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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Is Fecal Microbiota Transplantation Superior to Fidaxomicin for Recurrent *Clostridioides difficile* Infection?

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

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

SYNOPSIS: In a randomized clinical trial, researchers found the combination of oral vancomycin followed by fecal microbiota transplantation was superior to treatment with fidaxomicin or vancomycin alone for patients with recurrent *Clostridioides difficile* infection.

SOURCE: Hvas CL, Dahl Jørgensen SM, Jørgensen SP, et al. Fecal microbiota transplantation is superior to fidaxomicin for treatment of recurrent *Clostridium difficile* infection. *Gastroenterology* 2019;156:1324-1332.

Despite our nuanced understanding of both the transmission and pathophysiology of *Clostridioides difficile* infection (CDI), management of recurrent episodes remains challenging. Although multiple therapies are available, including prolonged courses of oral vancomycin, fidaxomicin, and fecal microbiota transplantation (FMT), it is unclear which of these gives the best chance for resolving recurrent CDI.

Hvas and colleagues conducted a randomized, open-label clinical trial at a single center in Denmark. Patients were eligible to participate if they were 18 years of age or older, had at least three liquid stools per day, had a positive PCR result for *C. difficile* toxin, and received at least one prior treatment for CDI with oral vancomycin or fidaxomicin. Exclusion criteria included pregnancy or breast feeding, sepsis or fulminant colitis,

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ongoing antibiotic treatment, allergy to vancomycin or fidaxomicin, or inability to give consent. All patients underwent fecal tests for other gastrointestinal pathogens (e.g., *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*). Patients with active inflammatory bowel disease (IBD) were treated concurrently. The participants were randomized to one of three groups: four to 10 days of oral vancomycin followed by FMT (n = 24); 10 days of fidaxomicin (n = 24); or 10 days of vancomycin (n = 16). Patients who could not be randomized received FMT off protocol. The study's primary end point was clinical resolution and a negative follow-up *C. difficile* test without the need for a rescue FMT or colectomy eight weeks after initial treatment. Patients who experienced clinical recurrence of CDI and a positive *C. difficile* test before or at week 8 were offered a rescue FMT.

The median age of randomized patients was 68 years, their comorbidity was low as evident by a median Charlson comorbidity index score of 1, and 15/64 (23%) had IBD. Combined clinical resolution with a negative *C. difficile* test occurred in 17/24 (71%; 95% confidence interval [CI], 49-87%) in the FMT group, 8/24 (33%; 95% CI, 16-55%) in the fidaxomicin group, and 3/16 (19%; 95% CI, 5-46%) in the vancomycin group (P = 0.009 for FMT vs. fidaxomicin; P = 0.001 for FMT vs. vancomycin; P = 0.31 for fidaxomicin vs. vancomycin). Clinical resolution without a negative follow-up *C. difficile* test occurred in 22/24 (92%; 95% CI, 73-99%) of those treated with FMT, 10/24 (42%; 95% CI, 22-63%) of those treated with fidaxomicin, and three (19%; 95% CI, 4-46%) of those treated with vancomycin.

All 24 patients who experienced a clinical relapse and a positive *C. difficile* test before or at week 8 received a rescue FMT. Twenty of these patients experienced clinical resolution and a negative test eight weeks after the rescue FMT. Risk factors for FMT failure included anemia (odds ratio [OR], 6.2; 95% CI, 1.27-30.9), age > 65 years (OR, 3.5; 95% CI, 0.72-17.4), Charlson comorbidity index ≥ 2 (OR, 4.5; 95% CI, 0.92-22.0), hospital admission at inclusion (OR, 2.2; 95% CI, 0.64-8.1), and receipt of immunosuppression therapy (OR, 2.0; 95% CI, 0.55-7.9).

■ COMMENTARY

This is an interesting study because the authors randomly compared three commonly used treatments for recurrent CDI. It is notable that fidaxomicin was inferior to FMT since studies have shown it to be more successful than vancomycin for CDI recurrences. The clinical success rate of 92% for FMT aligns with previous reports, most of which demonstrated resolution rates of 70% to 90%. Another notable finding was that five out of seven patients who had a positive *C. difficile* test eight weeks after a first FMT experienced clinical resolution and did not need a rescue FMT. This supports the current recommendation not to perform a test of cure.[1] The significance of a positive test despite clinical resolution is unclear. For example, are these patients at higher risk for recurrence? Are they still shedding spores and, if so, is there a potential to spread disease to family members, healthcare workers, or other patients? Future studies should be undertaken to address these concerns.

The presence of anemia had the highest odds ratio for FMT failure. This was an unexpected finding that has not been observed previously. The authors hypothesized that anemia might be a marker for disease burden and could help identify patients who may need multiple FMTs. Further evaluation of the role of anemia in recurrent CDI and its effects on FMT is warranted.

