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Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Neuraminidase Inhibitors Reduce Hospital Length of Stay in Patients With Clinically Suspected or Laboratory-Confirmed Influenza A

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

SYNOPSIS: A meta-analysis that included more than 18,000 patients from 70 clinical centers in 36 countries found that neuraminidase inhibitors started at the beginning of hospitalization in patients with clinically suspected or laboratory-confirmed influenza A reduced the length of hospitalization by 19%.

SOURCE: Venkatesan S, Myles PR, Bolton KJ, et al. Neuraminidase inhibitors and hospital length of stay: A meta-analysis of individual participant data to determine treatment effectiveness among patients hospitalized with nonfatal 2009 pandemic influenza A(H1N1) virus infection. *J Infect Dis* 2020;22:356-366.

There is ample evidence that neuraminidase inhibitors (NAIs) reduce illness duration, complications, and mortality in patients with influenza. Venkatesan and colleagues sought to determine whether early administration of NAIs (i.e., at the beginning of hospitalization) would reduce hospital length of stay (LOS) in patients with clinically suspected or laboratory-confirmed influenza A. Reducing LOS is an important goal for lowering healthcare costs and managing hospital bed surges.

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The study was a meta-analysis conducted with data from patients hospitalized during the 2009-2010 influenza pandemic. The specific pandemic virus was influenza A (H1N1), hereafter referred to as influenza A. The primary outcome was the LOS in whole days. Patients were excluded if they received NAI therapy before admission, continued NAI therapy after discharge, had an LOS less than one day, had nosocomial influenza, or died. The study center was used as a random intercept in the mixed-effects negative binomial regression model to account for clustering. A comparator group was designated as patients with influenza who did not receive NAI therapy. Adjusted incidence rate ratios (aIRRs) were used to determine the difference in LOS in days between a treated patient and an untreated patient with similar characteristics.

There were 18,309 patients with influenza A included in the analysis who were admitted to one of the 70 study centers from 36 countries between Jan. 2, 2009 and March 14, 2011. Of these, 81.1% were laboratory confirmed and 18.9% were clinically diagnosed. Most patients (57.3%) were hospitalized for more than 48 hours from the onset of influenza symptoms. For those who received NAIs on admission, researchers observed a 19% overall reduction in LOS (aIRR, 0.81; 95% confidence interval [CI], 0.78-0.85; median decrease, 1.19 days) compared to no therapy or if therapy was started later. The association remained significant across all subgroups. Paradoxically, early NAI therapy was associated with a 28% increase in LOS in patients with chest radiograph-confirmed influenza pneumonia (aIRR, 1.28; 95% CI, 1.11-1.48). There was no difference in LOS when patients had received the influenza vaccine previously (P = 0.68) or in-hospital antibiotic therapy (P = 0.20). There was a slight increase in LOS when corticosteroids were prescribed with NAIs (aIRR, 1.17 days; 95% CI, 1.00-1.36). Early NAI therapy decreased LOS by 39% in pregnant women (aIRR, 0.61; 95% CI, 0.52-0.70) and by 27% in obese patients (aIRR, 0.73; 95% CI, 0.65-0.83).

■ COMMENTARY

The primary finding of the study, that initiation of NAI therapy at admission reduced LOS by 19%, supports the so-called "treat-at-the-door" strategy for managing patients suspected or confirmed to have seasonal influenza. The study also highlights prior evidence that NAI therapy still is beneficial when given > 48 hours after symptoms start, albeit with some reduction in effectiveness.[1] Notably, 57.3% of patients included in the study were hospitalized > 48 hours after symptom onset. It often is difficult for clinicians to ascertain when patients became symptomatic, so treating all hospitalized patients with suspected or confirmed influenza with NAIs is a pragmatic approach. Indeed, the latest Infectious Diseases Society of America guidelines on the management of influenza recommend that "persons of any age who are hospitalized with influenza, regardless of illness duration prior to hospitalization, be started on antiviral treatment as soon as possible."[2] Nausea and vomiting are not uncommon with NAIs, especially in children, although these symptoms are manageable and usually do not require discontinuation of therapy.

The researchers did not observe a reduction in LOS in children in the present study. The authors rationalized this finding by noting the study might have been underpowered in children, as well as the fact that LOS typically is shorter in children compared to adults. Furthermore, influenza often is a milder illness in children, and serious outcomes (e.g., intensive care unit admission or death) are less common than in adults.

This was a large study, especially compared to previous ones that examined outcomes in hospitalized patients with influenza. Nonetheless, there are some limitations to consider. First, by excluding patients who died, the investigators could not determine the impact of NAI therapy on the relationship between LOS and in-hospital mortality. Indeed, by removing nonsurviving patients, the investigators altered the aggregate presenting patient characteristics. Second, the attempt to ascertain early benefit vs. late benefit of NAIs was subject to time-dependent bias. Third, other influenza pandemics have been associated with longer LOS than the median LOS of five days observed in the

present study. Finally, the prevalence of pregnancy (23%) was comparably high.

