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ABSTRACT & COMMENTARY

Meropenem vs. Piperacillin-tazobactam for Bacteremia Due to ESBL-Producers: The MERINO Trial

By Matthew Hitchcock, MD, MPH

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

SYNOPSIS: In an open-label, randomized, noninferiority trial evaluating the efficacy of piperacillin-tazobactam vs. meropenem for definitive therapy in treating bacteremia caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, piperacillin-tazobactam therapy did not result in noninferior 30-day, all-cause mortality compared to meropenem. Investigators stopped the trial early due to futility.

SOURCE: Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E. coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: A randomized clinical trial. *JAMA* 2018;320: 984-994.

With the steady progression of antimicrobial resistance in gram-negative bacteria, it is critical to maintain the effectiveness of broad-spectrum antibiotics. As carbapenems have emerged as a frontline treatment for infections caused by many resistant organisms, including those that produce extended-spectrum beta-lactamases (ESBLs),[1] and as ESBL-producing organisms have become more prevalent,[2] there has been significant interest in identifying alternative, carbapenem-sparing regimens to reduce the selective pressure favoring the emergence of carbapenem-resistant organisms. One such approach has involved the use of beta-lactam/beta-lactamase

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Infectious Disease [ALERT]

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inhibitors (BLBLIs), such as piperacillin-tazobactam, as tazobactam can inhibit many ESBLs.[3] Prior retrospective studies have evaluated use of BLBLIs vs. carbapenems in both empirical and definitive therapy of infections caused by ESBL-producing organisms, with mixed results and multiple studies showing no difference in outcomes.[4-6] However, at least one recent study showed improved outcomes with the use of carbapenems compared to piperacillin-tazobactam.[7]

Because of this ongoing debate, the MERINO trial was designed to evaluate the hypothesis that piperacillin-tazobactam was noninferior to meropenem for the definitive treatment of bloodstream infection caused by *Escherichia coli* and *Klebsiella pneumoniae* isolates resistant to third-generation cephalosporins in a multicenter, open-label, randomized, controlled trial.[8] It was designed to mimic clinical practice, allowing for empiric therapy at the discretion of the treating clinician prior to randomization for definitive therapy once microbiological results were available. Patients were eligible for inclusion if they had at least one blood culture positive for these organisms with local susceptibility results showing resistance to ceftriaxone or cefotaxime and susceptibility to both piperacillin-tazobactam and meropenem. Important exclusion criteria included drug allergy to either study drug or drug class, no expectation of survival beyond 96 hours, treatment without curative intent, polymicrobial bacteremia (with an exception for likely skin contaminants), and requirements for additional gram-negative antimicrobial therapy.

Patients were randomized within 72 hours of initial blood culture collection in a 1:1 fashion to meropenem 1 g q8 hours or piperacillin-tazobactam 4.5 g q6 hours intravenously and stratified by study site, infecting species, presumed infection source (urinary tract vs. elsewhere), and disease severity. Treatment was administered for a minimum of four days and a maximum of 14 days, with the option to stop all antibiotics on day 5, continue with the study therapy, or switch to an alternative agent as de-escalation. The primary outcome of the study was all-cause mortality at 30 days. The coordinating laboratory also collected and analyzed organisms isolated from study patients to confirm minimum inhibitory concentrations (MICs) to meropenem and piperacillin-tazobactam, establish ESBL presence by disk testing with clavulanate, and evaluate ESBL genes by whole-genome sequencing. A 5% margin for noninferiority was prespecified.

During the trial period, investigators screened 1,646 patients and enrolled 378 patients. Baseline patient characteristics generally were balanced, although patients in the meropenem arm were more likely to have a urinary source of infection and higher APACHE score at randomization. Patients in the piperacillin-tazobactam arm were more likely to have immune compromise.

The authors noted that 40.3% of all patients, balanced across arms, showed resolution of signs of infection at the time of study entry following receipt of empiric antibiotic therapy. Investigators stopped the trial early when interim analysis showed a significantly higher mortality rate in the piperacillin-tazobactam arm and full enrollment was not expected to demonstrate non-inferiority. Overall, 12.3% (23 of 187) of patients randomized to piperacillin-tazobactam died within 30 days, compared to 3.7% (7 of 191) of patients randomized to meropenem in the intention-to-treat analysis, and results were similar in the per-protocol analysis. Statistical adjustment within subgroups did not affect the primary outcome, as the noninferiority margin was not met and meropenem was favored in all subgroups. Patients received a similar mean duration of study drug (7.3 days for piperacillin-tazobactam and 7.6 days for meropenem) and total duration of antibiotic therapy (13.2 days vs. 13.7 days). Eighteen percent of patients received empiric therapy congruent with study allocation prior to randomization (20.7% with piperacillin-tazobactam and 15.2% with meropenem). Conversely, 13.8% of patients randomized to receive piperacillin-tazobactam were treated empirically with a carbapenem prior to allocation and 26.2% of patients randomized to meropenem were treated empirically with a BLBLI prior to

