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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Mumps Vaccine — Third Dose During Outbreaks

By Philip R. Fischer, MD, DTM&H

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

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

SYNOPSIS: Mumps immunity wanes over time, with a notable increase in risk of infection 13 or more years after completion of the currently recommended series of vaccines. During an outbreak of mumps, receipt of an extra (third, by American schedules) vaccine significantly reduces the risk of becoming sick with mumps.

SOURCE: Cardemil CV, Dahl RM, James L, et al. Effectiveness of a third dose of MMR vaccine for mumps outbreak control. *N Engl J Med* 2017;377:947-956.

With widespread measles-mumps-rubella (MMR) vaccination in the United States, mumps has become uncommon. However, there have been five outbreaks involving thousands of cases during the past 13 years. Many of these outbreaks have centered on university campuses, where more than 90% of students had received the recommended two-dose MMR series.

Public health specialists documented outcomes during a "natural experiment" of a mumps outbreak at the University of Iowa during the 2015-2016 academic year. There were 20,496 students enrolled at the time. Overall, 98.1% of the students had received at least two MMR vaccines prior to that school year. Because of the mumps outbreak, widespread vaccination was initiated, even in individuals who previously had been "fully" vaccinated. A total of 4,783 people received an MMR vaccine. During the outbreak, 256 university students developed mumps; students accounted for two-thirds of all mumps cases seen in that geographical area during that academic year.

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Students who received a third vaccine dose had an infection rate of 6.7 per 1,000 people, only about half the 14.5 rate seen in those who had received only two doses. If the second MMR had been given 13 or more years before the outbreak, there was a nine-fold increased risk of mumps infection if the third dose was not given during the outbreak.

The authors concluded that waning post-vaccine immunity was probably at least partially responsible for the propagation of the mumps outbreak. They also noted that the vaccine administration campaign providing a third dose of MMR vaccine improved outbreak control. It also is likely that a strong program of testing and case detection, as well as isolation of affected individuals, contributed to the resolution of the outbreak.

■ COMMENTARY

Vaccines are not perfect, even though they save lives and prevent lots of bothersome illness. The careful documentation of the effectiveness of mumps vaccination during an outbreak on a university campus is illustrative and informative. Especially when people are at risk of mumps exposure more than 12 years after completing the two-dose MMR vaccination series, they can be helped by receiving a third dose of vaccination.

So, should all students entering university receive an additional/third dose of MMR vaccine? That likely would be effective, but the costs of vaccination and of administration programs could be prohibitive. And, even though we hear about outbreaks of mumps on university campuses every one to three years, only a small minority of campuses have been affected.

After a large campus outbreak of mumps in Illinois, the Centers for Disease Control and Prevention (CDC) discussed a third MMR dose during outbreaks but did not have adequate effectiveness data to formalize a recommendation.[1] The Iowa experience provides that previously missing data. Thus, in late October 2017, the Advisory Committee on Immunization Practices proposed to the full CDC that a third dose of MMR vaccine be given to people deemed to be at risk of mumps during outbreaks, even if they previously received two MMR doses; the final CDC endorsement of this proposal is pending.[2]

Of course, mumps is not just an American problem. Investigators in France reviewed mumps outbreaks in military barracks and university campuses.[3] They noted that many cases were in individuals who had received the recommended two MMR vaccine doses, and that immunity waned after vaccination. In fact, there was a 10% increase in mumps risk each year after receipt of the second vaccine dose.[3] Based on these data, the French High Council of Public Health recommended in 2013 that a third MMR dose be given during outbreaks for those whose second dose was more than 10 years prior.[4] With the Iowa data showing effectiveness, the United States now is making a similar recommendation to what the French proposed four years ago, although the U.S. recommendation in its current draft form does not depend on the length of time since the second MMR.

International travel also is a risk factor for outbreaks and cases of measles and rubella, in addition to mumps.[5,6,7] Children, college students, and adults should be appropriately current on routine vaccination (as well as specific travel-related vaccines) prior to international travel.[8,9,10] Now, based on the Iowa data and pending CDC recommendation, people traveling to areas with active mumps outbreaks would be advised to get an "extra" third MMR dose. ■

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ABSTRACT & COMMENTARY

Lyme Disease in the United States — Good News, Bad News

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: The incidence of Lyme disease appears to have stabilized in states with known high incidences of the infection, but there is evidence of geographic expansion into neighboring states.

SOURCE: Schwartz AM, Hinckley AF, Mead PS, et al. Surveillance for Lyme disease — United States, 2008–2015. *MMWR Surveill Summ* 2017;66:1–12.