The findings from the study by Venkatesan and colleagues support current guideline recommendations and, if followed widely, may lead to reduced LOS for patients hospitalized with influenza. This would result in a significant decrease in healthcare expenses and better management of bed surge that commonly occurs during influenza season. ■

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2. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza A. *Clin Infect Dis* 2019;68: 895-902.

ABSTRACT & COMMENTARY

The Safety and Effectiveness of Pyrethroid Insecticides as the Battle Against Mosquitoes Continues

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: There is a statistical association between having a urine test suggestive of exposure to pyrethroid insecticides and increased mortality over the subsequent 14 years.

SOURCE: Bao W, Liu B, Simonsen DW, Lehmler HJ. Association between exposure to pyrethroid insecticides and risk of all-cause and cause-specific mortality in the general US adult population. *JAMA Intern Med* 2019 Dec. 30. doi:101.1001/jamainternmed.2019.6019.

Pyrethroid insecticides are synthetic analogues of permethrin, a naturally occurring insecticide found in chrysanthemum flowers. The synthetic insecticides are more stable with sun exposure than permethrin is, and pyrethroids are used widely for pest control, agricultural spraying, prevention of insect infestations on pets, mosquito-bite prevention in humans, and lice treatment. Pyrethroid use is widespread in the United States and, in the era when organophosphates have been deemed dangerous, increasingly used.

Once inhaled or ingested (or absorbed through the skin, although not much gets into the body this way), pyrethroids are metabolized and excreted in the urine. Although pyrethroids generally are considered to be nontoxic in mammals, chronic pyrethroid exposure has been postulated to relate to chronic diseases, including heart disease and diabetes.

Thus, to better determine the actual relationship between pyrethroid exposure and mortality, Bao and colleagues used data from the National Health and Nutrition Examination Survey (NHANES) to evaluate links between urinary levels of a pyrethroid metabolite, 3-phenoxybenzoic acid (3-PBA), and subsequent death rates. The subject sample used in the study is representative of the adult United States population. A total of 2,116 individuals aged 20+ years (mean age 43 years) were tested for urine 3-PBA during the years 1999 to 2002. Researchers then reviewed mortality data at the end of 2015, giving about 14 years of follow-up.

There were 246 deaths in the study cohort: 41 associated with cardiovascular disease and 52 with cancer. Higher levels of 3-PBA were associated with higher rates of death (8.5%, 10.2%, and 11.9% in the lowest, middle, and highest tertiles of 3-PBA levels). Controlling for all relevant factors, 3-PBA levels were associated with all-cause mortality and coronary vascular disease mortality, but not with cancer mortality.

The authors wisely noted some limitations to the study. First, single urine tests of pyrethroid metabolites might not be indicative of total chronic exposures over time. Second, 3-PBA can be ingested from the environment, without indicating actual exposure to or contact with the original pre-metabolism pyrethroid compounds. Third, only

one metabolite was measured, and this might not be relevant to exposure to different pyrethroids used in different regions of the world. Finally, the pyrethroid exposure measured by 3-PBA might merely have been a marker of concurrent exposure to other toxic insecticides and pesticides without the pyrethroid compound actually being responsible for the identified risk.

■ COMMENTARY

Pyrethroid insecticides are used widely and can be considered to be ubiquitous in the United States. Exposure is not easily avoided.[1] In fact, pyrethroids can be credited with a low risk of West Nile virus and other arthropod-transmitted infections in many urban areas. Before dropping pyrethroids from our armamentarium against West Nile, Zika, dengue, chikungunya, and malaria, we should realize that these new data are preliminary still and, as the authors suggested, in need of replication in other studies.

As detailed by Timothy Winegard in the 2019 book *The Mosquito*, mosquitoes have been responsible for the outcomes of many key battles in human history, for the rise and fall of empires and civilizations, and for the shortened lives of leaders, including Alexander the Great.[2] Even around the time of the founding of the United States, mosquito-borne illnesses caused lethal outbreaks in North America. Still, despite medical and public health advances, malaria kills nearly half a million children each year, mostly in sub-Saharan Africa. Controlling mosquitoes and mosquito-transmitted illnesses still is important.