The study had some limitations. No ribotype 027 strains were identified, so the results might not be generalizable to patients infected with that strain. The study was not blinded, which could have led to observer bias. Because of the small number of patients in the groups, many of the confidence intervals were wide. Indeed, the study is likely underpowered, which affects the ability to detect meaningful differences between the different treatments. Prolonged vancomycin tapers (i.e., more than six weeks) are a common treatment strategy. How this would have compared to FMT was not evaluated. Finally, the study was

conducted at a single institution in Denmark, so the results might not be generalizable to other settings and patient populations.

Compared to oral vancomycin alone and fidaxomicin, oral vancomycin followed by FMT was superior for treating recurrent CDI in this small trial. Larger studies are needed to confirm this finding and to elucidate the optimal timing for FMT in the management of *C. difficile* recurrences. ■

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ABSTRACT & COMMENTARY

Vancomycin for MRSA Pneumonia Following Influenza in Children

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: Coinfection with methicillin-resistant *Staphylococcus aureus* (MRSA) in children with influenza is associated with high fatality. Data support the addition of a second anti-MRSA antibiotic to vancomycin in severely ill children.

SOURCE: Randolph AG, Xu R, Novak T, et al. Vancomycin monotherapy may be insufficient to treat methicillin-resistant *Staphylococcus aureus* coinfection in children with influenza-related critical illness. *Clin Infect Dis* 2019;68:365-374.

Researchers enrolled 170 children younger than 18 years of age with influenza (127 with influenza A and 43 with influenza B) and respiratory failure from 34 pediatric intensive care units (PICU) across the United States between 2008 and 2016. Thirty children with influenza-methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia were identified. Eighty-seven percent of these children were previously healthy. Children with MRSA pneumonia were slightly older (mean age 12.7 years) than children with non-MRSA bacterial pneumonia or no bacterial superinfection (mean age, about 6 years).

Children with MRSA pneumonia were more likely than others to have leukopenia at admission to the PICU, to have acute lung injury, and to require vasopressors or extracorporeal life support (ECMO). They also had higher mortality. Mortality was 40% in children with MRSA compared to 4.3% in children without MRSA infection. Twenty-nine of 30 children with MRSA pneumonia received early vancomycin therapy. Of the children with MRSA pneumonia who received vancomycin plus a second MRSA agent within the first 24 hours of hospitalization, mortality was 12.5% (2/16). Mortality was 69% (9/13) in those children who received vancomycin monotherapy initiated within 24 hours of hospitalization. The most common second anti-MRSA agent added to vancomycin was clindamycin, followed by ceftaroline and linezolid. All isolates were susceptible in vitro to clindamycin.

■ COMMENTARY

This is an interesting study highlighting an area of concern that many clinicians who care for both adults and children with *S. aureus* pneumonia have had for many years. Although this was a small observational study and potentially can be criticized for all of the normal reasons, the "signal" that is evident from bottom line results is difficult to ignore. The potential reasons why patients who received a second agent in addition to vancomycin had better outcomes include:

- A relatively small difference between achievable blood and tissue levels of vancomycin relative to the MIC of most Staph isolates (the trough vancomycin levels were relatively low in both groups in this study);
- The potential role of "heteroresistance" of some Staph strains to vancomycin;
- Better tissue penetration of agents other than vancomycin;
- The potential beneficial effect of clindamycin and linezolid on downregulation of toxin production by *S. aureus*.

While in this particular study all isolates were susceptible to in vitro clindamycin, this is not true in all regions of the country and the rest of the world, so empiric monotherapy with clindamycin would seem unwise. Initial combination therapy with both agents while awaiting susceptibility results would seem prudent before potentially dropping the vancomycin would be one reasonable approach. Vancomycin combined with ceftaroline or linezolid initially (followed by potentially dropping the vancomycin after susceptibility results are available) would be another potential approach. Obviously, a larger, multicenter, randomized, controlled trial designed to evaluate different antimicrobial regimens would be the definitive way to sort this out. Animal models also could be helpful.

In conclusion, this study reinforces my decades long prejudice that "vancomycin is the second-best antibiotic for many infections." I have seen enough children and adults die of *S. aureus* pneumonia (MSSA, MRSA, with or without associated influenza infection) that I would certainly no longer treat any patient with *S. aureus* pneumonia with vancomycin monotherapy. I would recommend initial combination therapy until we have more solid data on which to base therapy. ■

ABSTRACT & COMMENTARY

Histoplasmosis — Expansion of Risk Areas and Need for More Standardized Practice

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Histoplasmosis is increasingly seen beyond the previous risk areas of the Ohio and Mississippi River valleys. Diagnostic and treatment practices vary widely.