allocation. Notably, 20.2% of patients randomized to piperacillin-tazobactam received a carbapenem (typically ertapenem) as step-down therapy, while only 2.6% of patients randomized to meropenem received a BLBLI as step-down therapy and 20.4% received a different carbapenem. Fifty-six percent of patients received no additional antibiotics after completion of the allocated therapy, with a similar proportion in each arm.

In the analysis of secondary outcomes, clinical and microbiological resolution by day 4 was similar in the treatment groups and the time to resolution of infectious symptoms also was similar. There was no difference in the rates of microbiological relapse, secondary infection with a multidrug-resistant organism, and *C. difficile* infection. The recovery of carbapenem-resistant organisms as a secondary infection was rare, and rates were similar across the arms (3.2% with piperacillin-tazobactam and 2.1% with meropenem).

In microbiological analysis, 306 total isolates, representing 80% of the participants, were available for additional testing (n = 266 *E. coli* and n = 40 *K. pneumoniae*). The median MIC for piperacillin-tazobactam was 2 mg/L (interquartile range [IQR], 1.5 to 4 mg/L); 12 (3.9%) isolates were resistant by EUCAST breakpoint for susceptibility, (≤ 8 mg/L), but only four (1.3%) isolates were resistant by the CLSI breakpoint (≤ 16 mg/L). Investigators found no significant difference in the median piperacillin-tazobactam MICs across the treatment arms and no association between piperacillin-tazobactam MIC and mortality rate. Regarding meropenem, 99.7% of isolates were susceptible, with a median MIC of 0.23 mg/L (IQR, 0.016 to 0.032 mg/L); the single resistant isolate was found to carry a variant OXA-48 carbapenemase. Researchers found confirmation of phenotypic ESBL production in 86.0% of isolates (85.0% of *E. coli* and 92.5% of *K. pneumoniae*) and ESBL genes were found in 85.3% of isolates by whole-genome sequencing, which were predominately $bla_{CTX\text{-}M}$-type (83.5%). Ten percent of isolates carried acquired *ampC* genes and 2.0% carried both an ESBL and *ampC*.

■ COMMENTARY

The MERINO trial was designed to reflect the actual management of infected patients in clinical practice and focused on the question of whether BLBLIs such as piperacillin-tazobactam are an adequate substitution for carbapenems in treating established ESBL infections, and it answered rather definitively in the negative. The increased mortality with BLBLI therapy appears to be independent of the presence of overt phenotypic resistance, as the vast majority of organisms were susceptible to piperacillin-tazobactam, which suggests that standard phenotypic methods may not accurately reflect the effectiveness of BLBLIs in vivo against organisms with complex resistance mechanisms. Although empiric therapy prior to randomization was outside the control of the study — by design — it seems less likely that this would explain the increased mortality with BLBLI therapy. The majority of patients in both arms were treated with an empiric antibiotic from a different class than either study drug, with many crossing over at the time of randomization. Cephalosporins would be expected to have limited efficacy against ESBL-producing gram-negative organisms. In addition, 40% of patients in each arm showed resolution of signs of infection prior to randomization and receipt of any study drug. It also is unlikely that the quality of supportive care adversely affected the primary outcome in either direction, as patients were enrolled in both arms at all study sites, and none of the sites had vastly disparate mortality rates compared to the overall findings. No patients from the United States were enrolled, and while that theoretically may limit the generalizability of these findings to an American context, the global spread of ESBL resistance mechanisms likely abrogates this limitation.

Because of the study design, the question of whether carbapenems are preferred for empiric therapy for patients with a reasonable likelihood of having a bloodstream infection with an ESBL-producing gram-negative bacteria was not addressed. The answer to that question is likely to be highly context-specific and based on the local prevalence of ESBL-producing organisms and the severity of illness. However, the MERINO results suggest that switching to a carbapenem immediately upon identification of an ESBL-producing organism may make up for suboptimal empiric therapy, given that 86% of patients in the meropenem arm were treated empirically with a noncarbapenem antibiotic. This may help balance the need for stewardship of carbapenem use to maintain future efficacy while also ensuring patients receive adequate empiric therapy.