The CDC received 275,589 reports of Lyme disease from 2008-2015. Of these, 208,344 were confirmed and 66,755 were probable. An average of 8,344 probable cases were reported annually.

Fourteen Northeast, mid-Atlantic, and upper Midwest states (Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, and Wisconsin) accounted for 95.2% of all reports. (*See Figures 1 and 2.*) Three-fourths of cases reported from these states were confirmed. There was no significant change in the median annual percentage change in the number of reported cases in these states over the period examined and, in fact, there was a decreasing trend in seven of the 14 states. (*See Figure 1.*) In contrast, in 11 states and the District of Columbia that neighbor the 14 high-incidence states, the overall median annual change in confirmed cases was 6.6% (range, -16.7% to 31.3%), with an increasing trend in eight of the 11 states. Thus, there is evidence of geographic expansion of the disease.

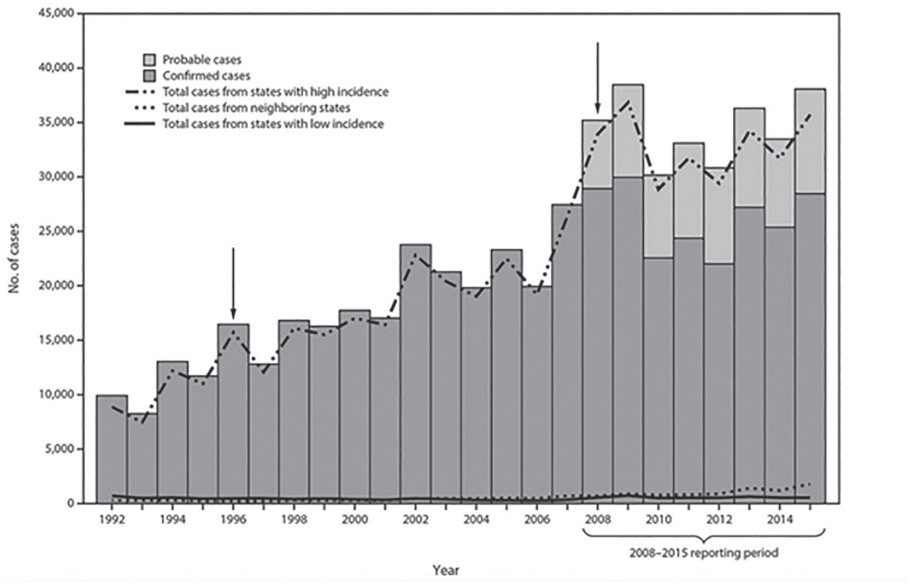
Peaks in incidence by age occurred bimodally, at 5-9 years and at 50-55 years. Erythema migrans was reported in 72.2% of patients, while 27.5% had arthritis and 1.5% had carditis. A neurological manifestation was reported in 12.5% of patients, with facial palsy in 8.4%, radiculoneuropathy in 3.8%, and meningitis in 1.3%. Less than 1.0% had encephalitis. The proportion of patients with erythema migrans was lower in low-incidence states (64.7%) than in high-incidence states (72.3%), while the reverse was true for neurological manifestations (20.0% and 12.2%, respectively).

[With more than 30,000 cases each year, Lyme disease is the most frequently reported vector-borne disease in the United States.]

■ COMMENTARY

With more than 30,000 cases each year, Lyme disease is the most frequently reported vector-borne disease in the United States. The apparent stabilization of the reported incidence of Lyme disease from 2008-2015 could be real or could be the result of changing case definitions over the period examined. Of note is

Figure 1. Number* of Confirmed and Probable Lyme Disease Cases, by State Surveillance Category† and Year — United States, 1992-2015§



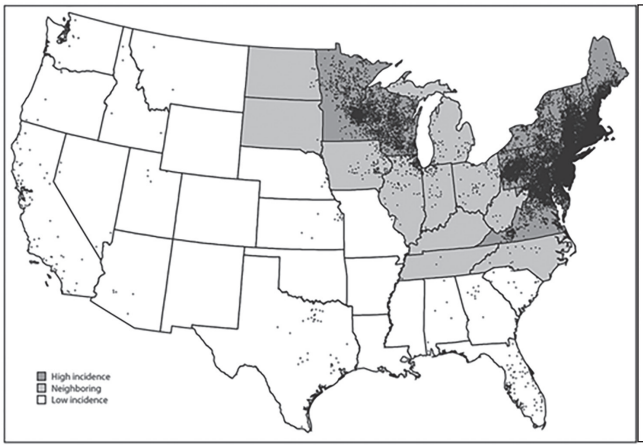
*N = 551,107

† State surveillance categories were determined using three classifications: high incidence, neighboring, and low incidence. States with an average annual incidence ≥10 confirmed Lyme disease cases per 100,000 population were classified as high incidence, states that share a border with those states or are located between states with high incidence were classified as neighboring, and all other states were classified as low incidence.