From 2000 to 2016, 61 different epidemiologic studies evaluated health outcomes as compared to pyrethroid exposures.[3] Unfortunately, none of those studies was uniformly strong, and clear cause-effect relationships between pyrethroid exposure and adverse human health outcomes have not been proven.[3] Helpful lay literature is available to counsel people concerned about pyrethroid safety.[4]

Pyrethroids continue to be a key weapon — if an imperfect one — against mosquitoes. However, the battle rages. Mosquitoes are becoming increasingly resistant to pyrethroids. At least in parts of West Africa, *Anopheles* mosquitoes increasingly express a sensory appendage protein (SAP2) that makes them resistant to the effects of pyrethroids.[5] The expression of this protein increases with exposure to pyrethroids.[5]

With concerns spreading for pyrethroid resistance among malaria-transmitting mosquitoes, bednets impregnated with pyrethroids have become less effective since 2015.[6] Host-seeking mosquitoes tend to fly and swoop from above the torso of the potential host.[6] Using added barriers (even including organophosphates) above bednets would provide additional insecticidal activity while keeping the more toxic barrier chemicals beyond the reach of the people (especially children) under the nets.[6] These combined "barrier bednets" have been shown to be effective in Burkina Faso.[6]

Another option is to add a pyrethroid synergist to bednets to make them more effective when mosquitoes develop resistance to pyrethroids. One such synergistic agent is piperonyl butoxide, which inhibits the metabolic enzymes in the cytochrome P450 pathway that detoxify pyrethroids. In Cote d'Ivoire, bednets impregnated with both piperonyl butoxide and a pyrethroid were approximately twice as effective in killing *Anopheles* mosquitoes as a standard pyrethroid-impregnated net.[7]

Thus, malaria and other mosquito-transmitted infections continue to plague humans in many parts of the world. Pyrethroid insecticides have been very helpful in reducing morbidity and mortality from mosquito-borne illnesses, but pyrethroid resistance among mosquitoes is increasing, and legitimate though unproven concerns exist that pyrethroid exposure might increase the risk of human heart disease. Barriers added to conventional pyrethroid-impregnated bednets and combinations of pyrethroids and synergistic agents on bednets might help extend the ability of bednets to protect against malaria. ■

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ABSTRACT & COMMENTARY

Candida auris Resistant to Azole Antifungals, Amphotericin B, and Echinocandins

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Infection with *Candida auris* resistant to azole antifungals, amphotericin B, and echinocandins was identified in three patients in New York. Resistance to echinocandins was first detected after the patients had received an echinocandin as treatment.

SOURCE: Ostrowsky B, Greenko J, Adams E, et al; *C. auris* Investigation Work Group. *Candida auris* isolates resistant to three classes of antifungal medications – New York, 2019. *MMWR Morb Mortal Wkly Rep* 2020;69:6-9.

Between 2016, when *Candida auris* was first identified in New York state, and June 28, 2019, 349 patients had clinical cultures positive for the organism, while an additional 452 were positive on screening swabs of skin or nares. Of the first 277 isolates, 276 (99.6%) were resistant to fluconazole and 170 (61.3%) were resistant to amphotericin B, while none were resistant to echinocandins. Testing of 331 subsequent isolates found that 330 (99.7%) and 210 (63.4%) were resistant to fluconazole and amphotericin B, respectively, while resistance to echinocandins has emerged, found to be present in 13 (3.9%). Testing of further isolates found three that were resistant to all three classes of antifungals.

The first two patients identified as being infected with pan-resistant *C. auris* were ventilator-dependent, had multiple comorbidities, and were residents of long-term care facilities. Fluconazole- and amphotericin-resistant isolates (blood, urine, and intravenous catheter tip in one; urine and tracheal aspirate in the other) were found to be echinocandin-resistant also after this class of agents was used for treatment. Both patients died, but the contribution of *C. auris* infection to these outcomes was uncertain.

A subsequent retrospective review identified a third patient with multiple comorbidities and prolonged acute care and long-term care with pan-resistant *C. auris* bloodstream infection. As with the other two cases, resistance to echinocandins only became apparent after treatment with one of this class of antifungals. All three cases were epidemiologically unrelated.

■ COMMENTARY

C. auris was first identified after its recovery from the ear canal of a patient in Japan in 2009 and now has been reported from five continents. Concern regarding this organism is the result of its resistance to several antifungal agents and its association with hospital infection outbreaks. The latter may be, at least in part, the result of its ability to persist in the environment and its resistance to some antiseptic agents.

New York is not a stranger to *C. auris*. Almost one-half of the 911 *C. auris* clinical cases reported to the Centers for Disease Control and Prevention as of October 2019 were from New York state and, as of June 28, 2019, 801 patients either infected or colonized by this organism had been identified. As described here, three of the 801 had infections that were due to pan-resistant strains. Although the strains initially were resistant to fluconazole and amphotericin B, in each case the emergence of resistance to echinocandins (making the strains pan-resistant) occurred only after treatment with an echinocandin.

Because of the frequent resistance to both azole antifungals and amphotericin B, echinocandins have been considered the treatment of choice most often. However, reduced susceptibility to this class of antifungals has become increasingly encountered and, in fact, isolates resistant to all three of these classes have been reported previously elsewhere in the world.

