\footnotesize ▲} \)

**References are available online at ContagionLive.com.**

**Table.** Pros and Cons of Polymyxin B vs Polymyxin E (Colistin)

<table>
<thead>
<tr>
<th>POLYMYXIN B</th>
<th>POLYMYXIN E (COLISTIN)</th>
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<tbody>
<tr>
<td><strong>Pros:</strong></td>
<td><strong>Pros:</strong></td>
</tr>
<tr>
<td>Achieves therapeutic concentrations rapidly</td>
<td>More recent literature to guide appropriate dosing</td>
</tr>
<tr>
<td>Provides predictable serum concentrations</td>
<td>Preferred over polymyxin B for UTIs</td>
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<tr>
<td>Does not require renal dose adjustments</td>
<td>Important inhalational option for pneumonia</td>
</tr>
<tr>
<td>May not require a loading dose</td>
<td>Despite flaws, equal patient mortality compared to polymyxin B in studies</td>
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<tr>
<td>Mainly eliminated via non-renal pathways</td>
<td><strong>Cons:</strong></td>
</tr>
<tr>
<td>Lower rates of nephrotoxicity</td>
<td>Cmax may not be reached for up to 7 hours</td>
</tr>
<tr>
<td>Little information regarding pharmacodynamic properties</td>
<td>Serum concentrations are unpredictable due to significant interpatient variability</td>
</tr>
<tr>
<td>Requires large solution volume</td>
<td>Renal dose adjustments must be considered</td>
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**AILEEN AHISKALI, PHARMD**

Aileen Ahiskali, PharmD, is an infectious diseases pharmacist and antimicrobial stewardship program coordinator at Hennepin County Medical Center in Minneapolis, MN, where she coordinates antimicrobial stewardship initiatives and rounds with the infectious diseases team daily.
The Reasons Individuals Refuse Vaccines May Surprise You
More Education on the Illnesses Individuals Are Risking May Help to Address the Issue.

BY SUSAN KREIMER, MS

Susan Kreimer, MS, is a medical journalist with more than 2 decades of experience. Her coverage has informed consumers, physicians, nurses, and health system executives. Ms. Kreimer holds a master’s degree in journalism from Columbia University and lives in New York City.

United States residents declined vaccines for preventable diseases at varying rates during their visits to health care providers before embarking on trips abroad, a new study reports, while also sounding the call for more effective education about disease risk.

“In addition to posing a risk to the individual traveler, vaccine-preventable diseases acquired during international travel can also spread among susceptible populations in the United States,” the researchers cautioned in The Journal of Travel Medicine.

The most frequent reason given for nonacceptance of one or more recommended vaccines was a lack of concern about the associated illness. In compiling the data, surveyors were tasked with recording one of three reasons for a traveler’s vaccine refusal: cost concerns, safety concerns, or not concerned with the illness.

“Going into the analysis, we had some preconceived notions that cost would be an important barrier, but, in fact, that did not play out,” Regina LaRocque, MD, MPH, the report’s senior author and an infectious disease specialist at Massachusetts General Hospital, told Contagion™ in a phone interview. “Similarly, safety was not the most commonly cited reason for refusing vaccines.”

With the paucity of concern about illness emerging as the main explanation for vaccine refusal, “that seems like something we can actually remediate by providing travelers more important information, more education, about the illnesses that these vaccines are designed to prevent,” said Dr. LaRocque, also an assistant professor of medicine at Harvard Medical School.

Researchers examined the findings on travelers seen for pre-travel health advice from July 1, 2012, through June 30, 2014, in the Global TravEpiNet (GTEN) consortium. Supported by the Centers for Disease Control and Prevention (CDC), GTEN consists of US clinical practices that provide pretravel health care to international travelers.

The 23 GTEN sites that contributed data to this analysis are spread across the United States and include academic practices, health care consortia, health maintenance organizations, pharmacy-based clinics, private practices, and public health clinics. At each location, an institutional review board either approved or exempted the study.