Questions also remain about whether an extended infusion of piperacillin-tazobactam or whether newer BLBLI agents such as ceftazidime-avibactam or ceftolozane-tazobactam may be more effective than piperacillin-tazobactam at standard dosing. Until these questions can be addressed in similar randomized, controlled trials, the results of the MERINO trial indicate that when an ESBL-producing, gram-negative bacteremia is found, carbapenems are preferred over BLBLIs for definitive therapy. ■

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ABSTRACT & COMMENTARY

IV to Oral Antibiotic Switch for Selected Cases of Endocarditis

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Completion of therapy of selected patients with infective endocarditis with orally administered antibiotics is feasible, safe, and effective.

SOURCE: Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med* 2018; Aug 28. doi: 10.1056/NEJMoa1808312. [Epub ahead of print].

Iversen and colleagues reported the results of a randomized noninferiority trial examining a strategy of intravenous (IV) to oral conversion of antibiotic therapy carried out at multiple centers in Denmark. The study involved 400 adults with left-sided endocarditis due to one of the following organisms: *Streptococcus*, *Enterococcus faecalis*, *Staphylococcus aureus*, and coagulase-negative staphylococci. The entry criteria are listed in Table 1. Approximately half of the cases were caused by streptococci and one-fifth were caused by *S. aureus* (none were methicillin-resistant). Antibiotic therapy was initiated based on European guidelines as modified by the Danish Society of Cardiology with development of oral antibiotic choice guideline by the study investigators. The latter were based on pharmacokinetic/pharmacodynamic principles and always included two antibiotics from different classes and with different targets and pharmacokinetics. Rifampin often was included as one of the antibiotics.

Although 1,954 patients with possible endocarditis were referred to the participating centers, 400 (20%) were enrolled. The most frequent reason for nonenrollment was not meeting entry criteria and unwillingness or inability to provide informed consent. The mean age of the participants was 67 years, and approximately three-fourths were male; 38% had significant comorbidities. Only five patients were injection drug users. The aortic valve was involved most frequently, and 27% of patients had a preexisting prosthetic valve. During their treatment for endocarditis, 38% of patients had undergone valve surgery prior to randomization. Thirty-five patients had an implantable cardiac device; pacemakers were removed from 14 patients with infection of the device.

The median time from diagnosis to randomization was 17 days in each group. After randomization, treatment was continued for a median 19 days in those assigned to IV therapy alone and 17 days in those assigned to switch to oral therapy. The median

Table 1: Entry Criteria

- Age ≥ 18 years
- Left-sided infective endocarditis
  - Fulfills modified Duke criteria
  - Native or prosthetic valve
- *Streptococcus*, *E. faecalis*, *S. aureus*, or coagulase-negative staphylococcus
- IV antibiotic for > 10 days and stable and ≥ 7 days after valve surgery (if performed)
- No abscess or valve dysfunction requiring surgery (by transesophageal echo) at time of randomization

Table 2: Primary Composite Outcome

From time of randomization until six months after completion of antibiotic therapy:

- All-cause mortality OR
- Unplanned cardiac surgery OR
- Embolic events OR
- Relapse of bacteremia with the primary pathogen

length of hospital stay after randomization was 19 days in the IV group and only three days in the oral switch group; 80% of the oral therapy group were treated partially or completely as outpatients.

Therapeutic drug monitoring was performed, and seven patients were found to have below-target plasma concentrations of one of their two antibiotics (rifampin in three patients, moxifloxacin in two, and linezolid and dicloxacillin in one each). Although no change was made, none had an unfavorable outcome.

The composite primary outcome occurred in 24 (12.1%) IV-treated patients and 18 (9.0%) orally treated patients (between-group difference, 3.1 percentage points; 95% confidence interval, -3.4 to 9.6; $P = 0.40$), indicating noninferiority.

■ COMMENTARY

Every protocol for IV to oral antibiotic conversion that I have seen excludes patients with endocarditis, as well as several other serious infections. The following appear to be the only mentions of oral antibiotic therapy for endocarditis in the 2015 American Heart Association guidelines.[1]

- "Absorption of orally administered antimicrobial agents may be unreliable and is generally not recommended for the treatment of endocarditis, especially during the initial phase of therapy."
- "In patients who will not comply with a course of parenteral antibiotic therapy, oral treatment may be an option. Two studies have evaluated the use of predominantly oral 4-week antibiotic regimens (ciprofloxacin plus rifampin) for the therapy of uncomplicated right-sided *S. aureus* endocarditis in IDUs. In each study, including one in which 70% of patients were HIV-seropositive, cure rates were 90%."