SOURCE: Benedict K, Beer KD, Jackson BR. Histoplasmosis-related healthcare use, diagnosis, and treatment in a commercially insured population, United States. *Clin Infect Dis* 2019; Apr 30. doi: 10.1093/cid/ciz324. [Epub ahead of print].

Histoplasmosis is an infection caused by inhalation of an environmental fungus. In the United States, it has been thought to primarily occur in the Ohio and Mississippi River valleys. A range of presentations occur, from asymptomatic infection to fatal disseminated disease, and risk factors for severe illness in immunocompromised patients have been described. However, Benedict and colleagues from the Centers for Disease Control and Prevention sought to characterize histoplasmosis among the general population. Realizing that diagnostic and management practices vary widely, they sought to characterize just how American physicians care for patients with histoplasmosis.

The researchers obtained information from a 2011-2015 database of individual insurance claims resulting from ambulatory and inpatient services provided to more than 230 million insured people (employees, family members of employees, and retired employees) in the United States. Patients with histoplasmosis were identified using billing codes. Of more than 85 million active enrollees in the database, there were 8,169 with a coded diagnosis of histoplasmosis during the years 2012 to 2014. Of these, 3,625 had pre-diagnosis data to determine care for symptomatic illness prior to the establishment of a new histoplasmosis diagnosis. From these, patients were included in the study if prescription data were available, leaving a total of 1,935 subjects available for full analysis.

Rigorously analyzing data, researchers found that about half of the subjects were thought to be "probable" cases of histoplasmosis, and the other half were "suspect" cases (since they had only one outpatient visit related to the diagnosis and no inpatient care or follow-up visit). Probable cases were more likely to be male (51% vs. 45%), younger (median 55 years vs. 58 years), and immunocompromised (24% vs. 13%). Of the total, 44% lived in the east north central region of the United States.

Analysis of pre-histoplasmosis diagnostic codes revealed that 54% of subjects had received medical care during the three months prior to the histoplasmosis diagnosis for respiratory symptoms or

signs that could have been due to histoplasmosis. The median time between the initial visit with concerning findings and the ultimate histoplasmosis diagnosis was 45 days. Azithromycin and amoxicillin were given commonly for the respiratory illness prior to the diagnosis of histoplasmosis.

Along the way toward the histoplasmosis diagnosis, only 33% of patients received a *Histoplasma*-specific antigen or antibody test. Overall, 44% had tissue analysis (biopsy or cytopathology). Immunocompromised patients were more likely to undergo *Histoplasma*-specific testing. Interestingly, 13% received the diagnosis of histoplasmosis without any laboratory testing and with no associated symptoms or signs of infection, and they received no antifungal treatment.

Treatment varied, with 29% receiving outpatient antifungal treatment. The duration of treatment was longer in immunocompromised than in immunocompetent patients (median 238 days vs. 98 days).

Of study subjects, 19% were hospitalized for histoplasmosis. Of the total cohort of subjects, 3% died while hospitalized.

The authors highlighted the wide spectrum of illness severity in patients with histoplasmosis, the infrequency of specific fungal testing, and the seeming delay in diagnosis for many patients. They also emphasized the fact that more than one-third of the patients with histoplasmosis in this national database resided outside of the geographic areas usually associated with the infection.

■ COMMENTARY

Even though this study was just a review of insurance claims data and did not include chart reviews by medical experts, the authors managed to uncover valuable information. We who are aware of this study now might need to broaden our geographic suspicion for histoplasmosis, increasingly consider conducting specific *Histoplasma* testing, and seek more standardized care plans.

Many of us have relegated concern for histoplasmosis to people who have contact with soil near the Mississippi and Ohio River valleys. Although these new data do not rule out travel through these areas as a means of infection for those residing elsewhere, the fact that less than half of the individuals identified as infected lived in an area of risk suggests that the transmission of histoplasmosis is probably occurring well beyond the Ohio and Mississippi River valleys. As noted in an editorial accompanying the paper, the "times have changed," and it is "time to redraw the map" of where histoplasmosis occurs.[1] Perhaps related to climate change and altered living patterns of bats and starlings (who deposit *Histoplasma*-laden "fertilizer" in soil), the endemic area for histoplasmosis is spreading north and west of the Ohio and Mississippi River valleys, with some patients becoming infected even much farther away.[1] At the same time, travelers who visit caves in Central America also are at risk of becoming infected.[2] Histoplasmosis also is increasingly recognized in people living with HIV and AIDS elsewhere in the Americas, such as in Brazil.[3]

[Whatever their immunocompromising condition, immunocompromised patients with respiratory symptoms should raise concern for histoplasmosis.]

