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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Adverse Reactions to Antibiotics in Patients Receiving Outpatient Parenteral Antimicrobial Therapy

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Approximately one-fifth of outpatient parenteral antimicrobial therapy recipients developed a clinically significant antimicrobial-related adverse drug event.

SOURCE: Keller SC, Williams D, Gavgani M, et al. Rates of and risk factors for adverse drug events in outpatient parenteral antimicrobial therapy. *Clin Infect Dis* 2018;66:11-19.

Keller and colleagues addressed the issue of adverse drug-related events (ADE) that occurred in 339 adults discharged on outpatient antimicrobial therapy (OPAT) from one of two tertiary care academic medical centers in Baltimore. All the patients had peripherally inserted central venous catheters and all had assistance from a home health agency. Most cases were managed by an infectious disease specialist. The primary outcome measure was clinician-documented clinically significant ADEs — ones resulting in hospital admission, a change in the antimicrobial administered, antimicrobial discontinuation, or the development of *Clostridium difficile* infection (CDI).

Clinically significant ADEs occurred in 49 (14.5%) patients, at an incidence of 2.24/1,000 patient-days. Independent risk factors for the occurrence of clinically significant ADEs were female gender and receipt of vancomycin or daptomycin, while both uncomplicated bacteremia and empiric (as opposed

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to targeted) therapy were associated with lower incidences of ADEs.

Sixty-one (18%) vancomycin recipients suffered an ADE, 19 (21.3%) of which were clinically important; 11 (18.0%) experienced nephrotoxicity. Three (37.5%) of eight daptomycin recipients developed elevated serum creatine kinase levels. No ceftriaxone recipient suffered a significant ADE. The incidence of ADE was highest in the first two weeks of OPAT.

■ COMMENTARY

This study found that approximately one in every five patients undergoing OPAT will suffer an ADE, a result not greatly different from that reported in inpatients. Thus, in a study of hospitalized patients at one of the institutions included in the analysis by Keller and colleagues, 298 (20%) of 1,488 experienced at least one antimicrobial-associated ADE, most frequently gastrointestinal, renal, and hematologic.[1] There was a 3% increased risk of ADE for each additional 10 days of antimicrobial therapy. The incidence of identified CDI (0.47%) was even less than that reported by Keller et al (1.5%) — but both seem remarkably low.

It is important to acknowledge that this OPAT evaluation only examined ADEs attributed to receipt of antimicrobials. Some serious adverse events not directly related to antibiotic therapy that may occur in OPAT patients include venous thrombosis and vascular access infections, including bloodstream infections.

Safe and effective OPAT requires a systematic approach. There should be a special focus on the transition from the inpatient to the outpatient setting, a time when error frequency is likely to be greatest. In fact, Keller et al found that the frequency of ADEs was greater in the first two weeks of OPAT than in subsequent weeks.

Muldoon and colleagues have proposed an OPAT bundle with six elements: "patient selection, infectious disease (ID) consultation, patient/caregiver education, discharge planning, outpatient monitoring/tracking, OPAT program review."[2] Appropriate patient selection includes, among other things, determining that the patient's status is acceptable for management outside the acute care facility in a conducive environment with adequate support and resolution of financial aspects of care. ID consultation (or stewardship team consultation) should be performed prior to discharge and prior to placement of a central vascular catheter. The ID consultant must assess the feasibility and need for OPAT and explicitly delineate the therapeutic course as well as the necessary laboratory and clinical monitoring. The use of checklists can be a very important element of a successful OPAT program.[3]

The OPAT program must provide an individual responsible for monitoring visit adherence and laboratory results. The plan must be documented and accessible and the patient/family/caregiver appropriately educated regarding their responsibilities.

Finally, it is critical that the process, outcomes, adverse events, and patient satisfaction be audited on an ongoing basis. All of this requires a comprehensive structure and dedicated personnel, and, thus, must have the support of the institution's administration. One solution is the provision of a clinical pharmacist or advanced practitioner to provide day-to-day oversight.

Many patients receiving OPAT do not require parenteral antibiotic administration and, in fact, some do not require any antibiotic therapy. Others can be treated with oral antibiotics alone. Furthermore, the role of the long half-life drugs dalbavancin and oritavancin may need to be taken into consideration. ■

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ABSTRACT & COMMENTARY

Letermovir Prophylaxis Is Effective in Preventing Cytomegalovirus Infection After Hematopoietic Stem Cell Transplantation

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

Associate Professor of Internal Medicine, Northeast Ohio Medical University; Division of Infectious Diseases, Cleveland Clinic Akron General, Akron, OH

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

SYNOPSIS: A Phase III, randomized, double-blind, placebo-controlled superiority trial that included patients 18 years of age or older undergoing allogeneic hematopoietic stem cell transplantation found that prophylaxis with letermovir resulted in significantly lower risk for cytomegalovirus infection in the first 24 weeks than placebo. Safety and adverse events were similar between letermovir and placebo.