§ Arrows indicate notable changes in case definitions. The case definition was revised in 1996 to recommend a two-step testing method and in 2008 to increase specificity of laboratory evidence of infection and to include provision for report of probable cases.

Source: Centers for Disease Control and Prevention

Figure 2. Average Annual Number of Confirmed Lyme Disease Cases, by County of Residence* — United States, 2008-2015†



* Each dot represents one confirmed case according to the patient's county of residence.

† State surveillance categories were determined using three classifications: high incidence, neighboring, and low incidence. States with an average annual incidence ≥ 10 confirmed Lyme disease cases per 100,000 population were classified as high incidence, states that share a border with those states or are located between states with high incidence were classified as neighboring, and all other states were classified as low incidence.

Source: Centers for Disease Control and Prevention

that the definition has been changed again in 2017, with the hope of increasing specificity. At the same time that the incidence of infections apparently has stabilized in high-incidence states, there is evidence that it is increasing in neighboring states, a finding consistent with evidence of an increase in the range of established populations of *Ixodes scapularis*, the vector of *Borrelia burgdorferi*. In the upper Midwest, *Borrelia mayonii* also causes Lyme disease and is transmitted by the same tick species. In the western Pacific region, the vector is *Ixodes pacificus*.

The clinical differences noted in cases in high- and low-incidence states may be due to the increase in false positives when tests are applied to low-prevalence populations. In addition, skin manifestations resembling erythema migrans may occur in states, including some with low incidences of Lyme disease, in which southern tick-associated rash illness is seen.

The apparent stabilization of cases in high-incidence states is encouraging. However, the geographical expansion into neighboring states can only engender concern. ■

ABSTRACT & COMMENTARY

Statin Use Is Associated With a Lower Risk of Community-acquired *Staphylococcus aureus* Bacteremia

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

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

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

SYNOPSIS: A population-based case-control study from Denmark found the use of statins was associated with a decreased risk for community-associated *Staphylococcus aureus* bacteremia, with the greatest benefit from higher doses.

SOURCE: Smit J, López-Cortés LE, Thomsen RW, et al. Statin use and risk of community-acquired *Staphylococcus aureus* bacteremia: A population-based case-control study. *Mayo Clin Proc* 2017;92:1469-1478.

Staphylococcus aureus bacteremia (SAB) is a serious and often fatal infection despite appropriate therapy. There is some evidence that statins have anti-staphylococcal activity. Therefore, Smit and colleagues sought to determine whether patients who took statins to lower their cholesterol had a reduced risk for developing community-acquired SAB.

The study was conducted in Denmark between Jan. 1, 2000, and Dec. 31, 2011. The investigators compiled data from multiple population-based medical registries. Patients were included if they were 15 years of age or older and had one or more positive blood cultures for *S. aureus* as the sole isolate collected within two days of hospital admission. For each case, 10 randomly selected controls were matched according to age, sex, and area of residence. Researchers used another database to identify all prescriptions filled for statins by cases and controls before the index date. Statin usage was defined further as new users, who filled their first-ever statin prescription within 90 days of the index date, and long-term users, who had previously filled a statin prescription. The databases also were used to record comorbid conditions and other prescriptions, including those for corticosteroids, immunomodulating drugs, chemotherapy drugs, and nonsteroidal anti-inflammatory drugs (NSAIDs).

The researchers identified 2,638 cases of community-acquired SAB. Only 13 (0.5%) of the cases were due to methicillin-resistant *Staphylococcus aureus* (MRSA). The median age was 69 years and the majority were males (61%). The patients with SAB were more likely than the controls to have comorbidities, including peripheral arterial disease, congestive heart failure, diabetes mellitus, and cancer. They also were more likely to have filled prescriptions for corticosteroids and NSAIDs. Compared to non-statin users, the adjusted odds ratio (aOR) was 0.96 (95% confidence interval [CI], 0.60-1.51) for new users, 0.71 (95% CI, 0.62-0.82) for long-term users, and 1.12 (95% CI, 0.94-1.32) for former users. The risk of SAB decreased with increasing statin doses, such that the aOR was 0.84 (95% CI, 0.68-1.04) for current users with daily doses < 20 mg/d compared to 0.63 (95% CI, 0.49-0.81) for current users with daily doses of 40 mg/d or more. The decrease in SAB risk was most pronounced in patients with chronic kidney disease (aOR, 0.51; 95% CI, 0.34-0.76) and patients with diabetes mellitus (aOR, 0.65; 95% CI, 0.50-0.85). There were no differences in the risk of SAB according to sex, age, Charlson comorbidity index, or between the different brands of statins.