Of the 24,478 participants, 23,768 (97%) were eligible for at least 1 vaccine, but 6,573 (25%) refused one or more recommended vaccines. Travelers were most frequently eligible for typhoid, hepatitis A, and influenza vaccines.
Eligible travelers overall declined the following vaccines: meningococcal disease; rabies; Japanese encephalitis; and influenza.

For nine vaccines (see Table 1), researchers calculated refusal rates among eligible travelers in accordance with CDC recommendations in effect at the time of travel. Vaccine advisories were updated continuously based on guidance issued by the CDC Travelers’ Health Branch (www.cdc.gov/travel).

“We always recommend that people discuss this with their provider and that they see their provider four to six weeks before they travel,” said Mark Sotir, PhD, MPH, epidemiology and surveillance team lead in the CDC Travelers’ Health Branch, in a phone interview. “Sometimes it takes time to do a clear evaluation for different illnesses and there are some vaccines where you need multiple doses.”

The study reviewed refusals for the following vaccines: hepatitis A, influenza, meningococcal disease, tetanus-diphtheria/ tetanus-diphtheria-acellular pertussis, and typhoid fever for all travelers; rabies for individuals staying longer than 28 days in a high-risk country; polio for visitors to countries where it was indicated, as defined by CDC recommendations in place at the time.
Eligible travelers overall declined the following vaccines: meningococcal disease; rabies; Japanese encephalitis; and influenza.

of travel: Japanese encephalitis for individuals heading to countries endemic for the illness; or yellow fever for travelers to entirely or partially endemic nations, based on CDC guidance for those travel dates. Researchers excluded travelers from their analysis of refusal if they had pre-existing immunity or a medical contraindication to the vaccine or if the clinician determined that the vaccine would not be relevant to the traveler’s itinerary.

In the multivariable analysis, travelers planning to visit friends and relatives in developing countries were less likely to consent to all recommended vaccines than those not visiting friends or relatives. Countries were classified per the 2011 United Nations Human Development Index (very high human development, high human development, medium human development, and low human development), as well as 2009 World Health Organization geographical regions.

Using a secure internet tool, travelers entered specifics about their medical history, destination countries, purpose(s) of travel, geographic scope of travel (urban, rural, or both), anticipated activities and accommodations, and trip’s length and dates. Travelers could select multiple responses for purpose of travel and destination. After confirming this information, clinicians recorded additional data about the traveler’s immunization history, health advice provided, vaccines accepted or declined, and medications prescribed during the pretravel consultation.

“These are motivated travelers—people who have taken the time to seek a pretravel health encounter," LaRoque said. “Obviously, many travelers don’t bother to do that, so you could suppose that in the whole spectrum of people who are traveling internationally that many people are not getting vaccinated as you would wish.”

In the future, the GTEN consortium of research sites plans to delve into “deeper reasons of why people don’t have the fear of these diseases,” said Dr. Sotir. Obtaining more data on different individuals “increases the generalizability of your results.”

References available online at ContagionLive.com.
Another Tick-Borne Disease Growing in the United States: Powassan Virus

Up to 90% of Some Mammal Populations in the Northeast Are Infected With the Virus.

AN INTERVIEW WITH HOLLY FROST, MD

Contagion™ sat down with Holly Frost, MD, pediatrics physician scientist at the Marshfield Clinic Research Foundation, in Minocqua, Wisconsin, to discuss the emerging infectious disease, Powassan virus.

What is Powassan virus?
Powassan virus is a tick-borne flavivirus that was first discovered in Ontario in 1956. Powassan virus is known to be carried by the *Ixodes scapularis*, or the black-leg tick (which is also known as the deer tick). [This is] the same vector that carries Lyme disease, *Anaplasma*, and *Babesia*.