C. auris previously has been misidentified often as *Candida haemulonii*, to which it is related — as it is to *Candida lusitaniae*, an organism often resistant to amphotericin B. Like *Saccharomyces* and *Candida glabrata*, and in contrast to *Candida albicans*, *C. auris* is haploid, a feature that may make resistance more likely to develop since mutation is required in only a single DNA strand. ■

ABSTRACT & COMMENTARY

Temperature Trajectories to Find Sepsis Subphenotypes

By Vibhu Sharma, MD

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

SYNOPSIS: The authors of this study used development and validation cohorts to retrospectively identify temperature trajectories over the first 72 hours from presentation in the setting of sepsis. Patients presenting with hyperthermia that resolved quickly (within the first 24 hours) had lower mortality compared to those with slow resolution or those presenting with hypothermia.

SOURCE: Bhavani SV, Carey KA, Gilbert ER, et al. Identifying novel sepsis subphenotypes using temperature trajectories. *Am J Respir Crit Care Med* 2019;200:327-335.

The authors of this study attempted to identify subphenotypes of sepsis based on the presenting temperature in the emergency department (ED) and the subsequent trajectory of the temperature curve over 72 hours. Patients with sepsis were selected if a blood culture order had been placed and intravenous antibiotics administered within 24 hours of presentation to the ED, defined as the time of first vital signs. Group-based trajectory modeling was used in the development cohort to assign groups based on temperature trajectories within the first 72 hours of data. Group-based trajectory modeling allows for the assessment of individual temperature patterns over time and then assigns individuals to the trajectory group with the highest membership probability. The statistical output computes groupings based on the temperature curve over time as well as individual probabilities of belonging to a specific group. Mean, maximal, and minimal temperatures were computed as well. Temperature measurements were standardized based on mean and standard deviation measurements to enable comparisons. Logistic regression was performed, with temperature trajectory grouping being the predictor variable and mortality being the outcome variable. A fever ("hyperthermia") was defined as a temperature of > 38°C and hypothermia was defined as a temperature below 36°C.

The authors identified four different subphenotypes in the development cohort based on body temperature trajectory: 1) hyperthermic, slow resolvers (HSR); 2) hyperthermic, fast resolvers (HFR); 3) normothermic (NT); and 4) hypothermic (H). Members assigned to the HSR group presented with a fever and had no substantial change in temperature over the first 24 hours. This group also had the highest mean, maximal, and minimal temperatures during the first 72 hours. Those assigned to the HFR group presented with hyperthermia and were more likely to have their temperatures drop close to normal within the first 24 hours. Individuals assigned to the NT group remained so during the 72 hours of observation, whereas individuals assigned to the H, or hypothermic, group presented with hypothermia and stayed hypothermic for the 72-hour observation period. The temperature curves for both the development cohort and the validation cohort were remarkably similar.

The authors discovered significant mortality differences among the four groups. Logistic regression in the validation cohort revealed higher odds of mortality among those in the HSR (odds ratio [OR], 2.15; 95% confidence interval [CI], 1.77-2.61) and H (OR, 1.68; 95% CI, 1.44-1.96) groups compared to those more likely to fall in the NT group. Membership in the HFR group was protective (OR, 0.55; 95% CI, 0.44-0.68). Fever was more common in survivors, and temperature variability was higher in non-survivors compared with survivors. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were higher in the hyperthermic groups, as were the proportion of patients with leukocytosis, attesting to immune upregulation in the hyperthermic groups. Within the hyperthermic groups, ESR and CRP, as well as the proportion of patients with leukocytosis, were higher in the HSR group compared to the HFR group. Hypothermic patients had the lowest ESR and CRP levels and the highest lactate and creatinine of the four groups. Furthermore, the hypothermic group had the highest proportion of patients requiring vasopressors (8.4%) and were the most likely to be exposed to either prednisone or methylprednisolone.

■ COMMENTARY

This is an interesting study that allows for consideration of temperature trajectories over time to be used to predict septic patients who may do poorly. The strength of this study lies in the large number of patients in both the development cohort and the validation cohort, as well as a tight correlation of temperature resolution curves over 72 hours in each cohort (derivation and validation) described.

The statistical technique applied to both the development and validation cohorts assigns a probability of membership of the individuals' temperature trends to a certain group and, therefore, is not a comparison of groups. With this in mind, this study drives home the importance of assessment of a trend and not an individual temperature. For example, transient hypothermia (temperature < 36°C) was fairly common in the development cohort; 81% of patients developed one episode during the observed 72 hours. The cohorts included all patients admitted to two different institutions. While a separate cohort of critically ill patients is not identified, the analysis controlled for severity of illness and, therefore, incorporates those admitted directly to the intensive care unit (ICU) from the ED. However, the results of this study cannot be applied to patients admitted to the ICU from the floor, for example. In an attempt to homogenize populations, the authors of the study incorporated only those patients presenting to and being treated for an infection in the ED. Within this framework, patients more likely to be in the HFR group had the least exposure to vasopressors and lower mortality compared to those more likely to be in the hypothermic trajectory group, which had the highest exposure to vasopressors and higher mortality.