SOURCE: Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med* 2017;377:2433-2444.

Reactivation of cytomegalovirus (CMV) is a major complication following hematopoietic stem cell transplantation (HSCT), especially in CMV-seropositive recipients. Prophylaxis options after HSCT are limited due to the myelosuppression that occurs with available antiviral agents (i.e., ganciclovir and valganciclovir). Marty and colleagues evaluated the safety and efficacy of letermovir, a recently FDA-approved inhibitor of the CMV-terminase complex, for CMV prophylaxis after HSCT in CMV-seropositive recipients.

The study was a Phase III, randomized, double-blind, placebo-controlled superiority trial that included patients 18 years of age or older undergoing allogeneic HSCT at 67 centers in 20 countries. Patients were eligible for inclusion if they were CMV-seropositive, had an undetectable CMV plasma DNA level within five days of randomization, and could start taking the trial drug by day 28 post-transplantation.

Exclusion criteria included severe liver or renal disease and current or recent receipt of a drug with anti-CMV activity. Asian patients were excluded briefly due to concerns related to pharmacokinetic issues, but the concerns were resolved, and these patients were included in the analysis.

The patients were randomized in a 2:1 ratio to receive letermovir or placebo through week 14 after transplantation. Letermovir was prescribed at 480 mg daily except for those patients receiving cyclosporine, whose dose of letermovir was decreased to 240 mg daily due to a drug-drug interaction. Patients were evaluated weekly through week 14 after transplantation, then every two weeks through week 24, then every other month through week 48. Plasma CMV DNA was measured at every visit.

Those who developed clinically significant CMV infection discontinued the trial regimen and began anti-CMV therapy according to local practice. The primary endpoint was the proportion of patients with clinically significant CMV infection through week 24 after transplantation among patients without detectable CMV DNA at randomization. The secondary endpoints were the proportion of patients with clinically significant CMV infection through week 14 and the time to clinically significant CMV infection.

Of the 570 patients who underwent randomization, 295 of those assigned to receive letermovir and 136 of those assigned to receive placebo completed the trial to week 24. Patients began either letermovir or placebo a median of nine days (range, 0 to 28 days) following HSCT. Fewer patients in the letermovir group compared to the placebo group developed a clinically significant CMV infection in the first 24 weeks after transplantation (37.5% vs. 60.6%, respectively; $P < 0.001$). Regarding the secondary endpoints, significantly fewer patients developed a CMV infection by week 14 in the letermovir group compared to the placebo group (19.1% vs. 50.0%, respectively; $P < 0.001$).

Starting around week 18, the incidence of CMV infection began to increase in the patients receiving

letermovir, likely as a result of graft vs. host disease (GVHD) and/or steroid use. All-cause mortality at 24 weeks after transplantation was lower in the letermovir recipients compared to the placebo group (10.2% [95% confidence interval {CI}, 6.8-13.6] vs. 15.9% [95% CI, 10.2-21.6]; $P = 0.03$). At 48 weeks, all-cause mortality was 20.9% (95% CI, 16.2-25.6) in the letermovir group and 25.5% (95% CI, 18.6-32.5) in the placebo group ($P = 0.12$).

Adverse reactions were similar between the letermovir and placebo groups, with vomiting (18.5% vs. 13.5%, respectively), edema (14.5% vs. 9.4%, respectively), dyspnea (8.0% vs. 3.1%, respectively), myalgias (5.1% vs. 1.6%, respectively), atrial fibrillation (4.6% vs. 1.0%, respectively), and acute kidney injury (9.7% vs. 13.0%, respectively) being the most common. One patient who received letermovir had breakthrough viremia. Genotyping revealed the UL56 V236M mutation, which is known to confer letermovir resistance. Finally, the mortality benefit from letermovir was more pronounced for high-risk patients, which included those with GVHD, mismatched donor HLA gene loci, use of umbilical cord blood as the stem cell source, and the use of ex vivo T-cell-depleted grafts.

■ COMMENTARY

Because of the unacceptably high rate of myelosuppression with antiviral prophylaxis, clinicians instead employ a preemptive strategy following HSCT in which there is active surveillance for CMV in the blood. When the virus is detected, antiviral therapy is begun. The study by Marty et al is important because it reopens the possibility of using an antiviral agent for CMV prophylaxis after HSCT. Only one patient developed breakthrough viremia while on letermovir, which was due to a UL56 mutation. Previous studies have shown that these CMV mutants remain susceptible to other antivirals, including ganciclovir.