It’s a relatively newly discovered virus, and so we don’t know exactly how prevalent it is in humans in the United States, but we do know that about 7% of ticks in endemic areas for Lyme disease also carry Powassan virus and that in some mammal populations in the Northeast, up to 90% of the population can have Powassan virus.

What is the prevalence of Powassan virus in humans in the United States?
This was the first study that looked at the prevalence of Powassan virus in humans. We found that of patients presenting in the upper Midwest with suspected tick-borne disease, about 10% of patients had serologic evidence of Powassan virus.

We also looked at patients who were presenting just for routine chemistry screening, and we found that about 4% of those patients had serologic evidence of a past Powassan virus infection. We know that the prevalence in humans is likely to be higher than what we had previously estimated because the [virus’s] prevalence in ticks is growing; so, about 7% of *Ixodes scapularis* ticks in some endemic regions now carry Powassan virus and up to 90% of mammals in some endemic regions of New England have serologic evidence of Powassan virus.

Why should healthcare providers be aware of Powassan virus?
Powassan virus can cause severe neurologic symptoms, including encephalitis, in some patients. The majority
If you do have a patient [who’s] critically ill or a patient [who] has encephalitis and you live in an area endemic for Lyme, those patients should be tested for Powassan virus.

Can you explain the differential diagnosis for Powassan virus?
For all patients who live in areas where the *Ixodes scapularis* tick is present, it’s important to consider things like Lyme, *Anaplasma*, *Babesia*, *Ehrlichia*, as well as some of the other *Borrelia* species.

In a patient who is presenting with neurologic symptoms or encephalitis, that differential diagnosis can be a lot broader. So, that can include things like West Nile virus, which is commonly found in areas that are endemic for Powassan [virus] and for Lyme disease.

What can you tell us about the treatment options available for Powassan virus?
Currently, the treatment [for Powassan virus] is largely supportive. Very little is known about the virus because we don’t have a lot of data in humans, so there’s no specific treatment that we can recommend.

In general, for supportive care, we recommend fluids, if needed, [and] providing basic care for encephalitis, [which] can include ICU care, neuro-rehabilitation after the infection. We recommend treating this like you would any other patient with encephalitis or possibly as you would a patient who has West Nile encephalitis because we don’t know what the best course of treatment is.

Should there be routine testing for Powassan virus?
At this point, we wouldn’t recommend testing patients routinely for Powassan virus because we don’t know what clinical benefit that would have or how it would alter treatment. If you do have a patient [who’s] critically ill or a patient [who] has encephalitis and you live in an area endemic for Lyme, those patients should be tested for Powassan virus.

Is the prevalence of Powassan virus increasing in humans?
Powassan [virus] is an emerging infection, and so, we know that the amount of Powassan that we’re been seeing in ticks has been increasing and the seroprevalence in mammals has been increasing. [As a result], it’s likely that we’re going to see more of this as time progresses. I think we need to do further studies looking at what the true clinical presentation of Powassan virus is. We know very little aside from patients who have neurologic disease because that’s the population we’ve really tested before. We also need to learn more about patients [who] have co-infection with other tickborne diseases, such as patients [who] have both Lyme disease and Powassan at the same time present, and if they have a higher severity of illness or if their illness lasts for a longer period of time.

ABOUT THIS MAP:
This map is not meant to represent risks for a specific tick-borne disease, because disease transmission is influenced by multiple factors beyond mere tick presence. This map has been designed to answer the question “What ticks should I be concerned about at a regional scale?” Please consult a local public health authority or US Department of Agriculture Agricultural Extension Office to determine more specific information at the state, county, or municipal level. Background data for this map is from the US National Atlas.

MAP IMAGE:
*Ixodes scapularis*, more widely known as the blacklegged tick, can be found in the Northeastern and upper Midwestern United States. This tick can transmit Lyme disease, *Anaplasma*, *Babesia*, and Powassan disease. According to the Centers for Disease Control and Prevention, although risk of being bitten by a blacklegged tick increases in warmer weather, some adult ticks may bite in the winter when temperatures are above freezing.