Recent literature has begun to assess the utility of signs assessed on physical examination of critically ill patients. For example, the authors of one study found that a fluid resuscitation strategy that targeted normalization of capillary refill time (CRT) was non-inferior to a strategy that used a lactate-driven strategy and even may have been better among those with lower severity of illness scores.[1] The Simple Intensive Care Studies-I (SICS-I) group investigators focused on the predictive value of clinical signs acquired within the first 24 hours of ICU admission with respect to outcomes.[2] Prolonged CRT and low peripheral temperature may predict the development of acute kidney injury (AKI).[2] A particular combination of physical findings, including low central temperature, reduced urine output, and higher respiratory rate, may predict mortality as well as the APACHE score.[3]

The one question that the study reviewed here does not address is how temperature trajectory correlates and/or clusters with other parameters commonly assessed in tandem, such as blood pressure, respiratory rate, oxygenation indices, and possibly urine output trends over time. Based on the results of this study, it appears reasonable to investigate more aggressively those hyperthermic patients who fail to defervesce (i.e., those who could be in the HSR group) in the first 24 hours and look for persistent sources of infection when a source is apparent (e.g., pneumonia leading to meningitis or endocarditis). Similarly, patients who present with hypothermia and continue to be hypothermic over the course of hospital admission require aggressive evaluation given the increased odds of mortality. Further studies to assess how temperature trajectory interacts with the trajectory of other vital signs may allow for further subphenotyping of patients presenting with sepsis. ■

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PHARMACOLOGY UPDATE

Cefiderocol (Fetroja)

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

Cefiderocol is a novel siderophore cephalosporin with activity against several clinically relevant aerobic gram-negative bacteria, including carbapenem-resistant strains expressing serine- and

metallo-β-lactamases. Cefiderocol received expedited approval by the Food and Drug Administration (FDA) in November 2019 for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis in adults with limited or no treatment options.[1]

Cefiderocol exerts an effect on cell wall synthesis through inhibition of penicillin binding proteins. Unlike earlier cephalosporins, cefiderocol's siderophore moiety at C-3 complexes with ferric iron in the host and then is actively transported into the periplasmic space via iron transporters on the outer cell membrane of bacteria.[2,3] This "Trojan horse" approach makes cefiderocol less susceptible to upregulation of efflux pumps and porin channel mutations.

MICROBIOLOGY

Cefiderocol has demonstrated clinical efficacy and in vitro activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* complex.[1] Additionally, in vitro activity has been demonstrated in multinational surveillance studies for several gram-negative clinical isolates, including carbapenem-resistant strains. Among carbapenem-nonsusceptible strains of *Enterobacteriaceae*, *P. aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*, cefiderocol had a greater susceptibility ratio relative to ceftazidime-avibactam, ceftolozane-tazobactam, colistin, and ciprofloxacin.[2,4,5] The FDA susceptibility breakpoint for cefiderocol is ≤ 2 mcg/mL and ≤ 1 mcg/mL for *Enterobacteriaceae* and *P. aeruginosa*, respectively.[6] Cefiderocol does not have activity against gram-positive organisms.

PHARMACOKINETICS/PHARMACODYNAMICS

The pharmacodynamic parameter most closely associated with bactericidal efficacy for cefiderocol is the fraction of the dosing interval during which the free drug concentration exceeds the minimum inhibitory concentration (MIC) (%fT>MIC). In vivo murine thigh and lung infection models demonstrated a bactericidal effect (i.e., ≥ 1 log10 reduction) at roughly 55% to 88% fT>MIC.[7] In multiple rat lung infection models, prolonging the infusion time from one hour to three hours resulted in greater efficacy. Additionally, neutropenic murine thigh infection models meant to simulate humanized exposures of cefiderocol demonstrated consistent reductions in bacterial density for most of the pathogens tested (i.e., *K. pneumoniae*, *E. coli*, *P. aeruginosa*, and *A. baumannii*) with MICs ≤ 4 mcg/mL.[7]

Data regarding the pharmacokinetics, safety, and tolerability of cefiderocol are available from Phase I single- and multiple-dose studies in healthy volunteers and those with renal impairment. Additionally, data from patients with cUTIs with or without pyelonephritis or acute uncomplicated pyelonephritis also are available from licensing studies. Plasma and urine concentration data from subjects enrolled in Phase I studies were used to design a three-compartment model used to predict a target of 75% fT>MIC. A dose of 2 grams administered every eight hours (as either a one-hour or three-hour infusion) achieved the target in greater than 90% of patients for MICs ≤ 4 mcg/mL.[7] In patients with renal impairment, dose adjustments were designed to simulate an area under the curve similar to that achieved with standard dosing in healthy volunteers. Cefiderocol is the first antibiotic to have FDA-approved dosing recommendations for patients with augmented renal clearance.[1]