Overall, letermovir appears to be safe, and the absence of myelotoxic effects allows for the initiation of prophylaxis before engraftment. The lack of nephrotoxicity with letermovir also was a welcome finding, given the complex medication regimens HSCT recipients receive, which carry the potential for a multitude of drug-drug interactions. Data on the use of letermovir to treat active CMV disease currently are limited to case reports and one small trial. This is an area that needs further investigation.

The impressive study by Marty et al represents the culmination of a decade-long effort to produce a safe and effective drug that prevents CMV infection after HSCT. Importantly, future pharmacoeconomic studies are needed to determine the cost vs. benefit ratio between prophylaxis with letermovir and our current preemptive strategy. Ongoing surveillance for letermovir-resistant strains, particularly those with the UL56 mutation, will be needed as the drug becomes more widely used in clinical practice. ■

ABSTRACT & COMMENTARY

Pneumococcus, Sickle Cell Disease, Vaccination, and Penicillin

By Philip R. Fischer, MD, DTM&H

Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN

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

SYNOPSIS: Even in the era of newborn screening, pneumococcal vaccination, and penicillin prophylaxis, children with sickle cell disease continue to be at risk of morbidity and mortality from invasive pneumococcal disease, mostly from non-vaccine serotypes.

SOURCE: Oligbu G, Collins S, Sheppard, et al. Risk of invasive pneumococcal disease in children with sickle cell disease in England: A national observational cohort study, 2010-2015. *Arch Dis Child* 2017 Dec. 27. doi:10.1136/archdischild-2017-313611. [Epub ahead of print].

Sickle cell disease is associated with vaso-occlusion and functional asplenia with negatively altered antibody production, poor opsonization, and decreased phagocytosis. This leads to increased susceptibility to infection with encapsulated bacteria, including pneumococcus. Without special protective intervention, children with sickle cell disease, as compared to healthy peers, have a 600-fold increased risk of invasive pneumococcal disease. Use of pneumococcal polysaccharide vaccines led

to reduced but still significant risk. The advent of a 7-valent pneumococcal conjugate vaccine further reduced the risk of invasive pneumococcal disease in children with sickle cell disease in the United States. Subsequently, a 13-valent pneumococcal conjugate vaccine was used in an effort to prevent pneumococcal disease more successfully. The authors reviewed outcomes of children identified by newborn screening to have sickle cell disease during the era of the 13-valent vaccine to determine current risks of invasive disease.

Annual birth cohorts of children born between September 2010 and August 2014 who developed illness associated with pneumococci identified in a normally sterile site (such as blood, spinal fluid, and pleural fluid) were evaluated. There were 881 cases of invasive pneumococcal disease, and 12 of those children had sickle cell disease (11 with homozygous hemoglobin SS [HbSS], one with combined heterozygous hemoglobin SC [HbSC]).

Each of the 11 HbSS children had received appropriate 13-valent pneumococcal vaccine, but only one of the two who became ill after 24 months of age had received the recommended 23-valent polysaccharide pneumococcal vaccine around the time of the second birthday. Three of the 11 children (27%), two who had been born prematurely, died. Serogroup 15 was implicated most commonly, including each fatal case and eight of 11 cases overall. One child had a vaccine strain of illness but was only 3 months old at the time of the infection, and so had only received one vaccine dose. The child with HbSC was infected with a non-vaccine strain (33F) in the second year of life and recovered from the infection.

With good data about the number of children born in England during the study and the number who screened positive for sickle cell disease, the authors could calculate relative risks. The risk in the overall birth cohort was 32 per 100,000 children compared with 1,571 per 100,000 children with HbSS. (The risk was 329 per 100,000 for those with HbSC.)

The 49-fold increase in risk of invasive pneumococcal disease in the era of screening, prophylaxis, and vaccination was still less than the 600-fold risk without protective interventions. Of note, the only child with infection by a pneumococcal serotype included in the 13-valent vaccine had been only partially immunized due to young age. It is concerning that three of the 11 infected children with HbSS died even though their infections were with penicillin-sensitive germs.

The authors highlight the importance of strict adherence to penicillin prophylaxis starting by 3 months of age in children with sickle cell disease. This is essential since most of the remaining cases of invasive pneumococcal disease are by pneumococcal strains not included in the current conjugate vaccines.