[In vitro studies suggest that statins exert several pleiotropic effects that theoretically could decrease the risk for SAB.]

COMMENTARY

In this study, current users of statins experienced an almost 30% reduction in the risk of SAB compared to nonusers. The risk decreased as the statin dose increased, with the association most pronounced in patients with chronic kidney disease and diabetes.

These findings are consistent with other evidence showing statins to be associated with a lower risk of pneumonia, sepsis, and post-operative infections.

In vitro studies suggest that statins exert several pleiotropic effects that theoretically could decrease the risk for SAB. First, statins have a direct antimicrobial effect against *S. aureus*. The minimum inhibitory concentration of simvastatin against *S. aureus* ranges from 15 to 32 mg/mL, although this is considerably higher than the concentration of 0.02 mg/mL attained from 40 mg of the drug. Second, statins inhibit host cell invasion and biofilm formation by *S. aureus*. Third, statins enhance the ability of neutrophils to kill *S. aureus*. Thus, it would appear that statins may have a role as a complementary strategy in preventing SAB.

The study by Smit and colleagues should serve as a foundation for a randomized, placebo-controlled clinical trial to confirm the beneficial effects of statin use in reducing the risk for SAB. This possibility is exciting because statins are relatively inexpensive, have a favorable safety profile, and do not have the drawbacks associated with using antibiotics for SAB prevention, such as increasing the spread of antimicrobial resistance and *Clostridium difficile* infection.

The study had a few limitations that deserve mentioning. First, the investigators assumed that by patients filling their statin prescription they actually were taking it, which is unlikely in all cases. Second, the rate of SAB due to MRSA (0.5%) in the study was extremely low compared to what is seen in the United States (approximately 40%), which hinders extrapolation of the results to other settings where the incidence of MRSA is higher. Third, there may have been bias from the so-called "healthy user" effect, whereby statin users are more likely to engage in other healthy behaviors (e.g., less obesity, not smoking, more exercise, etc.) compared to non-statin users.

Smit and colleagues have presented persuasive evidence for a beneficial effect from statins in preventing community-acquired SAB. However, a randomized, placebo-controlled trial will be necessary before a strong evidence-based recommendation for this indication can be endorsed. ■

Meropenem-vaborbactam

By Jamie Kuo, PharmD, BCCCP

Department of Pharmacy, Stanford Health Care

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

Meropenem-vaborbactam (Vabomere) is the latest β-lactam/β-lactamase inhibitor (BLI), approved by the FDA in August 2017 for treatment of complicated urinary tract infections (cUTI), including pyelonephritis, caused by susceptible *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* species complex in adults older than 18 years of age. Meropenem is an existing carbapenem antibacterial that exhibits bactericidal activity by binding to intracellular penicillin-binding proteins (PBP) and inhibiting bacterial cell wall synthesis. Vaborbactam is a novel boronic acid, non-suicidal, reversible BLI without intrinsic antibacterial activity.

Vaborbactam prevents degradation of meropenem by serine β-lactamases to restore activity against *Enterobacteriaceae* including *Klebsiella pneumoniae* carbapenemase (KPC). Meropenem-vaborbactam has activity against most Ambler class A, C, and some class D β-lactamases (oxacillinases without carbapenemase activity). Notably, meropenem-vaborbactam is not active against metallo-β-lactamases (MBL). The addition of vaborbactam did not significantly improve activity of meropenem against *Acinetobacter baumannii* or *Pseudomonas aeruginosa* in vitro, nor did it affect activity against anaerobes when studied in combination with biapenem.

Table 1. Mean Population Pharmacokinetics of Meropenem-vaborbactam

Pharmacokinetic Parameter	Meropenem	Vaborbactam
Protein binding	2%	33%
Vd at steady-state	20.2 L	18.6 L
Cl (L/h), multiple doses	15.1	10.9
t½ (h)	1.22	1.68
Metabolism	Hydrolysis, 22%	None
Excretion	Urine, 40-60% unchanged Feces, 2%	Urine, 75-95% unchanged

Table 2. TANGO-1 Trial Summary

<table>
<tr><th>Trial</th><th>Intervention</th><th>Results</th></tr>
<tr><td>TANGO-1
Phase III
Multi-center, double-blind, double-dummy, randomized, controlled trial

N = 545 adult patients with cUTI, including acute pyelonephritis</td><td>Meropenem-vaborbactam
4 g IV q8hr
(3-hr infusion)

vs.