CLINICAL DATA

Cefiderocol was designated a Qualified Infectious Disease Product and approved by the FDA based on results of a multinational, noninferiority, double-blinded, randomized controlled trial in hospitalized adult patients with cUTI, with or without pyelonephritis or acute uncomplicated pyelonephritis.[8] Patients were randomized to receive cefiderocol 2 g IV every eight hours (n = 300) or imipenem/cilastatin 1 g/1 g IV every eight hours (n = 148) for a period of seven to 14 days. The study protocol allowed for inclusion of immunocompromised patients, including renal transplant recipients, and excluded patients with carbapenem-resistant isolates. Cefiderocol demonstrated noninferiority against imipenem/cilastatin for the composite endpoint of microbiological eradication and clinical cure in the microbiological intent-to-treat population at test of cure (73% vs. 55%; $P = 0.004$).

Cefiderocol also was evaluated against meropenem for treatment of nosocomial pneumonia (i.e., hospital-acquired pneumonia [HAP], ventilator-associated pneumonia [VAP], or healthcare-associated pneumonia [HCAP]) in a Phase III, multinational, noninferiority, double-blinded, randomized controlled trial.[9,10] Patients were randomized to receive either cefiderocol 2 g IV every eight hours (n = 148) or meropenem 2 g IV every eight hours (n = 150) for a period of seven to 14 days. At baseline, 59.7% of patients were ventilated, 32.6% had failure of prior antibiotic therapy, and 6.0% had concomitant gram-negative bacteremia. Cefiderocol demonstrated noninferiority against meropenem with respect to the primary outcome of 14-day all-cause mortality in the modified intention-to-treat population (12.4% vs. 11.6%, respectively).

In Europe, The European Medicines Agency allowed the manufacturer to move forward with a pathogen-focused, multinational, descriptive, open-label, randomized controlled trial in adult patients infected with carbapenem-resistant gram-negative organisms (n = 150).[11] The study evaluated outcomes in patients receiving cefiderocol 2 g IV every eight hours (n = 101) or best available therapy (BAT) (n = 49) for a total treatment duration of up to 21 days. BAT was at the discretion of the treating provider and could include one, two, or three antibiotics used together. In contrast, cefiderocol-treated patients were allowed only one additional gram-negative antibiotic as adjunctive therapy (except for patients with cUTI, who received cefiderocol monotherapy). Given the unique trial design, patients with nosocomial pneumonia (i.e., HAP, VAP, HCAP), bloodstream infection and/or sepsis, and cUTI were enrolled. The most common baseline pathogens in both treatment groups included *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa*. Although cefiderocol had similar rates of clinical cure, there was an increased rate of mortality noted in patients receiving cefiderocol at multiple timepoints.

The manufacturer concluded that in patients with adverse events leading to death, the difference between groups was driven by infections and infestations, representing the progression of or worsening of infection. Mortality appeared to be driven primarily by patients in the nosocomial pneumonia subgroup (n = 67) and bloodstream infection/sepsis. Compared to the Phase III trial in patients with nosocomial pneumonia mentioned previously, patients in this study had a higher rate of infections with *A. baumannii* (55.2% vs. 16%) and a higher rate of treatment failure prior to randomization (64% vs. 33%). Although cefiderocol currently is approved by the FDA for management of cUTI, results of this study prompted language in the prescribing information regarding an increase in all-cause mortality in patients with carbapenem-resistant gram-negative bacterial infections.

CONCLUSION

Cefiderocol is a novel siderophore cephalosporin with a wide spectrum of activity against difficult-to-treat gram-negative organisms for which there currently are limited treatment options. Although targeted antibiotics have been developed in recent years for *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Enterobacteriaceae* (e.g., ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam, etc.), there are limited treatment options for infections due to carbapenem-resistant organisms expressing Ambler Class B carbapenemases (i.e., NDM, IMP, VIM). Existing antibiotics with in vitro activity against NDM-producing gram-negative organisms have variable in vitro activity, pharmacokinetic limitations, and concerns regarding tolerability and toxicity. Additionally, novel beta-lactam/beta-lactamase inhibitors do not have activity against Ambler Class D (e.g., OXA-23) producing *Acinetobacter*. Given the mortality imbalance noted in a pathogen-focused study in Europe, however, the role of cefiderocol in clinical practice will require further exploration with a critical appraisal of real-world outcomes. ■

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By Carol A. Kemper, MD, FACP

Step-Wise Interventions for Hospital-Onset *Clostridioides difficile*

SOURCE: Rohde JM, Jones K, Padron N, et al. A tiered approach for preventing *Clostridioides difficile* infection. *Ann Intern Med* 2019;171(Suppl 7):S45- S52.