■ COMMENTARY

The seminal study about the value of penicillin prophylaxis for children with sickle cell disease was published in the *New England Journal of Medicine* in 1986.[1] Two-hundred fifteen children younger than 3 years of age were randomized to receive penicillin V potassium (125 mg by mouth twice daily) or placebo. After about 15 months of follow-up, the study was terminated early when preliminary analysis revealed an 84% reduction in pneumococcal sepsis in penicillin-treated children (13 of 110 untreated children developed sepsis [with three deaths] vs. two of 105 treated children [with no deaths]).[1] Based on that study and as advised by the authors, newborn screening for sickle cell disease became standard in the United States, and penicillin prophylaxis by 4 months of age through at least 3 years of age was implemented for children with sickle cell disease.

Beginning in 2000, 7-valent pneumococcal conjugate vaccines became available for infants in the United States, and the 13-valent conjugate vaccines became available a decade later.[2] The 23-valent polysaccharide vaccine still was given at 2 years of age.[2] A single-center study in the United States from 2000-2014 identified 11 cases of invasive pneumococcal disease (estimated 417 per 100,000 person-years, similar to the English study with 1,571 per 100,000 children over five years).[2] Interestingly, the U.S. study was similar to the English study, with all isolates being sensitive to penicillin and the vast majority (89%) due to non-vaccine strains of pneumococcus.[2] However, unlike in the United Kingdom, the majority of the U.S. children with pneumococcal disease were older than 5 years of age; this raises the question of continuing penicillin prophylaxis well beyond the fifth birthday.

While the benefits of penicillin prophylaxis are clear, the target population and duration of treatment are less certain. Everyone suggests prophylaxis for children with HbSS and even combined heterozygotic children with both sickle cell and beta thalassemia hemoglobin. In addition, some use limited data,[3,4] as compatible with Oligbu's study, to suggest prophylaxis also for children with HbSC disease. There is variation between centers regarding how long penicillin should

be used, but continuation commonly is suggested until at least 5 years of age.[3,4,5]

However, penicillin prophylaxis is not used widely in some African countries.[4] A mathematical modeling study of the cost-effectiveness of newborn screening and prophylactic interventions for children with sickle cell disease showed that it would cost only $184 for each saved year of healthy life if preventive measures were implemented in high-risk African countries.[6]

The risk of sickle cell disease varies between African countries; Nigeria and the Democratic Republic of Congo account for half of the 228,000 babies born with sickle cell disease each year in Africa.[6] By this modeling study, the mean life expectancy for African children with sickle cell disease without screening and preventive intervention is 1.7 years in rural areas and 6.7 years in urban areas.[6] With screening and preventive strategies, the life expectancy rises to about 27 years.[6]

Of course, prophylactic penicillin is not effective if it is not given. A systematic review found that prophylactic penicillin was used as prescribed only 40-44% of the time.[7] Beliefs about safety and effectiveness of the medication compromised adherence, but increased parental knowledge correlated with better adherence.[7]

Thus, the new study of invasive pneumococcal disease in patients with sickle cell disease reminds us that screening, penicillin prophylaxis, and vaccination combine to be very effective in preventing serious illness and death. However, the risk of serious infection in patients with sickle cell disease still is too high, even in resource-rich countries. Improvements depend on adherence to medical recommendations and on extending the reach of medical care to rural areas of sub-Saharan Africa. ■

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ABSTRACT & COMMENTARY

Updated Recommendations for Prevention of Hepatitis B Virus Infection

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

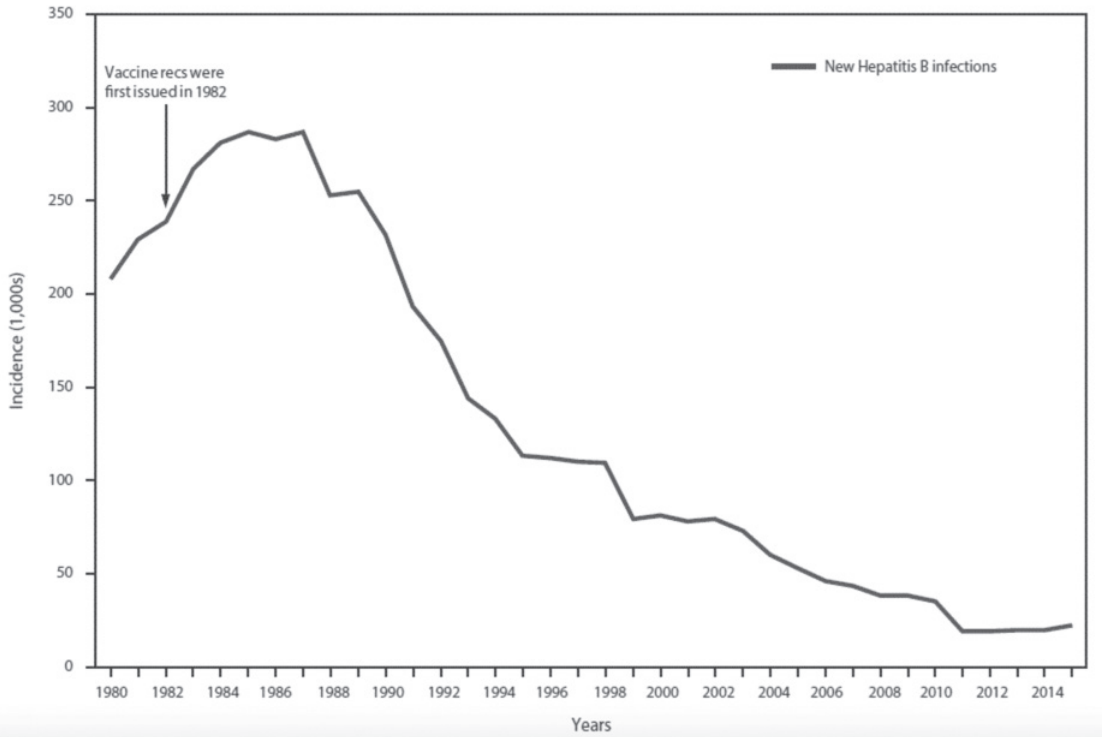
Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: New recommendations for prevention of hepatitis B virus infection focus on testing and management of newborns.