It is hard to judge a population incidence of histoplasmosis from insurance data in a select population of employed individuals. However, the data in this study would suggest that the incidence of histoplasmosis in the general population is in the range of "one in a million." Bacterial and viral causes of respiratory infection are much more common. However, histoplasmosis should not be ignored, especially with severely ill individuals. When the diagnosis is considered, *Histoplasma*-specific antibody or antigen testing could be considered; this was not the case for two-thirds of the subjects in the Benedict et al study. Interestingly, the most recent (2007) histoplasmosis management guidelines from the Infectious Diseases Society of America did not mention diagnostic testing.[4]

With improving HIV management and with increasing solid organ transplantation, HIV-infected patients accounted for only 11% of the immunocompromised patients in this study. The others had immune-mediated inflammatory disease, a hematologic malignancy, or a transplant. Whatever their immunocompromising condition, immunocompromised patients with respiratory symptoms should raise concern for histoplasmosis.

Benedict et al conducted their study when the 2007 Infectious Diseases Society of America's histoplasmosis treatment guidelines were established but still recent. Many patients do not need antifungal treatment. However, as noted in the editorial accompanying the

Benedict paper, when treatment is given, more than one-third of patients received a non-preferred regimen.[1] When dealing with conditions that we do not treat often, physicians should seriously consider following standard guidelines for the good of their patients. ■

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Omadacycline (Nuzyra)

By Denise Kwong, PharmD, BCPS

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

Omadacycline is a next-generation semisynthetic tetracycline derivative (aminomethylcycline) with broad spectrum in vitro activity against gram-positive and gram-negative aerobic organisms, anaerobes, atypicals, and other organisms such as *Yersinia pestis* and *Bacillus anthraxis*.[1] The drug was approved on Oct. 3, 2018, by the U.S. Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP).[2]

In the OASIS-1 Phase III, double-blind, randomized, controlled trial, patients with cellulitis were treated with either intravenous omadacycline or linezolid with the option to switch to oral antibiotics after three days. The total treatment duration was seven to 14 days. The patient population and study design were similar in OASIS-2, with the intervention arms consisting of strictly oral omadacycline vs. oral linezolid. The primary end point was early clinical response and survival with at least 20% reduction of ABSSSI lesion size within 48-72 hours. In both trials, omadacycline met 10% noninferiority margin compared to linezolid.[3,4]

The Optic study was a Phase III double-blind, randomized, noninferiority controlled trial comparing omadacycline with moxifloxacin in patients with CABP. Omadacycline met noninferiority criteria with the primary end point of early clinical response in omadacycline (81.1%) vs. moxifloxacin (82.7%), 95% confidence interval (CI), -7.1 to 3.8.[5] Currently, omadacycline is being evaluated for use in treating other infections, including cystitis and acute pyelonephritis.[1]

PHARMACOLOGY

Omadacycline is a semisynthetic tetracycline derivative (aminomethylcycline) that binds the 30s-ribosomal subunit to block protein synthesis. The chemical structure includes an aminomethyl group at the C9 position, which helps improve binding affinity and antimicrobial potency compared to tetracycline. Omadacycline has similar binding affinity as glycylcycline tetracyclines such as tigecycline and eravacycline.[7-9]

MICROBIOLOGY

Omadacycline demonstrates in vitro activity against several tetracycline-resistant strains. Some examples include gram-positive bacteria expressing tetracycline resistance (*tetK*, *tetL*, *tetM*) and *Enterobacteriaceae* expressing efflux gene (*tetB*). *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* with macrolide resistance (*erm A*, *B*, and/or C) and ciprofloxacin resistance genes (*gyrA* and *parC*) also were susceptible to omadacycline in vitro.[2]

Some notable gram-positive organisms with in vitro susceptibility data from the 2017 SENTRY Antimicrobial Surveillance Program include *S. aureus* (MRSA and MSSA) and *Enterococcus faecalis* with MIC50/90 0.12/0.25 mg/mL ABSSSI breakpoints. *E. faecium* isolates had MIC50/90 0.06/0.12 mg/L ABSSSI breakpoints. *Enterococcus* species tested included VRE isolates. For *Streptococcus*, FDA-identified susceptibility ABSSSI and CABP breakpoints for omadacycline are ≤ 0.12 mcg/mL with isolates of MIC 0.25 and ≥ 0.5 conferring intermediate susceptibility and resistance, respectively.[10] FDA-identified MSSA CABP breakpoints for omadacycline are

Table: Clinical Trials Summary[3-6]