This map is meant to identify geographic regions where *Ixodes scapularis* can be found, but not risk of specific disease transmission.
From September 2012 to September 2014, 34% (181 of 525) of women returned for repeat testing within three months of their positive diagnosis. After the clinic began to use the STD Tracker (October 2014 to September 2015), the rate of repeat testing within three months grew to 43% (104 of 243; \( P \leq .05 \)). At 6 months, the rate remained higher in the women contacted using the STD Tracker (57% vs 47%; \( P < .01 \)). Reinfection rates for chlamydia or gonorrhea at 3 months were 17% (16% before and 19% after the STD tracker was introduced).

Thomas Gift, PhD, and his colleagues estimated the impact and cost-effectiveness of the US Preventive Services Task Force and the CDC’s chlamydia and gonorrhea screening guidelines and advised that screening can benefit the nation’s health. Using data from the National Health and Nutrition Examination Survey, they compared the expected change in chlamydia prevalence in men and women who were screened with those who were not screened and they estimated the impact of a combined chlamydia-gonorrhea screening program. Their findings included the estimates that offering annual chlamydia and gonorrhea screening to all eligible women aged 15 to 44 years would reduce the population prevalence of chlamydia and gonorrhea by 32.1% in women and 10.4% in men compared with not screening women, with a net cost of $32,825 per quality-adjusted life-year.

Shantel Muldrew, MPH, and her colleagues found that in 1,346 men who have sex with men (MSM) who visited 12 STD clinics conducted by the Los Angeles County Department of Public Health, a pilot universal extragenital chlamydia/gonorrhea screening protocol identified more infections. Ms. Muldrew and her co-authors reviewed the medical records of MSM patients seen during the 6 months before the new protocol took effect (February-August 2014) and 6 months from the date the new protocol began (February-August 2015).

For each clinic, they compared before and after percentages of visits that included universal (urogenital, oropharyngeal, and anorectal) screening and positive chlamydia/gonorrhea lab tests anywhere on the body. They calculated the before and after percentages of visits that included universal screening, and they scored improvement as high (>10% increase), medium (1%-10% increase), or no improvement or decrease.

In multivariate models, the odds ratios of chlamydia/gonorrhea diagnoses during the before and afterprotocol periods were 1.40 (95% CI, 1.12-1.76; \( P < .01 \)) and 1.37 (95% CI, 1.05-1.78; \( P = .02 \)), respectively, times greater at high- and medium-improvement clinics compared with no- or decreased-improvement clinics.

Adam Cohen, MPH, PhD, discussed his study results showing that the smartphone application Healthvana, used by the AIDS Healthcare Foundation (AHF), reports chlamydia, gonorrhea, and syphilis test results to the patient as soon as the lab puts them online, shortening the time from testing to notification and from testing to treatment by roughly two days each compared with AHF’s previous system of notifying people who tested positive by phone.

“Clients have less time to unknowingly infect others, and the pressure on the staff due to the need to notify clients by phone is eased,” Dr. Cohen told Contagion®. For clients who used the app, the test-to-treatment period was shortened by 1.87 days \( (P < .05) \), the test-to-notification period decreased by 1.95 days \( (P < .05) \), and the number of days from notification to treatment increased a nonsignificant 0.07 days \( (P = .810) \).

Brooke Hoots, PhD, MSPH, presented findings about chlamydia and gonorrhea testing and diagnosis among MSM in 20 US cities. To assess the differences between 2011 and 2014 in self-reported chlamydia and gonorrhea testing and diagnosis in the previous 12 months among MSM, Dr. Hoots and her colleagues used data from the National HIV Behavioral Surveillance; and they estimated the differences in chlamydia and gonorrhea testing and diagnosis between those years using adjusted prevalence ratios (aPR). Testing for chlamydia increased from 37.8% in 2011 to 47.1% in 2014 \( (aPR, 1.19; 95\% CI, 1.15-1.24) \) and for gonorrhea from 38.8% to 47.8% \( (aPR, 1.18; 95\% CI, 1.14-1.22) \). Testing for both STDs was more prevalent among younger MSM and those who had more education, had health insurance, and were HIV positive; all subgroups showed similar increases.