SOURCE: Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* 2018;67(No. RR-1):1–31.

As part of its commitment to eradicate hepatitis B virus (HBV) infection in the United States, the CDC has published an update of recommendations for the prevention of HBV infection by the Advisory Committee on Immunization Practices. The first two of four elements of the overall strategy have been routine HBsAg testing of all pregnant women and vaccination and hepatitis B immune globulin (HBIG) administration in the United States of all infants

Figure. Incidence of Hepatitis B Virus Infection — National Notifiable Diseases Surveillance System, 1980-2015



Source: Centers for Disease Control and Prevention

born to antigenemic mothers, as well as vaccination of all other infants shortly after birth. The third and fourth elements are vaccination of all previously unvaccinated children and adolescents, together with routine testing of at-risk adults.

The new recommendations include the following: The update now recommends that all pregnant women found to be HBsAg positive undergo testing for HBV DNA, which allows identification of infants at the greatest risk of infection.

The recommendations note evidence that antiviral therapy during pregnancy reduces the risk of transmission and point out that the American Association for the Study of Liver Diseases recommends treatment, preferably with tenofovir, of the mother if her HBV DNA level in plasma is > 200,000 IU/mL. All infants born to mothers for whom the results of testing during pregnancy are not known, but who have had prior evidence of HBV infection, should be treated as if born to antigenemic mothers.

Many of the new recommendations deal with the management of newborns and include the following. All clinically stable infants with a birth weight > 2,000 grams born to antigen-negative mothers should receive their first dose of vaccine within 24 hours of birth. Vaccinated infants born to mothers whose antigen status remains unknown should be tested for the presence of a protective anti-HBs level at 9-12 months of age. All vaccinated antigen-negative infants with anti-HBs levels < 10 IU/mL should receive another dose of vaccine and undergo repeat anti-HBs antibody testing 1-2 months later. The originating institution, upon transferring the infant to another facility, should communicate its status of vaccination and HBIG receipt.

The following unvaccinated adults have been added to those previously considered at high risk of HBV infection and who should be vaccinated:
- Travelers to endemic countries with population HBsAg prevalences > 2%;
- HCV-infected individuals;
- Individuals with chronic liver disease;
- HIV-infected individuals;
- Incarcerated individuals;
- Anyone who desires vaccination, even in the absence of acknowledgement of specific risk.

All newborns weighing < 2,000 grams at birth should receive vaccine and HBIG within 12 hours of birth, regardless of knowledge of the HBsAg status of the mother. If it proves not possible to determine the mother's status, the vaccine schedule should be completed as if the mother were antigenemic. In addition, they should undergo anti-HBs at 9-12 months and, if the serum level is < 10 IU/mL, they should undergo revaccination.

■ COMMENTARY

The incidence of newly reported cases of HBV infection since vaccination was first recommended has decreased from 9.6 cases per 100,000 population in 1982 to 1.1 per 100,000 in 2015, an 85% reduction. Taking into account lack of diagnosis and under-reporting, it is estimated that there were 21,900 new cases in 2015. Despite the overall decrease, there was a 114% increase in 2009-2013 in combined data from Kentucky, Tennessee, and West Virginia, which has been attributed to increasing injection drug use. In contrast to acute infections, 95% of chronic HBV infections occur in those who are foreign-born, approximately 3.5% of whom are infected. Thus, while there has been remarkable progress toward the elimination of HBV infection in the United States, much remains to be done. ■

ABSTRACT & COMMENTARY

REPROVE: Ceftazidime-avibactam vs. Meropenem in Hospital-acquired Pneumonia

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Ceftazidime-avibactam therapy was non-inferior to meropenem treatment in a double-blind, randomized trial that included patients with nosocomial pneumonia, including those with ventilator-associated pneumonia.