Thus, except for right-sided endocarditis due to *S. aureus*, any oral therapy generally has been eschewed. However, this has not been the result of evidence that well-chosen orally administered antibiotics lead to failure of therapy, but a lack of any evidence. Iversen and colleagues now have provided strong evidence that follow-on oral therapy in stable patients after a period of IV antibiotic administration is effective in carefully selected patients. Although the published data are remarkably limited, an alternative consideration could be given to administration of lipoglycopeptides with very slow clearance, such as dalbavancin[2] or oritavancin.

[Iversen and colleagues now have provided strong evidence that follow-on oral therapy in stable patients after a period of IV antibiotic administration is effective in carefully selected patients.]

From a personal viewpoint, I have treated several patients with left-sided endocarditis in this way. However, the cases I selected were infected with one of two types of organisms: viridans streptococci with very low penicillin minimum inhibitory concentrations and HACEK organisms, which usually are exquisitely susceptible to fluoroquinolones. I remain a bit anxious in applying this approach to staphylococcal or enterococcal endocarditis or to cases of prosthetic valve infection, but I am willing to be convinced.

A final note: This paper deserves careful reading not only of the main paper but also of the accompanying 31-page supplemental appendix. ■

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ABSTRACT & COMMENTARY

Infections Associated With Travel *to* the United States

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Infectious illness is common in travelers from other countries visiting the United States. Skin and soft tissue infections, respiratory infections, and gastrointestinal illness are most likely, but specific geographic illnesses such as Lyme disease also occur.

SOURCE: Stoney RJ, Esposito DH, Kozarsky P, et al. Infectious diseases acquired by international travelers visiting the USA. *J Travel Med* 2018;25:1-7.

Typically, travel medicine specialists are concerned with health risks to travelers leaving a home in a "developed" country and traveling to a low-resource country. However, nine of the top 10 international tourist destinations are in North America or Europe; the United States had more than 77 million visits by international tourists in 2015 alone. Infections in travelers to the United States have not been studied extensively.

Therefore, researchers participating in the GeoSentinel Network reviewed data about all nonmigrant, non-U.S.-resident international travelers who experienced an illness during or soon after a trip to the United States and who sought care in a GeoSentinel Network clinic from January 1997 through December 2016. The GeoSentinel Network includes 70 participating travel and tropical medicine clinics in 30 different countries and was created in 1995 as a collaboration between the Centers for Disease Control and Prevention and the International Society of Travel Medicine. Data-sharing allows for dissemination about outbreaks of illnesses and facilitates research about travel-related diseases.

During the 10 years of the study, there were 1,393 relevant diagnoses made in 1,222 travelers. The sick travelers had come from 63 different countries (more than half from Canada or Europe). Of the ill travelers, 82% had been traveling as tourists, and the median duration of the trip was 14 days (range, one day to seven years). Overall, 52% were female, and 9% were younger than 18 years of age.

A total of 177 patients were seen for an illness at a GeoSentinel site in the United States during their trip. Of the ill patients, 14% had skin and soft tissue infections, 7% had an acute gastrointestinal illness, and 7% had pneumonia. Sepsis, pyelonephritis, and influenza each were seen in 2% of ill travelers. Three travelers died while still in the United States, one with pneumonia and a subsequent cardiac event, one from pulmonary embolus, and one with cancer and pre-existing peritonitis who became septic.

The study included 1,045 travelers who sought care at a GeoSentinel site after the conclusion of the U.S. travel. Among them, insect bites/stings were common (15% of diagnoses), while flu-like illness (6%), upper respiratory infection (5%), acute gastrointestinal infection (4%), and skin and soft tissue infection (4%) also were seen. Influenza and Lyme disease each were diagnosed in 4% of returned travelers. There were nearly twice as many infections diagnosed in returned travelers during 2009 than in any of the other nine study years; this coincided with a global pandemic of influenza H1N1 infection.

In addition to Lyme disease, several other specific regional diseases were identified. There were 13 cases of coccidioidomycosis, mostly from Arizona. There was one case of Zika following travel in south Florida. There were three cases of dengue fever after travel in Florida and Hawaii. Two travelers acquired West Nile virus infection in the United States. Two travelers had spotted fever rickettsiosis, and one had ehrlichiosis.