Trial	Patient Population	Intervention	Outcomes	Results	Comments
O'Riordan, et al, 2018 (OASIS-1 trial) Phase III, randomized, double-blind, multicenter study Clinical trial NCT02378480	N = 655 adult patients with ABSSSI Cellulitis (38%), wound infection (33%), major abscess (29%) Mean age 47 years Male (65%) White (92%) Mean BMI 28.1 kg/m^2	Omadacycline 100 mg IV BID x 2 doses, then 100 mg IV once daily vs. linezolid 600 mg IV BID Duration: 7-14 days Could switch to oral after minimum 3 days	Primary end point: • Early clinical response: Survival with at least 20% reduction of ABSSSI lesion size within 48-72 hours • Investigator assessment of clinical success: Survival, resolution, and improvement at post-treatment evaluation visit 7-14 days after last day of therapy • Secondary end point: • Safety and tolerability (AE, vital signs, ECG, labs from 0 -37 days)	Early clinical response in omadacycline (84.8%) vs. linezolid (85.5%) 95% CI [-6.3 to 4.9] in mITT population* Clinical success in omadacycline (86.1%) vs. linezolid (83.6%) 95% CI [-3.2 to 8.2] in mITT population Success rates in *S. aureus*, MRSA, *S. anginosus*, and mixed infections similar in both groups in microbiologically mITT population Efficacy and safety similar in the following subgroups: CKD, higher BMI, IV drug use history, hepatitis C Trend toward higher clinical success in DM2 subgroup for omadacycline	
2018 (OASIS-2 trial) Phase III, randomized, double-blind, multicenter study Clinical Trial: NCT02877927	N = 735 adult patients with ABSSSI Excluded: immune compromised, ESRD on dialysis, septic shock, allergy to tetracyclines or linezolid Wound infection (58%), cellulitis (24%), major abscess (18%) Mean age 44 years Male (63%) White (91%) Mean BMI 27.9 kg/m^2	Omadacycline 450 mg/d on days 1 and 2, then 200 mg daily or linezolid 600 mg BID Duration: 7-14 days	Primary end point: • Early clinical response: Survival with at least 20% reduction of ABSSSI lesion size within 48-72 hours • Investigator assessment of clinical success: Survival, resolution, and improvement at post-treatment evaluation visit 7-14 days after last day of therapy	Early clinical response in omadacycline (87.3%) vs. linezolid (82.2) 95% CI [-2.0 to 10.5] Clinical success in omadacycline (83.9%) vs. linezolid (80.5%) 95% CI [-2.3 to 9.1] in mITT population	Omadacycline met 10% noninferiority margin compared to linezolid
Stets R, et al, 2017 (OPTIC study) Phase III, randomized, double-blind, multicenter, noninferiority study Clinical Trial: NCT02531438	N = 774 adult patients with CABP Excluded: known or suspected HAP, immune compromised, allergy to tetracycline or fluoroquinolone Mean age 62 years > 75 years (20.4%)	Omadacycline 100 mg IV every 12 hr x 2 doses, then 100 mg IV daily vs. moxifloxacin 400 mg IV daily Minimum 3 days IV, then option to switch to oral (omadacycline 300 mg daily or moxifloxacin 400 mg daily) Total duration: 7-14 days	Primary end point: • Early clinical response: Survival, no rescue antibiotic given, symptom improvement within 72-120 hours after first dose • Investigator assessment of clinical success: Survival, resolution, and improvement at post-treatment evaluation visit 5-10 days after last dose Secondary end point: • Clinical success at post-treatment evaluation	Early clinical response in omadacycline (81.1%) vs. moxifloxacin (82.7%) 95% CI [-7.1 to 3.8] Clinical success in omadacycline (87.6%) vs. moxifloxacin (85.1%) 95% CI [-2.4 to 7.4] Clinical success in clinically evaluable cohort for omadacycline (92.9%) vs. moxifloxacin (90.4%) 95% CI [-1.7 to 6.8]	Omadacycline met 10% noninferiority margin compared to moxifloxacin Eight patients with *S. pneumoniae* resistant to tetracycline still responded to omadacycline

(*continued*)

Table: Clinical Trials Summary (continued)[3-6,13,14]

Trial	Patient Population	Intervention	Outcomes	Results	Comments
Adaptive Phase II, randomized, double-blind, multicenter, noninferiority study	Est. N = 200 female adults uncomplicated urinary tract infections/ cystitis	Omadacycline oral vs. nitrofurantoin Total duration: 14 days	• Clinical success defined by resolution of cystitis symptoms • Investigator assessment of clinical response post-treatment evaluation	N/A — study still recruiting and not yet complete	
Adaptive Phase II, randomized, double-blind, multicenter, noninferiority study	Est. N = 200 female adults acute pyelonephritis	Omadacycline IV or IV/oral vs. IV/ oral levofloxacin	Investigator assessment of clinical response post-treatment evaluation	N/A — study still recruiting and not yet complete	