Clostridium difficile, also known as *Clostridioides difficile*, infection (CDI) has emerged as the most important — and insubmissive — healthcare-associated infection (HAI). From 2001 to 2010, cases of CDI doubled in hospital patients in the United States, with an increased incidence of 4.5 cases to 8.2 cases per 1,000 non-maternal adult discharges during the 10 years of observation.[1] The incidence of CDI was highest among those 65 years of age and older (11.6 cases per 1,000 adult discharges). In 2011, CDI caused an estimated 29,000 deaths in the United States. By 2015, government data indicated the rate had further increased to 14.2 cases per 1,000 hospital discharges, although better metrics found that 79% of these infections were present on admission and 21% occurred during the hospital stay.[2] Nonetheless, healthcare-associated exposure is still believed to be the most common source for community-acquired CDI, with 80% of affected patients reporting contact with the healthcare system. Interestingly, while government data indicate the rate of CDI is slowly increasing throughout the United States, hospital-acquired CDI has modestly declined.

Combating CDI in the hospital environment requires a multi-pronged approach, including maximized hand hygiene and contact precautions, enhanced environmental measures, minimization of host risk factors through antimicrobial stewardship, and improved diagnostics. From personal experience, I can attest to the importance of each of these interventions. None by itself is sufficiently effective. In 2016, the Centers for Disease Control and Prevention (CDC) launched a quality initiative to provide a non-randomized, tiered approach to four cohorts of hospitals and long-term acute care facilities struggling with higher rates of CDI. A series of interventions was introduced — and then certain interventions were amplified later when needed. I will add my own personal comments to this list.

These CDC-based initiatives included:

• Reinforced antimicrobial stewardship: Antimicrobial stewardship remains the single most important intervention in all U.S. guidelines. In my experience, curtailing the use of unnecessary antibiotics and limiting the duration of antibiotics is helpful, but many hospitalized patients require antibacterials, putting them at immediate risk for active CDI, especially if colonized. You just cannot get beyond that fact. I would add to this recommendation that Infectious Disease consultation has been shown to improve antimicrobial use and reduce days of hospitalization.

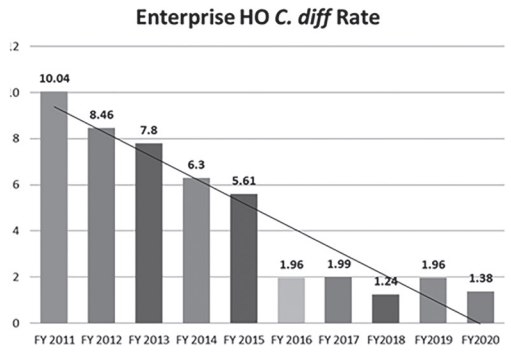
• Improved *C. difficile* (CD) diagnostics: Current guidelines advocate for the use of two types of tests in a step-wise approach: testing for the presence of organism (molecular or other), and enzyme immunoassay for the presence of CD toxin production. The ability to test separately for the presence of the organism and toxin production has greatly expanded our ability to manage patients with colonization vs. those with active disease. Unfortunately, modern methods of testing remain confusing to many physicians, and patients with colonization may not be tested for toxin production and may receive unnecessary treatment (and an incorrect diagnosis). Further, repeated testing and multiple tests are no longer needed, and only those with clinically significant symptoms should be tested for toxin production. From my perspective, the most strategic advantage of the newer diagnostics is the ability to detect fecal colonization, allowing for preemptive contact isolation and enhanced environmental measures.

• Precautions and equipment: Contact precautions and appropriate personal protective equipment (PPE) with gowns and gloves is key to cutting down on hospital transmission of the organism, regardless of colonization or active CDI.

• Reinforced hand hygiene: Even with the appropriate use of contact precautions and PPE, hand hygiene remains one of the most important interventions. At least 20% to 40% of CDI in the hospital can be attributed to transmission of organism and/or spores via hands. Newer technologies to monitor hand hygiene better would be welcome.

• Environmental measures: From my perspective, this is the final and perhaps the most important intervention a hospital can invest in. Good cleaning staff are important. Since CD spores can persist in

Figure 1: *C. difficile* Hospital Onset Rate (per 10,000 Patient Days), Fiscal Years 2011-2020



the environment for months, a room with a prior occupant with CD clearly puts the next occupant at risk. We provide enhanced daily room cleaning while a patient with CDI is hospitalized, and "terminal cleaning" is done at exit. The number of room changes is limited when possible.