■ COMMENTARY

Travel-related infections are not limited to visitors to resource-limited countries. We must abolish any residual notion of "us and them" where "we" are from clean countries and "they" are at risk in dirty countries. This paper serves as a good reminder that international visitors to the United States are at risk of infections during travel, and some of these

infections could have been prevented with repellent use to reduce tick and mosquito bites.

In addition, recent outbreaks of *Salmonella*,[1,2] *Campylobacter*,[1] norovirus,[2,3] *Escherichia coli*,[2,3] and *Cryptosporidium*[3] in the United States remind us that food, water, and hand hygiene still are important in the United States, whether one is traveling or not.

Indeed, a textbook about geographic infections is in its second edition and includes a chapter on infections in the United States that is 19 pages long.[4] Even as Americans are at risk of mosquito-borne diseases when visiting Africa, international travelers are at risk of various travel-related infections in the United States.

Perhaps it is helpful to review geographical illnesses in the United States, even beyond the current report in travelers. Specifically, the following states and regions have been linked with the noted specific infections:

- Hawaii: leptospirosis, dengue fever, *Angiostrongylus cantonensis*;
- Southwest: coccidioidomycosis;
- Texas: dengue fever, leprosy (with armadillo contact);
- Midwest: Lyme disease, babesiosis;
- Florida: dengue fever, Zika, chikungunya;
- East-Central: histoplasmosis, blastomycosis;
- Northeast: Lyme disease, babesiosis.

This paper also provides a good reminder to all of us who live and travel within the United States. We should avail ourselves of annual influenza vaccines. We should clean injured skin carefully. We should avoid close contact with people who are actively coughing and sneezing. And we should use insect repellent on skin that is exposed in areas where dengue, Zika, and Lyme disease occur. Respiratory illnesses after visits to Arizona and California could prompt consideration of coccidioidomycosis. ■

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ABSTRACT & COMMENTARY

Oral Vancomycin Is the Most Cost-effective Treatment for the First Recurrence of *Clostridium Difficile* Infection

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

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

SYNOPSIS: The authors of a pharmacoeconomic study comparing bezlotoxumab plus oral vancomycin, oral vancomycin alone, and fidaxomicin found that oral vancomycin alone was the most cost-effective regimen to treat the first recurrence of *Clostridium difficile* infection.

SOURCE: Lam SW, Neuner EA, Fraser TG, et al. Cost-effectiveness of three different strategies for the treatment of first recurrent *Clostridium difficile* infection diagnosed in a community setting. *Infect Control Hosp Epidemiol* 2018;39:924-930.

Approximately 10% to 30% of patients with *Clostridium difficile* infection (CDI) experience a recurrence, and the optimal management of recurrences is uncertain. Several different therapies are available, although data about their cost-effectiveness are limited. Therefore, Lam and colleagues sought to compare oral vancomycin, oral vancomycin plus bezlotoxumab, and fidaxomicin for cost-effectiveness to treat the first recurrence of CDI.

The study included data from randomized, controlled trials of outpatients who presented with their first episode of recurrent CDI. One of four treatment strategies was chosen: oral vancomycin every six hours for 10 days; fidaxomicin every 12 hours for 10 days; bezlotoxumab once plus oral vancomycin every six hours for 10 days; or a six-week oral vancomycin taper. The physician could choose to admit the patient for treatment, which did not affect the treatment strategy. Regardless of admission, patients were classified as cure or failure, the latter of which then were treated with an oral vancomycin taper, fecal microbial transplantation (FMT), or colectomy. The efficacy outcome was described in quality-adjusted life years (QALY), which ranges from 0 (death) to 1 (perfect health). The cost included direct costs, such as medications, hospitalizations, colectomy, FMT, and therapies for additional recurrences, and was viewed from the perspective of the payer. Indirect costs, such as loss of work, patient travel, and out-of-pocket expenses, were not included in the analysis.

Oral vancomycin alone involved the lowest cost and a QALY gain of 0.8019. Treatment with fidaxomicin had the second lowest cost and a QALY gain of 0.8046 over vancomycin alone. Bezlotoxumab plus vancomycin had the highest cost but also an incremental decrease in QALY. These findings demonstrated vancomycin alone to be the most cost-effective treatment because the incremental cost-effectiveness ratio (ICER) of fidaxomicin was > $100,000 per QALY gained. At a willingness-to-pay (WTP) threshold of $100,000 per QALY gained, vancomycin exhibited a probability of 68% as the most cost-effective, compared to 29% for fidaxomicin and 2.4% for bezlotoxumab plus vancomycin. When researchers increased the WTP threshold to $500,000 per QALY gained, oral vancomycin still was the most cost-effective therapy.