*Patients without a potentially causative monomicrobial gram-negative infection

≤ 0.25 mcg/mL with isolates of MIC 0.5 and ≥ 0.1 conferring intermediate susceptibility and resistance, respectively.[11]

Some notable gram-negative organisms with in vitro susceptibility data from the 2017 SENTRY Antimicrobial Surveillance Program include *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* with MIC50/90 4/8 mg/L. *Pseudomonas* was not susceptible to omadacycline.[10] FDA-identified susceptibility ABSSSI breakpoints for omadacycline against *Enterobacteriaceae* are ≤ 4 mcg/mL with isolates of MIC 8 and ≥ 16 conferring intermediate susceptibility and resistance, respectively. Of note, omadacycline is not active in vitro against *Morganella*, *Proteus*, and *Providencia*. FDA-identified susceptibility CABP breakpoints for omadacycline against *Haemophilus* are ≤ 2 mcg/mL with isolates of MIC 4 and ≥ 8 conferring intermediate susceptibility and resistance, respectively.[11]

Omadacycline has a broad spectrum that includes in vitro activity against anaerobes such as *Bacteroides fragilis* with MIC90 4 mcg/mL and *Clostridioides difficile* with MIC 90 0.25 mcg/mL. Omadacycline also has in vitro activity against *Mycobacterium* species, including *M. abscessus* (MIC90 2 mcg/mL), *M. fortuitum* (MIC90 0.5 mcg/mL), and *M. chelonae* (MIC90 0.25 mcg/mL).[1,10]

PHARMACOKINETICS

Omadacycline comes in oral and intravenous formulations, with 34.5% bioavailability of the oral formulation. Absorption is affected by food and divalent cations, with max concentrations and AUC decreasing by 42% and 63%, respectively, when a high-fat meal with dairy is administered two hours prior to omadacycline dosing. Omadacycline is not metabolized by the liver. It is excreted primarily in the urine unchanged with the intravenous formulation and in the feces with the oral formulation. Compared to tigecycline, omadacycline has higher lung penetration compared to plasma AUC.[2]

PHARMACODYNAMICS

Qtc prolongation was not appreciable in Phase III clinical trials compared to moxifloxacin. Transient tachycardia was observed in Phase I studies.[2]

Omadacycline does not require renal or hepatic dose adjustment. The oral formulation should be taken with water on an empty stomach fasting four hours prior to administration. Avoid concurrent dairy

Table: Dosage and Administration[2]

Indication	Dose	Treatment Duration
Adult CABP	Load: 200 mg IV x 1 or 100 mg IV BID on day 1 Maintenance: 100 mg IV daily or 300 mg oral daily	7-14 days
Adult ABSSSI	Load: 200 mg IV x 1 or 100 mg IV BID on day 1 Maintenance: 100 mg IV daily or 300 mg oral daily	7-14 days
Adult ABSSSI (tablets only)	Load: 450 mg oral daily on day 1 and day 2 Maintenance: 300 mg oral daily	7-14 days

CABP = community-acquired bacterial pneumonia; ABSSSI = acute bacterial skin and skin structure infection

Table: Cost[7]

Drug Name	How Supplied	Average Wholesale Price	Cost Per Day (maintenance dose)	Cost Per 7-Day Course
Omadacycline for injection	100 mg single-dose vial	$414.00	$414.00	$3,312
Omadacycline tablet	150 mg tablet	$237.00	$474.00	$3,792

products, antacids, or multivitamins two hours before or four hours after administration. The intravenous formulation is infused in a dedicated IV line over 30-60 minutes and flushed with 0.9% sodium chloride or 5% dextrose before and after medication administration.[2,12]

CONTRAINDICATIONS

Use of omadacycline is contraindicated in patients who have known hypersensitivity to omadacycline or to the tetracycline class of antibacterial medications.[2]

WARNINGS/PRECAUTIONS

In the CABP clinical trial, there were eight deaths among patients with community-acquired bacterial pneumonia treated with omadacycline (2%) compared to four deaths (1%) with moxifloxacin. Deaths occurred in patients > 65 years of age with multiple comorbidities. Although this mortality imbalance was noted in the clinical trial, the cause and clinical significance were not defined.[2] Pregnancy was excluded in the clinical trials, although tetracyclines as a class can cause tooth discoloration, enamel hypoplasia, and inhibition of bone growth during the second and third trimesters of pregnancy.[2]

ADVERSE EFFECTS

Common (> 2%) adverse effects include nausea, vomiting, infusion site reactions, ALT/AST/GGT increase, hypertension, headache, diarrhea, insomnia, and constipation.[2]

SIGNIFICANT DRUG INTERACTIONS

Omadacycline absorption is impaired by antacids containing aluminum, calcium or magnesium, bismuth subsalicylate, and iron. No notable antagonistic interactions with other antimicrobials were identified.[2]