SOURCE: Torres A, Zhong N, Pachl J, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): A randomised, double-blind, phase 3 non-inferiority trial. *Lancet Infect Dis* 2017 Dec 15. pii: S1473-3099(17)30747-8. doi: 10.1016/S1473-3099(17)30747-8. [Epub ahead of print].

In the double-blind non-inferiority REPROVE study, 879 patients with hospital-acquired pneumonia at 136 hospitals in 23 countries were randomized to treatment with either ceftazidime-avibactam (CAv) or meropenem. CAv (2,000 mg/500 mg) was infused over two hours, while meropenem (1,000 mg) was infused over 30 minutes. Each was administered every eight hours for 7-14 days, and dosing was adjusted for altered renal function. Randomization was stratified by presence or absence of ventilator-associated pneumonia (VAP) and by geographic region. The study had a > 85% power to reject non-inferiority with a lower margin of difference of -12.5%.

Of the patients with identified baseline pathogens (the microbiological modified intent-to-treat population) for whom a Gram-negative bacillus was found in respiratory culture, the most frequently identified were *Klebsiella pneumoniae* (37%) and *Pseudomonas aeruginosa* (30%). Among these baseline isolates, 11 (two *K. pneumoniae* and nine *P. aeruginosa*) were resistant to CAv and 37 (five *K. pneumoniae*, one *Serratia marcescens*, and 31 *P. aeruginosa*) were non-susceptible to meropenem. Ten isolates (two *K. pneumoniae* and eight *P. aeruginosa*) were resistant to both CAv and meropenem. *S. aureus* was recovered in 15%. Approximately 5% in each treatment group were bacteremic.

There was no statistically significant difference in clinical cure rates between the treatment arms in either the clinically modified intent-to-treat (ITT) or the clinically evaluable population. In the former population, clinical cure was achieved in 245 (68.6%) of 356 CAv recipients and 270 (73.0%) of 370 patients randomized to receive meropenem (difference -4.2% [95% confidence interval [CI], -10.8 to 2.5]). Clinical cure in the clinically evaluable cohort was achieved in 199 (77.4%) of 257 CAv and 211 (78.1%) of 270 meropenem recipients (difference -0.7% [95% CI, -7.9 to 6.4]). Crude mortality was low in each group at 8% and 7%, respectively.

Microbial persistence of isolates with the same genotype with a greater than fourfold increase in minimum inhibitory concentration occurred in only one pair of isolates from CAv recipients but in 11 from meropenem recipients. Seventy-five (19%) CAv recipients and 54 (13%) meropenem recipients experienced serious adverse events, with four (all in the ceftazidime group) considered treatment-related.

■ COMMENTARY

CAv initially received approval from the Food and Drug Administration in February 2015. Avibactam is a non-beta-lactam beta-lactamase inhibitor whose spectrum includes several carbapenemases, most notably KPC. The study by Torres and colleagues reviewed here demonstrates the statistical non-inferiority of CAv to meropenem therapy in patients with hospital-acquired pneumonia, including those with ventilator-associated pneumonia. However, the major deficit in this study is that meropenem was put at a disadvantage as a result of its dosing at 1 gram given over 30 minutes. It has become clear that extended duration infusion is more likely to achieve pharmacodynamic targets with this and other beta-lactam antibiotics.

A concern regarding CAv was raised last year when Shields et al reported bacteriologic failure in 10 (27%) of 37 patients with infection due to carbapenem-resistant *Enterobacteriaceae* (CRE).[1] Furthermore, in three of the 10 microbiological failures, the organism had become resistant to CAv as a consequence in blaKPC3. However, in REPROVE only one isolate became resistant to CAv. In contrast, this occurred with isolates from 11 meropenem recipients. One could speculate that this was the consequence of inadequate exposure related to 1 gram doses infused over only 30 minutes. ■

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ABSTRACT & COMMENTARY

Root Causes of Hepatitis A Outbreak in California

By Dean L. Winslow, MD, FACP, FIDSA

Professor of Medicine, Division of General Medical Disciplines, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine

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

SYNOPSIS: During 2017, a large outbreak of hepatitis A was identified in California. The majority of patients were homeless. Addressing the problem of homelessness should be a priority for our country.