Diagnosis of chlamydia grew from 9.2% in 2011 to 11.4% in 2014 \( (aPR, 1.28; 95\% CI, 1.10-1.49) \). Chlamydia diagnosis increased among MSM in the white and “other” racial categories, MSM with more education, and HIV-positive MSM. Diagnosis of gonorrhea rose from 12.1% in 2011 to 15.1% in 2014 \( (aPR, 1.41; 95\% CI, 1.23-1.61) \). Gonorrhea increased more among MSM in the white and “other” racial categories and those who had more education, health insurance, and more sex partners during the previous 12 months. ▲

SOURCES
Complicating the issue is the geography of the outbreaks. Medical knowledge generated south of the equator can face hurdles when it comes to acceptance in the north. The reported link between Zika virus infection and microcephaly was initially viewed with some reserve, despite prior knowledge from the outbreak in French Polynesia. Preliminary data suggesting the involvement of the genitourinary, cardiac, and digestive systems have yet to gain traction.

In addition, the real risk of congenital Zika virus syndrome may be greater than the present perception. “Up to 6% of Zika virus-infected pregnant women will miscarriage or have stillborn deliveries. Actual rates might be even higher. Surviving infants have as much as a 13% chance of Zika-related microcephaly and associated mental, ocular, and hearing impairments. Many could be impaired in less obvious ways, with disabilities appearing later in a child’s development,” Dr. Torres explained. “Is the substantial size, severity, and unexpected complications of the Zika virus outbreak in the Americas compared with what has been seen in the past in other areas due to immunological enhancement from prior dengue virus exposure or key sequence changes in the virus genome making it more virulent?”

Another pathogen that has spread extensively in the Americas is carbapenem-resistant Enterobacteriaceae (CRE). Maria Virginia Villegas, MD, International Center for Medical Research & Training, Cali, Columbia, discussed the situation in Latin America.

CREs, especially Klebsiella pneumoniae carbapenemases (KPCs), are global pathogens; this is reflected in their widespread occurrence throughout Latin America. The first case of KPC in Latin America was reported in 2005 in Columbia. Cases were reported the following year, in Argentina, Brazil, Venezuela, Chile, Ecuador, Peru, Uruguay, Mexico, and the Caribbean. In addition, New Delhi metallo-beta-lactamase was first described in 2008. By 2012, it had spread from the Indian subcontinent to Latin America, first in Guatemala and then throughout the continent.

The pattern of appearance and geographical expansion has been repeated for other pathogens as well. “The increasing incidence of CRE is an important threat to public health. CRE cause a variety of diseases, ranging from pneumonia to urinary tract infections to serious bloodstream or wound infections. Few clinical studies have reported the clinical impact of carbapenemases in Latin America,” Dr. Villegas said in her session. “The lack of surveillance, due to limited resources in Latin America, is contributing to under-reporting of a probable epidemic situation. Clinical studies are needed and joint efforts should be made between countries.”

Another pathogen of concern has been multi-drug-resistant tuberculosis (MDR-TB) followed more recently by extremely-drug resistant TB (XDR-TB). Eduardo Gotuzzo, MD, FACP, FIDSA, director of the Institute of Tropical Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru, addressed the problem in Peru. “Resistant TB is not a new phenomenon. In the 1950s, there was no effective treatment against TB. MDR-TB is an emerging problem due to globalization. There are significant epidemiological differences between countries.”