CONCLUSION

Omadacycline is a synthetic tetracycline derivative that shows promise with overcoming tetracycline resistance. This medication is FDA-approved for CABP and ABSSSI. There are new Phase II clinical trials in recruitment for cystitis and pyelonephritis. Its place in therapy is still being established. ■

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Updates

By Carol A. Kemper, MD, FACP

California Inmates With Cocci Lose Appeal

SOURCES: United States Court of Appeals for the Ninth Circuit, Feb. 1, 2019; http://cdn.ca9.uscourts.gov/datastore/opinions/2019/02/01/15-16145.pdf; California Department of Public Health. Coccidioidomycosis in California Provisional Monthly Report, January-April 2019. Available at: https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/CocciinCAProvisionalMonthlyReport.pdf. Accessed May 6, 2019.

In February 2019, in response to four consolidated appeals, the United States Court of Appeals for the Ninth Circuit reversed, in part, earlier district court rulings stating that inmates at several California state prisons were exposed to an increased risk of coccidioidomycosis, constituting a violation of their Eighth Amendment rights. African-American inmates also sued under the 14th Amendment, alleging unequal protection based on an increased risk of acquiring coccidioidomycosis because of race. Recall that the Eighth Amendment is the right to be free from cruel and unusual punishment; whereas the Equal Protection Clause of the 14th Amendment says prisoners are protected against discrimination or unequal treatment based on race, sex, age, national origin, and creed. The original court filings alleged the increased risk of coccidioidomycosis in prison facilities located near Coalinga, in Fresno County, and in Avenal, in Kings County, had resulted in the deaths of 40 inmates, and more than 100 others required long-term medical care for chronic infection.

The Appeals Court for the Ninth Circuit stated that specific state and prison officials were entitled to qualified immunity against such claims they had acted with deliberate intent, as the right to be free from exposure to Valley Fever had not been established at the time the officials acted. Further, there was no evidence that society shared the attitude that involuntary exposure violated current standards of decency, since millions of people voluntarily choose to live in endemic areas in California, despite a recognized risk, and that coccidioidomycosis occurs in areas outside of California (i.e., Arizona). The Appeals Court also stated that African Americans did not clearly have an established right to be segregated to avoid the risk of exposure.

The history behind these district appeals and current decision is of interest. Beginning in 2005, an increase in coccidioidomycosis infection in prisoners in certain facilities located in the California Central Valley prompted investigation by the California Department of Public Health (CDPH) of an increased number of cases at Pleasant Valley State Prison (PVSP) located in Coalinga, CA. In January 2007, CDPH reported that 166 cocci infections had occurred in prisoners at PVSP, including 29 hospitalizations and four deaths. This infection rate was approximately 38 times higher than the rate among residents of Coalinga and 600 times higher than that of Fresno County at the time. It was recommended that removing immunosuppressed patients from the facility would help reduce the risk. In response, in November 2007, a statewide prison policy was established to remove — or not house in the first place — individuals at risk for cocci, based on six different criteria. These included HIV infection, a history of solid organ transplant or other immunosuppression, current chemotherapy, a history of lymphoma, or moderate to severe chronic obstructive pulmonary disease (COPD). This policy was amended and broadened in 2010.

Despite these policy changes, the risk of cocci infection in inmates at certain California facilities remained high. From 2006 to 2010, the risk of cocci infection was 7% at PVSP and 1.3% at Avenal State Prison, both significantly higher than the rate of infection in those communities. From 2006 to 2011, 36 inmates in Central Valley prisons died from cocci infection. Notably, 71% of these were African American, more than double the percentage of African American prisoners at the time. Following this report, in 2012, a district court overrode state objections and suspended the transfer of African Americans and prisoners with diabetes to Central Valley facilities.

The reasons for the apparent higher rates of infection in inmates are not entirely clear. PVSP was next door to a large construction project at the time of the original outbreak. Undoubtedly, individuals who lack immunity to cocci and move into a hyperendemic area are at greater risk for acquiring infection compared with residents who have lived in the area for years and who may have acquired immunity. It would be helpful, therefore, to compare the rates of infection in inmates to residents moving into these endemic areas, rather than to overall county statistics. A colleague of mine once examined the

risk of acquiring cocci infection in individuals who lived in western Washington state in the summer and wintered in Arizona, finding that approximately 3% acquired cocci annually.