■ COMMENTARY

Recurrent CDI is a challenging condition for physicians to manage. Despite myriad treatment options, knowing which one will work best for an individual patient is difficult. The current Infectious Diseases Society of America (IDSA) guidelines for CDI recommend treating the first recurrence of CDI with either a tapered pulsed regimen of oral vancomycin (weak recommendation, low quality of evidence), a 10-day course of fidaxomicin (weak recommendation, moderate quality of evidence), or a 10-day course of vancomycin instead of a second metronidazole course if that drug was administered to treat the initial episode of infection (weak recommendation, low quality of evidence).[1] Because it was not approved at the time, no recommendations about bezlotoxumab were made in the guidelines.

In addition to clinical efficacy, physicians also must weigh financial concerns when deciding on the treatment regimen. Thus, the study by Lam et al is welcome because it clarifies the cost-effectiveness of three widely used strategies for the first recurrence of CDI. It also is the first to evaluate bezlotoxumab in this setting. Although some previous studies showed a decrease in recurrences with fidaxomicin and bezlotoxumab compared to vancomycin, the authors of the present study found similar overall effectiveness with all three drugs. Although fidaxomicin had a slightly higher gain in QALY, its cost was well above the WTP threshold such that vancomycin alone emerged as the most cost-effective option.

The researchers did not include FMT as one of the treatment options in the study. This decision seems reasonable given that, in current clinical practice, FMT usually is reserved for patients with multiple recurrences and often after a vancomycin taper has failed. However, this strategy seems to be evolving, especially as the use of oral capsules becomes more commonplace.

The study had some notable limitations. First, the data were collected from randomized clinical trials and, therefore, the cure and recurrence rates may depict best-case scenarios and not real-world clinical settings. Second, the authors of the study did not take into account adverse events of the three treatment options. Third, differences in *C. difficile* strains were not considered. Thus, the cost-effectiveness results might not hold true when high toxin-producing strains (e.g., BI/NAP1/027) are prevalent. Finally, the investigators did not determine if there was a difference in the cost effectiveness between a six-week vancomycin taper and a 10-day course.

Currently, oral vancomycin, either as a 10-day course or a six-week taper, seems to be the most cost-effective approach for managing the first recurrence of CDI. As novel treatments become available, it will be important to conduct further pharmacoeconomic studies that compare multiple strategies in real-world settings. ■

REFERENCE

1. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018;66:e1-e48.

ABSTRACT & COMMENTARY

Prophylactic Antibiotics for Acute Aspiration

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: Researchers compared outcomes in patients with aspiration pneumonitis who received prophylactic antibiotics during the first two days after macro-aspiration to patients who received only supportive care during this time. Among the 200 patients meeting the acute aspiration pneumonitis case definition, antimicrobial prophylaxis was not associated with improvement in mortality. However, patients receiving prophylactic antibiotics required more frequent escalation of antibiotics and received more days of antibiotics than those who were managed initially with supportive care alone.

SOURCE: Dragan V, Wei L, Elligsen M, et al. Prophylactic antimicrobial therapy for acute aspiration pneumonitis. *Clin Infect Dis* 2018;67:513-518.

The authors of this paper report on a retrospective cohort study conducted in Toronto of a large number of patients. The authors evaluated outcomes for patients with aspiration pneumonitis who received prophylactic antibiotics compared to those who received supportive care only in the first two days after the observed aspiration event. The primary outcome was in-hospital 30-day mortality. The secondary outcomes were transfer to critical care, antimicrobial therapy received between day 3-14 after aspiration, escalation of antibiotic therapy, and antibiotic-free days.

Of the 1,483 patient charts reviewed by investigators, 200 met the acute aspiration pneumonitis case definition. Thirty-eight percent received prophylactic antimicrobials and 62% received just supportive care in the first two days after the macroaspiration event. After investigators adjusted for patient-level predictors, they found that antimicrobial prophylaxis was not shown to improve 30-day mortality or prevent transfer to the intensive care unit (ICU). However, patients who received early prophylactic antimicrobials subsequently underwent antibiotic therapy escalation more frequently (8% vs. 1%; P = 0.002) and had fewer days free of antibiotics (7.5 vs. 10.9; $P < 0.0001$).