Factors contributing to the failure of control include delayed treatment, the increased prevalence of the important co-morbidities of diabetes and HIV, and a public health system in which subjects are lost to follow-up. XDR-TB has reared its head in the Americas, as elsewhere, with South Africa as the most recognized country. Linezolid produced promising results in one study: 79% (15 of 19 patients) had negative sputum culture after 4 months of treatment, with the rate climbing to 87% (34 of 39 patients) at 6 months and 71% (27 of 38 patients) being considered cured after 1 year. Other promising drugs include clofazimine and thioridazine. The latter is not yet in the World Health Organization guidelines. A

Disclosures available online at ContagionLive.com.
How can healthcare providers work to better prevent *Clostridium difficile* in post-acute care facilities?

"The way that healthcare providers can help improve the prevention and management of *C. difficile* in post–acute care facilities is a complex answer; this is a difficult disease. One of the keys here is prevention, and that relies, in large part, on antimicrobial stewardship, [such as] avoiding unnecessary antibiotic exposure, and also upon infection control.

Antimicrobial stewardship is a burden that falls upon both the providers in post-acute [care] as well as the hospitals themselves, and if we can all work together to minimize antibiotic exposure to our patients and our long-term care [patient] residents, that will help reduce their vulnerability, and that’s key.

Infection control, both in the hospital and in post-acute care, is important and is also very challenging. *C. difficile* spores can last on surfaces for a period of months. We have evidence that says they can last for five months on surfaces. They’re also very hard to remove with routine cleaning agents, so the quaternary ammonium compounds that most hospitals and long-term care facilities use for disinfection aren’t effective against *C. difficile* spores; neither is the alcohol [sanitizer] that we all use. The spores are resistant to that as well, so it’s hard to get them off of hands, which means that the fundamental infection control maneuver that we have to do as healthcare workers is handwashing with soap and water.

[In addition, we need to] reduce transmission by having all healthcare workers wear gowns and gloves when they interact with people that have *C. difficile* infection and [they need to] take off that personal protective equipment [properly.]

Early contact precautions are also imperative. If we think that someone may have *C. diff*, my preference, and I think that of many people, is to put them in contact precautions early until we’ve actually ruled out the disease. This usually takes about two days and reduces the possibility of transmitting spores to other patients or residents throughout the facility.

Another way that post–acute care facilities can prevent *C. difficile* infection through infection control is through really good cleaning. This is daily disinfection and cleaning of high-touch surfaces in residence rooms [is needed] as well as in other high-touch areas, like in the nursing station.

One of the big challenges of post–acute care is trying to clean the resident’s room. In the hospital, once someone is known to have *C. diff*, they stay in contact precautions for the duration of their hospitalization, and if that’s three days or five days or seven days, [cleaning the room] is not so hard. When they go, when they’re discharged, their room gets a terminal clean. In a long-term care facility this is so much more challenging because they live there and they’re supposed to be there for a long time, be it two weeks or two months or two years. Daily disinfection, using bleach to clean surfaces, will [only] get you so far when people have a lot of personal possessions; it becomes more challenging. That’s where some of these more technologically innovative disinfection devices come into play.

Can you discuss some of the more recent decontamination technologies designed for use in healthcare facilities?

There are two relatively recent technologies that have come on the market that are important for infection control diseases.

One of these technologies is hydrogen peroxide vapor, and people [often] use this to disinfect or decontaminate large spaces. Some of the downsides of using hydrogen peroxide vapor is that we have to close off the ventilation system, close off the doors, and create a seal within the room.

The UV devices seem to be more user-friendly. So the device goes in, the door gets shut, and the device is then programmed to disseminate UV light throughout the room; [the light] bounces around so it can get to those difficult-to-reach surfaces, like underneath things and around things, and it works to kill the spores. It can take up to about 45 minutes to an hour, and it may have to be done in two sessions—so one time in the room and one time in a bathroom, for example. If we’re looking at 2 hours to do a cleaning of a room or 2 hours to get the spore burden down, it’s completely worth doing that, and that can serve as the terminal clean to then allow the resident, and perhaps their roommate, to be back in the room.