Since the rates of coccidioidomycosis continue to increase in California, the risk to inmates in high-risk areas also is likely to increase. In 2017, more than 14,343 cases of Valley Fever were reported to the Centers for Disease Control and Prevention — approximately half of these cases were from California. Provisional data for 2018 suggest cases have increased 36% over 2016 figures, including approximately 3,000 cases in Kern County, followed by Los Angeles (1,046), Fresno (633), and Tulare (507). ■

Tuberculosis Testing in Small Children

SOURCE: Velasco-Arnaiz E, Soriano-Arandes A, Latorre I, et al. Performance of tuberculin skin tests and interferon-gamma release assays in children younger than 5 years. *Pediatr Infect Dis* 2018;37:1235-1241.

Tuberculosis (TB) screening in small children remains controversial. Although Interferon-gamma release assays (IGRA) largely have replaced TST skin testing in many healthcare facilities, at least in first-world countries, current guidelines in the United States, Canada, and Europe still advocate for skin testing over IGRA as the preferred screening tool in children younger than 5 years of age, regardless of a history of BCG vaccination. However, in some countries, such as Spain, IGRA testing is recommended as an adjunct, especially in those at risk for TB with a negative skin test or those with a history of BCG vaccination and a positive skin test. Investigators in Spain examined the use of skin testing vs. IGRA testing (Quantiferon-TB Gold In-Tube) in children younger than 5 years of age at risk for TB who were evaluated at two tertiary pediatric TB units in Barcelona. The study was conducted from 2005 to 2015.

A total of 383 children younger than 5 years of age were included in the study, all of whom received both skin testing and IGRA testing. Children with immune suppression or steroid use were excluded from analysis. The children were undergoing evaluation for latent TB infection (LTBI) as either part of contact tracing or as a new immigrant exam, or were being assessed for suspected active TB. Children with a history of BCG vaccination were statistically older and more likely to be screened for a new entrance exam.

A total of 304 children were considered uninfected. During a median of 47 months of follow-up, one of these children, a 3-year-old Pakistani boy, developed active TB. He had a history of BCG vaccination, a positive skin test at 8 mm, and a negative IGRA test. The skin test had been attributed to his BCG testing and he had not received treatment for latent TB.

Forty children were diagnosed with latent TB and treated with either isoniazid for six to nine months or isoniazid and rifampin for three months, per current guidelines in Spain. With a median of 42 months of follow-up after completion of anti-TB medications, none of them developed TB.

Thirty-nine were diagnosed with active TB, including 15 with confirmed TB and 23 with suspected TB. The sensitivity in children with confirmed TB was 100% for skin testing and 93.7% for IGRA testing. Test results in the 23 children with suspected TB were more variable, and included five children (22%) with concordant negative skin and IGRA testing. All five of these children had symptoms and radiographic evidence consistent with active TB and responded to therapy. Two others had positive skin tests and negative IGRA, and one child with suspected TB had a positive skin test and an indeterminate IGRA. This suggests that IGRA was negative or indeterminate in 53% of those children with suspected TB.

In those without active TB, discordance between the two tests was 16.8% (similar to screening test results in U.S. adults at low risk for TB). All of this was attributed to positive skin testing and negative IGRA results. However, if those children with BCG vaccination were excluded, the agreement between the two tests was much better (94.6%). Only 3.6% of the children had indeterminate IGRA test results. Most of these were in children younger than 2 years of age (8.7%) compared with older children (0.8%), $P < 0.001$.

For those children with a history of BCG vaccination and a positive skin test/negative IGRA, it is still not possible to determine whether they have latent TB. Some argue that because discordance is so much more common in BCG-vaccinated children, the negative IGRA test should be believed. Others argue that the risk of a positive skin test in such children is only 8% to 20% depending on the age of BCG vaccination and age of testing, so a history of BCG vaccination should be disregarded. In the end, pre-test probability should be taken into account, similar to the decision-making for adults with a history of BCG in the United States. If such children are from a country endemic for TB, then the history of BCG should be disregarded. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. **In the study by Hvas et al, patients with recurrent infections due to *Clostridioides difficile* were randomized to one of three treatment arms. Which of the following is correct regarding the results?**

   a. Fecal microbiota transplantation was significantly better than fidaxomicin.

   b. Fidaxomicin was significantly better than vancomycin.

   c. Fecal microbiota transplantation and fidaxomicin provided identical results.

   d. Fidaxomicin and vancomycin provided identical results.

2. **Which of the following statements is true regarding histoplasmosis?**

   a. It is a fungal infection associated with bites from bats.

   b. It is more common in the Western United States than elsewhere in the country.

   c. It is uniformly fatal in HIV-infected patients.

   d. It may be diagnosed using *Histoplasma*-specific antibody and antigen detection tests.

3. **Which of the following is correct regarding omadacycline?**

   a. It is FDA-approved for treatment of ventilator-associated pneumonia.

   b. It is available for both oral and intravenous administration.

   c. Significant dosage adjustments are necessary for patients with hepatic dysfunction.

   d. It is highly active against *Pseudomonas aeruginosa*.

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.