Several personal comments to add to this list:
• For the past 10 years, our facility in Mountain View, CA, has worked hard to implement a series of step-wise measures, similar to those outlined above, aimed at reducing hospital-onset CDI (HO-CDI). I am proud to say our facility's HO-CD rates are now among the lowest in California. (*See Figure 1.*) This was not done in a controlled fashion, but simply as we gained information and experience, and as resources were available. From the figure, you can see the resulting gradual improvement in HO-CD rates at our facility.

• Beginning in 2009, we launched a Hand Hygiene Campaign, beefed up our antimicrobial stewardship program, hired a PharmD to manage the program, and introduced increasingly more aggressive contact precautions.

• Patients with CDI are maintained on contact precautions for a minimum of two months following successful completion of treatment. Data suggest that excretion of spores/organism is greatest in the two weeks following completion of treatment, not during treatment.

• In 2014, two-step testing became available, and we began routinely screening high-risk admissions for CD colonization, including patients with a history of CD (ever), patients admitted from long-term care or from an outside facility, and patients on hemodialysis. We provide surveillance screening for about 600 admissions every quarter, with an overall rate of colonization in asymptomatic high-risk persons of ~16%. Rates of CD colonization remain highest in those with a history of CDI (46%), followed by admissions from skilled care (13%), and dialysis patients (12%). (Previously, 30-day readmissions were screened, but the rates of CD colonization were so low, this step was not economical.) Unfortunately, surveillance is not billable and is done purely at the hospital's expense. Providing funding for this important public health safety measure would be helpful to hospitals. My guess is that many hospitals cannot afford this important measure.

• Further, patients with a history of CDI or colonization are "flagged" upon readmission, immediately go back into contact isolation, and receive surveillance rectal swab PCR testing. Contact precautions are removed when two separate surveillance swabs obtained one week apart are negative (not while receiving agents active against CD).

• Beginning in 2013, environmental measures were constantly improved. Terminal cleaning is performed in all critical care and CD rooms. We used our own data to fight intended cuts in cleaning and fought for additional staff.

• Routine adenosine triphosphate (ATP) monitoring following room cleaning was introduced, both as a means to provide feedback and education to the cleaning staff, but also to ensure quality cleaning. Environmental cleaning staff receive regular competencies, using ATP monitoring.

• With the gradual implementation of all of the above from 2009-2015, our facility was able to reduce the HO-CDI rates by more than half. But it was not until our facility went the extra step and invested in ultraviolet (UV) disinfection in 2015 that HO-CDI rates significantly dropped. (*See Figure 1.*) UV disinfection now is done on every CD room and every critical care room at patient exit, following terminal cleaning. The hospital originally invested in three UV robots, but has expanded to five. Despite this, the use of UVC is limited by hours in the day — about 30 additional minutes are required per room for cleaning staff to set up the robot and run the program. Although it does not replace good elbow-grease cleaning methods, this added measure has been highly effective.

• At present, ~40% of our HO-CDI cases are known to be colonized on presentation to the hospital. In other words, despite our best efforts, patients with recognized colonization on presentation who developed active CDI during hospitalization are classified as HO-CDI. Current Centers for Medicare and Medicaid Services (CMS) punitive measures

unfairly burden hospitals like ours that support a large skilled nursing population with a high rate of CD colonization, and undermine hospital efforts to control this important disease.

• Now that patient colonization can be confirmed, what next? It has yet to be determined whether preemptive treatment for CD colonization in patients admitted to the hospital, who are receiving antibacterials, is appropriate. Recognizing that ~40% of these patients will develop active CDI has prompted many of us to preemptively treat such patients. Urgent data are needed regarding which patients at risk are candidates for preemptive treatment, as well as the optimal approach. ■

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CME INSTRUCTIONS

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CME QUESTIONS

1. Pyrethroid-impregnated bednets:

a. have not been directly linked to death from cardiovascular events.

b. are less effective than in the past due to resistance proteins in mosquitoes.

c. might be improved by adding compounds that alter the metabolism of pyrethroids in mosquitoes.

d. All of the above are correct.

2. Among patients with sepsis in the study by Bhavani and colleagues, which group had the lowest risk (odds ratio) of associated mortality?

a. Hyperthermic patients with slow resolution of fever

b. Hyperthermic patients with fast resolution of fever

c. Hypothermic patients

d. There was no statistically significant difference among the groups.

3. Which of the following is correct?

a. Cefiderocol is actively transported into bacteria via their iron transport systems.

b. Cefiderocol has no activity against *Stenotrophomonas maltophilia*.

c. *Klebsiella pneumoniae* carbapenemase-producing *Enterobacteriaceae* are uniformly resistant to cefiderocol.

d. The pharmacodynamic parameter most closely associated with bactericidal efficacy of cefiderocol is its Cmax.

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.