Robin Jump, MD, PhD, assistant professor in the Department of Medicine at the Case Western Reserve University
New Technologies for Detecting Antimicrobial Susceptibility and Resistance

AN INTERVIEW WITH ROMNEY HUMPHRIES, PHD, D(ABBM)

Ideally, a technology would be really rapid so that we can detect resistance and susceptibility in our patients as soon as possible.

To watch the full interview with Dr. Humphries, visit ContagionLive.com.

(continued from cover)

Can you tell us a little about the new technologies that we should expect to see on the market soon?

Today, we have a lot of new technologies in development to detect antimicrobial resistance. A lot of focus has been placed on detecting resistance, but really, the ability to detect susceptibility is equally important. The traditional methods that we use today are methods that were developed in the 1970s and 1980s, and so it’s well past time for newer technology.

Ideally, a technology would be rapid so that we can detect resistance and susceptibility in our patients as soon as possible. [Preferably], at the bedside. In this way, you could tailor therapy to the patient’s specific infection, right off the bat, rather than starting on very broad-spectrum therapy and having to de-escalate or escalate as susceptibility or resistance is detected.

...[U]sing a phenotypic method is really important because it can accurately detect susceptibility. In this way, you observe how the bacteria behaves in the presence of the antimicrobial. There are several new technologies in development, which is very exciting, that do this in a much more rapid way than the traditional methods that we use today. (Which, from collection of a patient’s specimen, to results, can be up to 5 days.)

The most recent [technology] was [developed by] Accelerate Diagnostics. They have a system called the Phenom system, and it does a susceptibility test directly from a positive blood culture. This method reviews the performance of the antimicrobial against the organism in real time through microscopy. You’re actually imaging the cells and watching how they behave. They can do a susceptibility test within 6.5 to 7 hours.

Another method that is further along in development is through a company called LifeScale. They actually weigh the bacteria through the use of a microfluidic channel with a cantilever. As the organisms, one-by-one, enter through this channel, they cause a change in the cantilever vibrations so [lab technicians] can count the number of organisms. Of course, if the antimicrobial is killing the bacteria, there will be fewer organisms, and if it’s not, there will be lots of organisms as they continue to grow.

Both [of] those technologies we expect to see in the next year or two coming to the clinical labs.

There are several other technologies that have been developed more to identify bacteria rapidly, but could be adopted to do a susceptibility test. [One of these is] the BacterioScan method, which is an optical density measurement that counts bacteria. Again, you could count [the bacteria] in the presence of an antimicrobial, after a given time, to see if there is a reduction or an increase in the number of organisms—meaning they are either susceptible or resistant to the antimicrobial.

Another technology has recently been acquired by Roche that evaluates the viability of an organism, or whether it’s alive or dead, based on its ability to take up a gene which is delivered through a bioparticle that they engineer. When [the bacteria] acquire this gene, it gives them the ability to produce light. You look for bacteria being alive [by their] ability to generate light, and as they die, they are no longer able to generate the light, and so the lights go off as the organism is killed by the antimicrobial. These bioparticles can be very specific to a given species of bacteria or they can be much more broad and look at a whole family of bacteria, like the Enterobacteriaceae, for example.

How can stewardship recommendations drive change in patient management?

“We’ve done some work at UCLA looking at novel technologies [in the research lab]. [This is] because the business case that needs to be put together to bring these into the clinical lab and justify the cost for testing is pretty big.

[Additional work has been done] looking at, ironically, genotypic methods for organisms that we don’t grow routinely, including Neisseria gonorrhoeae. Through this, we’ve learned [that] while reporting the results of a rapid test in the electronic medical record, which is what all labs do to report their results, is good, it doesn’t ... make much impact on how the physician manages that patient because they already [had] an idea when they ordered the test [of] how they’re going to be managing that patient.