SOURCE: Kushel M. Hepatitis A outbreak in California — addressing the root cause. *N Engl J Med* 2017 Dec. 6. doi: 10.1056/NEJMp1714134. [Epub ahead of print.]

In 2017, at least 649 people in California were infected with hepatitis A, 417 were hospitalized, and 21 died. This is the largest outbreak of hepatitis A in the United States in the past 20 years.[1] The vast majority of those affected have been homeless. Almost all of these patients were unsheltered.

■ COMMENTARY

This large outbreak of hepatitis A mainly is focused in homeless patients in San Diego and highlights the physical threats associated with homelessness, which sadly affects a growing proportion of Americans. The cited article discusses the problems of crowding, lack of sanitation, and lack of a safe food supply associated with individuals living in homeless encampments and shelters. These factors facilitate the initiation and perpetuation of infectious diseases such as hepatitis A.

While we commonly think of antimicrobial agents as being responsible for much of the success we have achieved in the battle against infectious diseases during the 20th and 21st centuries, the fact is that much of our progress occurred many decades before these therapies were available. In Europe, the British Isles, and North America, it was well-recognized by the middle of the 19th century that crowded living conditions, lack of access to clean food and water, poor hygiene, and lack of shelter contributed greatly to infectious disease transmission and prevalence. Accordingly, as deliberate improvements in public health came about, the prevalence of these diseases fell dramatically.

I had the good fortune of spending this past fall quarter teaching in Oxford, England. While I did see a few homeless people in the United Kingdom, homelessness does not exist there on the magnitude that it does in the United States. I honestly

believe that the reason we have such a problem of homelessness in the United States is because of both a lack of will and lack of compassion on the part of both our politicians and much of our country.

Data do not support the misconception that homeless people are lazy. It is ironic that the President was criticized roundly recently for his comments about immigrants from Africa, Haiti, and El Salvador while he welcomed immigrants from Norway. In actuality, countries like those in Scandinavia and the Netherlands have largely solved the problem of homelessness by providing housing, universal healthcare (including mental healthcare), and free education to their population. In addition, these countries have no gun violence. Somehow, I don't believe the United States will be inundated anytime soon by immigrants from Norway. We really can and should do better in the United States to care for our most vulnerable. ■

REFERENCE

1. California Department of Public Health. Hepatitis A outbreak in California: CDPH Weekly Update as of Nov. 10, 2017. Available at: https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Immunization/Hepatitis-A-Outbreak.aspx. Accessed Jan. 15, 2017.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Providers Facilitate Transmission of Resistant Organisms

SOURCE: Grabowski ME, Kang H, Wells KM, et al. Provider role in transmission of carbapenem-resistant *Enterobacteriaceae*. *Infect Control Hosp Epidemiol* 2017;38:1329-1334.

Researchers investigated the provider role in patient-to-patient transmission of carbapenem-resistant *Enterobacteriaceae* (CRE) in a hospital facility with a robust CRE surveillance program. Between 2011 and 2015, researchers conducted a case-controlled study of patients who acquired CRE during their hospitalization and those who did not. Cases had negative stool CRE surveillance within 48 hours of admission, with a subsequent positive CRE culture, and a hospital stay of at least nine days.

Controls had two or more negative stool surveillance studies with a similar length of hospital stay (LOS). Patient-provider interactions were documented per day. CRE status was documented in the electronic record, and any patient with a history of CRE was placed in contact isolation with use of gowns and gloves. Hand hygiene was actively monitored, and compliance with hand hygiene was 81%.

A total of 121 patients acquired CRE during their hospital stay during the six-year study period. Cases were admitted more commonly to the general surgery/transplant unit, intensive care unit, or burn unit. The median LOS for cases was 49 days compared with 20.5 days for controls. Cases had an average of 43 ± 8 unique documented provider interactions in one week (an average of 10.5 ± 3 per day) compared with 41 ± 8.7 for controls (an average of 9.5 ± 3 per day).

Case patients were statistically significantly more likely to be cared for by a CRE-shared provider, meaning providers caring for another patient with CRE, than controls. Case patients had an average of four more shared providers per week than controls. Controlling for age and intensive care unit stay, the odds of a case being exposed to a shared-source provider was 2.27 higher than for controls. Providers caring for a known CRE patient appear to have an active role in patient-to-patient transmission.

The Time Is Now — Stop CRKP

SOURCE: Centers for Disease Control and Prevention. Carbapenem-resistant *Klebsiella pneumoniae* associated with a long-term care facility – West Virginia, 2009-2011. *MMWR Morb Mortal Wkly Rep* 2011;60:1418-1420.