■ COMMENTARY

During the last five years since I have been working full time at our university hospital and our excellent VA (where I receive my own medical care), I have been attending more on the inpatient medicine service than I have on the infectious disease consult service, and have had the opportunity of seeing day-to-day clinical decision-making in a university hospital up close. Probably at least once each week, I'll overhear a resident sign out something to the effect: "Patient X vomited and aspirated last night, was a bit wheezy, so I covered him/her with vancomycin and piperacillin-tazobactam." I often challenge the residents by asking where they learned that "covering" patients after aspiration with broad-spectrum antibiotics is a good idea. The answer I often receive is, "This is standard of care." Additionally, a few days later, I'll hear them say, "Patient X has been on vancomycin and piperacillin-tazobactam for empiric coverage for aspiration for four days and his WBC went from 6,000 to 10,000 last night, so we empirically broadened coverage to meropenem." Again, I'll often challenge that decision, too. Now, I have a good article to forward to the house staff that I hope will reassure them that it is OK to withhold empiric antibiotics after aspiration. ■

Updates

By Carol A. Kemper, MD, FACP

Pet Snake Snacks: A *Salmonella* Treat

SOURCE: Marin C, Martelli F, Rabie A, Davies R. Commercial frozen mice used by owners to feed reptiles are highly externally contaminated with *Salmonella enteritidis* PT8. *Vector Borne Zoonotic Dis* 2018;18:453-457.

Who would imagine those little pink mice that people feed to their pet snakes and reptiles are highly contaminated with *Salmonella*? It turns out, these innocent-looking, little, pink bodies may be responsible for repeated outbreaks of *Salmonella* infections in the United States and in the European Union. Two larger outbreaks have been ongoing for many years, due to *Salmonella enteritidis* or *Salmonella typhimurium*, and have been linked to ownership of pet snakes and other reptiles. A common food source for many pet reptiles is feeder mice, which are commercially raised, frozen, packaged, and shipped throughout the world. Evidence points to frozen feeder mice as the source of reptilian *Salmonella* infection. In 2008, *Salmonella* infections were linked to a small commercial feeder mouse facility in Georgia, which recalled millions of frozen mice in 2010. Molecular analysis has revealed that another sustained outbreak of *S. enteritidis* infection from 2012-2015, resulting in more than 400 infections, also likely was secondary to feeder mice. During this outbreak, more than 40% of the infections occurred in children ages 10 years or younger; 30% of those affected owned pet snakes or reptiles.

Feeder mice are shipped frozen and packaged in large bags, and often are kept in the family freezer. Many owners find using frozen mice simpler to manage than trying to run back and forth to the pet store for live mice every time their snake is hungry. Even more damning, owners often thaw the mice by microwaving them or heating them in a pan of water on the stove-top, so their pet snake can have a warm treat (rather than a mouse ice-pop). Reptiles become colonized with *Salmonella* but seldom become ill. But they serve as a source for infection and contamination of the household environment, where the bacteria may persist in the environment for months (> 12 months in some studies).

In the United States, commercial facilities that distribute frozen mice are required to place safe handling labels on packages. In the United Kingdom, snakes are not considered pets; therefore, feeder mice are not considered "pet food," so specific labeling is not required.

These researchers examined 295 feeder mice for evidence of *Salmonella* colonization of the integument and internal organs. Different types and sizes of feeder mice, including fuzzies, pinkies, small, large, and extra-large mice, were processed and cultured in 12 batches of five mice each. A batch was considered positive if any one mouse in a batch was culture-positive. *Salmonella* was isolated from the external carcasses of one or more mice from nearly one-third of the batches. Fuzzies showed the highest proportion of external colonization, with positive mice found in 10 of 12 batches (83.3%); five of 12 of the smaller mice batches were positive, followed by one of 12 of the batches of both the pinkies and extra-large mice. This suggests that fuzzies, which have been implicated previously, are highly externally contaminated with *Salmonella* relative to other mouse types.

Salmonella colonization of internal organs was found to potentially infect all organs examined (liver, spleen, kidneys, bladder, cecum, intestine; up to 5% of organs), but was found mostly in the intestines, as anticipated. Rates of colonization were similar between mouse types. Two different strain types of *S. enteritidis* were isolated (PT8 and PT13) and were sensitive to all 16 antimicrobial agents tested.