Follow up with the physician to let them know of the results and perhaps [to] let them know [that] institutional or stewardship recommendations on how to respond to the results is really what’s going to drive change in the management of these patients.”

Romney Humphries, PhD, D(ABMM), section chief of Clinical Microbiology at the University of California, Los Angeles
West Nile Virus Infections May Prove Deadlier Than Previously Thought

BY CONTAGION™ EDITORIAL STAFF

(continued from cover)

focus on Zika virus, for many people in the United States today, West Nile virus is the much more serious mosquito-borne threat, and that threat may persist even for patients who appear to have survived the infection unscathed.

For their research study, the scientists reviewed 4,144 cases of West Nile virus infection in Texas that occurred between 2002 and 2012. They focused on acute deaths that were recorded within 90 days of infection, as well as those who recovered from a West Nile virus infection months or years prior, but still died sooner than their peers of good health. The researchers found that although 286 individuals had died within the 90-day period after infection (the acute phase), 268 individuals had survived the infection, but still died earlier than they would have had they been otherwise healthy. The researchers referred to this as “delayed mortality” due to the virus.

After combining the acute deaths with the delayed deaths, the researchers determined that West Nile virus had a 13% fatality rate (554/4,144 over a 10-year period). This rate is higher than the 4% national fatality rate predicted by the Centers for Disease Control and Prevention (CDC) between 1999 and 2015. The low rate highlighted by the CDC only accounted for acute deaths; it did not include those that were potentially delayed.

According to Dr. Murray, this was the largest study to date investigating what healthcare providers have seen in smaller groups of West Nile-infected patients: which is that the virus appears to be capable of causing health problems after an individual is recovered from the initial infection. “For several years, we had followed smaller groups of patients and felt that many had died prematurely.” Murray said.

For each patient included in the study, the scientists had access to information about the course of the patient’s initial infection and information from the Texas state death registry on the cause of death. According to Dr. Murray, the patients who experienced a delayed death “had suffered significant neurological complications during the acute phase of their illness” and kidney disease was “statistically found to be a significant cause of death.” Researchers have long thought kidney disease to be a long-term complication of a West Nile virus infection.

Fatal Measles Complication More Frequent Than Previously Thought

BY BRIAN HOYLE, PHD

(continued from cover)

California Department of Public Health, Richmond, California at the annual conference of the Infectious Diseases Society of America (IDSA) in New Orleans, Louisiana, and was discussed in a press briefing by James Cherry, MD, University of California Los Angeles, one of the other study researchers.

SSPE develops years after measles has abated. Evident initially as behavioral changes that are not recognized as serious, the symptoms become more serious, and include seizures that become increasingly severe and more frequent with time. This complication of measles is always fatal; death occurs 1 to 3 years after diagnosis. Only after SSPE-associated death is the diagnosis definitive, with detection of characteristic brain changes and measles antibodies in the cerebrospinal fluid.

“We used to think it was quite rare,” said Dr. Cherry. A prior study indicated a rate of one for every 1700 measles infections among children less than 5 years of age. Not only is the presently indicated rate much higher, but it could, in fact, be an underestimate, according to Dr. Cherry.

Many patients in the California outbreak had been vaccinated according to the inoculation schedule. However, they had been infected by the measles virus before the first injection of the live attenuated vaccine. If coverage of the vaccinated population had been near 100%, herd immunity would have been protective. The problem was the refusal by some parents to have their children immunized. If enough children go uninoculated, and particularly if they are concentrated in the same community or school, herd immunity can be lost.

The 17 cases of SSPE that occurred from 1998 through 2015 involved children born in the US in about half of the cases, with three-quarters being ethnic minorities. Measles infection that was confirmed or suspected based on febrile illness with rash occurred in 12 children who were younger than 15 months of age, with 11 being less than 1 year old.

Because the data is retrospective, the reported rate is not an absolute number. Still, the indication that SSPE is likely more prevalent than expected and the demonstration of the vulnerability of herd immunity are sobering.
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