The first recognized outbreak of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) in a West Virginia acute care facility occurred in January 2011, involving 19 patients, and prompting public health involvement and field investigation. Sixteen of 19 hospitalized cases were admitted from long-term care facilities, with 14 from facility A. Cultures from 10 of these patients were obtained within less than two days of admission, suggesting patients presented to the hospital with existing CRKP infection and/or colonization.

Investigators conducted a case control study comparing the 19 cases with 38 non-CRKP-infected controls, demonstrating that, in fact, prior stay at long-term care facility A was a significant risk for CRKP. Case patients also were significantly more likely to be non-ambulatory, and to have not spent much time at home during the previous year.

Field investigation at the acute care hospital found no significant infection control deficiencies. In contrast, investigation of long-term care facility A revealed numerous deficiencies: They had no available infection control expertise, cultures were not identified as multidrug-resistant, and the laboratory used for cultures did not stipulate whether isolates were carbapenem resistant. Patients with resistant organisms were not isolated, gowns and gloves were not conveniently available, and isolation and environmental cleaning practices were generally deficient.

Point surveillance at long-term care facility A found 11/118 (9%) residents were positive for CRKP, including eight previously recognized patients.

Long-term care facilities are increasingly serving as a reservoir — to the community and to their locally serving hospitals — for increasingly drug-resistant organisms and *Clostridium difficile*. For more than two years, our local hospital has been dealing with the presence of NDM carbapenemase-producing CRE (CP-CRE), both in patients coming from India, but also with documented inter-facility transmission between the hospital and a local skilled nursing facility (SNF). As a result, the hospital staff now screen all admissions from this facility for stool colonization with CP-CRE — and every patient admitted from this facility is placed in contact isolation until their CRE stool surveillance comes back negative (much to the patients' and their families' consternation). Further, 11% of all SNF admissions to our facility are colonized with toxigenic strains of *C. difficile*, and 17% are colonized with ESBL.

Such surveillance is expensive and not reimbursed by Medicare or third parties, and is conducted solely at hospital expense in an effort to prevent inter-facility and in-hospital transmission of these pathogens. And yet, we know that stool surveillance is not sufficiently sensitive. Some patients have had active urine or bloodstream infections with negative stool surveillance. Patients with negative stool surveillance on presentation later demonstrate emergence of a resistant organism under the selective pressure of broad-spectrum antibiotics.

I chose to review this 2011 *MMWR* article simply to make a point. There needs to be a coordinated, regional approach to the emergence of these multidrug-resistant organisms in our communities and in long-term care facilities across the United States, facilitated by state and federal governments. Resources must be made available to long-term care facilities to improve their infection-control practices and to provide active surveillance of admissions to their facility so they can protect their long-term elderly residents and their local community hospitals.

Guidelines for isolation and cohorting of patients in long-term care facilities need to be developed. Many elderly patients essentially live in care facilities the last years of their lives, and permanent contact isolation is a depressing prospect; however, no systems have been developed to provide an alternative. Electronic alerts should be triggered when patients are transferred between facilities. (We've even had two CP-CRE patients and their families intentionally lie about their culture status when moving between different hospitals, even though they had been counseled and educated appropriately, because they didn't wish to be placed in isolation, much to their own risk, as well as that of others.)

Forget Zika — *this* will be the emerging infection of the decade in the United States, with anticipated high rates of mortality. If the federal government is serious about controlling hospital-associated infections, resources and expertise need to be extended in this direction to long-term care facilities, as well as hospitals. ■

ABIM CME MOC ACCREDITED

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
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CME QUESTIONS

1. Common, effective means of preventing invasive pneumococcal disease in children with sickle cell disease include:

a. use of 23-valent pneumococcal polysaccharide vaccine beginning at 2 months of age.

b. daily use of oral penicillin through age 12 years.

c. splenectomy.

d. prophylactic use of oral penicillin beginning by 3 months of age.

2. Regarding the results of the study of adverse reactions in patients receiving outpatient parenteral antibiotic therapy (OPAT) by Keller et al, which of the following is the single best correct answer?

a. Independent risk factors were female gender and receipt of daptomycin or vancomycin.

b. Approximately one-fifth of OPAT patients suffered an adverse reaction.

c. No ceftriaxone recipients developed an adverse reaction.

d. All of the above.

3. Which of the following is correct regarding letermovir and its use as prophylaxis in hematopoietic stem cell transplantation in cytomegalovirus seropositive patients?

a. Letermovir inhibits thymidine kinase.

b. When compared to placebo, letermovir prophylaxis significantly reduced the incidence of clinically significant cytomegalovirus infection in the first 24 weeks after transplantation.

c. Letermovir is associated with significantly more adverse reactions when compared to placebo.

d. Letermovir is associated with a very high risk of myelotoxicity.

CME OBJECTIVES

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

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