Radiation of feeder mice before packaging has been proposed as a way to reduce the risk of *Salmonella* infection, but this would not affect internal colonization. The environments of these facilities — the dust, the droppings, the cages — must be persistently contaminated with *Salmonella*. A wholesale new approach to "growing" pet food would be required to reduce the risk of bacterial infection.

Linking HIV-positive Inmates to Outpatient Care

SOURCES: Cunningham WE, Weiss RE, Nakazono T, et al. Effectiveness of a peer navigation intervention to sustain viral suppression among HIV-positive men and transgender women released from jail. The LINK LA

Randomized Clinical Trial. *JAMA Intern Med* 2018;178:542-553. Accompanying editorial: Metsch LR, Pugh T, Colfax G. An HIV behavioral intervention gets it right — and shows we must do even better. *JAMA Intern Med* 2018;178:553-555.

It is a sad commentary, as we so often noted at the county HIV clinic: Some patients did better when they were in jail. Linking jail care to outpatient care, so that former inmates can be transitioned smoothly to outpatient care and outpatient medications without being lost to care or disenfranchised, remains an important concern.

Jails have become an important focal point for detection of previously unrecognized HIV infection and recognition of persons with HIV who are not in care or who have fallen out of care. Using national surveillance data, approximately 1.5% of all persons in state and federal facilities are HIV-positive. About one-fourth of those are unaware of their HIV status, and another one-third of those who are aware of their HIV status are not in care. These data extrapolate to suggest that upward of 13,600 inmates per year do not receive HIV medical care once released to the community.

Getting these individuals into medical care and keeping them there is critical. However, the reasons this may not occur are complex and variable. To frame the problem, one author identified four points where the system breaks down, as follows: lack of knowledge of HIV status; awareness of HIV status but not in care; having entered care at one point but disengaged; irregular participation in care and noncompliance with medical recommendations. Such a breakdown allows programs to identify methods for addressing the varying social and psychological barriers.

To address some of these gaps, the authors of a randomized clinical trial designed a peer navigation intervention to transition former inmates into outpatient HIV care. LINK LA trained peer navigators to work with inmates to establish goals and solve problems to establish care, secure outpatient medications, and improve medication adherence. Participants were randomized either to participate in the 12-session, 24-week intervention, beginning in jail and continuing through to the outpatient setting, or to standard traditional case management. Navigators participated in at least two outpatient clinic visits and continued to follow inmates for up to 12 months after their release. The success of the intervention was measured by one powerful endpoint: HIV virological suppression (< 75 copies/mL) at 12 months.

From 2012-2016, 356 individuals leaving Los Angeles County Jail were recruited for the project, including 303 men (82%) and 53 (15%) transgender women; 42% of these were black and 31% were Latino. At 12 months, HIV viral suppression was achieved in 62/125 (49.6%) of the participants in the intervention arm vs. 45/125 (36%) of those in the control arm. In an adjusted model for repeated measures, viral suppression was much better maintained in those in the intervention arm than the control arm. Virological suppression declined from 52% at baseline to 49% at 12 months in the intervention group compared to 30% among controls, for a difference-in-difference of 22% (P = 0.02).

LINK LA successfully steered many former inmates into care, and nearly half of study participants in the intervention arm had sustained virologic suppression one year later. For anyone who has attempted behavioral/adherence trials, these results are remarkable, especially with this patient group — and even more so that the results were sustained for one year. And yet, despite a high level of personalized attention, just less than half of those in the intervention arm achieved their treatment goal. Half is a long way from the national goal of > 90% virologic suppression. It is unclear whether expanding such a program would be feasible financially and what more would be required to bring outliers into care. ■

ABIM CME MOC ACCREDITED

CME INSTRUCTIONS

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CME QUESTIONS

1. **A 54-year-old woman with bacteremic urinary tract infection improves after initiation of cefepime therapy but remains febrile. Blood culture yields growth of *Escherichia coli* resistant to third-generation cephalosporins, raising suspicion of ESBL production. The isolate is reported to be susceptible to piperacillin-tazobactam and meropenem. Which of the following is most likely to be successful as definitive therapy for treatment of this infection?**

   a. Ampicillin-sulbactam

   b. Piperacillin-tazobactam

   c. Meropenem

   d. Cefepime

2. **International visitors to the United States are at risk of becoming ill with which of the following?**

   a. Influenza

   b. Dengue fever

   c. Lyme disease

   d. All of the above

3. **In which state would a resident or visitor be most likely to acquire infection with *Angiostrongylus cantonensis*?**

   a. Florida

   b. Hawaii

   c. New Mexico

   d. Rhode Island

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.