Piperacillin-tazobactam
4.5 g IV q8hr
(30 min infusion)

Then step down to levofloxacin 500 mg PO q24hr after ≥ 5 days IV therapy

Total treatment duration 10-14 days</td><td>
<table>
<tr><th>Primary Outcomes</th><th>Meorpenem-Vaborbactam</th><th>Piperacillin/Tazobactam</th><th>Different (95% CI)</th></tr>
<tr><td>Clinical cure or improvement AND microbiological eradication at EOIVT (m-MITT)</td><td>189/192 (98.4%)</td><td>171/182 (94%)</td><td>4.5%
(0.70-9.1%)</td></tr>
<tr><td>Microbiological eradication at TOC (ME)</td><td>118/178 (66.3%)</td><td>102/169 (60.4%)</td><td>5.9%
(-4.2-16%)</td></tr>
</table>
• Infections included 59% pyelonephritis and 27 patients with bacteremia: meropenem-vaborbactam 12 (6%), piperacillin-tazobactam 15 (8%). 10/12 (83.3%) patients who received meropenem-vaborbactam had clinical and microbiological response.
• Patients with ESBL-positive pathogens had similar rates of clinical and microbiological response as ESBL-negative pathogens at EOIVT but had lower rates of response at TOC.
• Some isolates of E. coli, K. pneumoniae, E. cloacae, C. freundii, P. mirabilis, P. stuartii producing β-lactamases, including KPC, CTX-M, TEM, SHV, CMY, and ACT were susceptible to meropenem-vaborbactam (MIC ≤ 4 mcg/mL). One isolate of K. pneumoniae that produced CTX-M, TEM, SHV, and OXA β-lactamases was not susceptible to meropenem-vaborbactam (MIC ≥ 32 mcg/mL)
• 10% of patients in each arm violated protocol by receiving PO levofloxacin step-down therapy for resistant pathogens and were included in m-MITT population.
<table>
<tr><th>Safety Outcomes</th><th>Meorpenem-Vaborbactam N = 272</th><th>Piperacillin/Tazobactam N = 273</th></tr>
<tr><td>Treatment emergent adverse events (TEAE)</td><td>106 (39%)</td><td>97 (35.5%)</td></tr>
<tr><td>Drug-related TEAE</td><td>41 (15.1%)</td><td>35 (12.8%)</td></tr>
<tr><td>Study drug discontinuation due to adverse event</td><td>7 (2.6%)</td><td>14 (5.1%)</td></tr>
<tr><td>Serious adverse events</td><td>11 (4%)</td><td>12 (4.4%)</td></tr>
<tr><td>Death</td><td>2 (0.74%)</td><td>2 (0.73%)</td></tr>
</table>
</td></tr>
<tr><td colspan="3">cUTI = complicated urinary tract infection; m-MITT = microbiological modified intent-to-treat; EOIVT = end of IV treatment visit (Days 5-14), includes patients with piperacillin-tazobactam-resistant organisms at baseline; ME = microbiologic evaluable; TOC = test of cure visit after completion of treatment (Days 15-23), excludes patients with piperacillin-tazobactam-resistant organisms at baseline; CI = confidence interval</td></tr>
</table>

PHARMACOKINETICS/PHARMACODYNAMICS

(*See Table 1.*)

- Meropenem exposure is affected by renal impairment, resulting in increased AUC.
- Both meropenem and vaborbactam are removed by hemodialysis. Following administration of 2 g meropenem-vaborbactam, 38% of the meropenem and 53% of the vaborbactam dose was recovered in the dialysate.
- Pharmacokinetics of meropenem are not affected by hepatic impairment. Vaborbactam is not anticipated to be affected by hepatic function, either, given it does not undergo hepatic metabolism.
- Meropenem demonstrates time-dependent bacterial killing while the pharmacodynamics target of vaborbactam appears to be AUC:MIC based on in vitro and animal studies.

CLINICAL TRIALS[3,4]

The efficacy and safety of meropenem-vaborbactam compared to piperacillin-tazobactam were examined in a Phase III multi-center, double-blind, double-dummy, randomized, controlled trial for the treatment of cUTI, including acute pyelonephritis, in adults. (*See Table 2.*) Meropenem-vaborbactam met statistical significance for superiority over piperacillin-tazobactam in the FDA primary endpoint of clinical cure or improvement and microbiological eradication at the end of IV treatment in the microbiological modified intent-to-treat population. For the primary endpoint of microbial eradication at test of cure visit, meropenem-vaborbactam was non-inferior to piperacillin-tazobactam in the microbiolic evaluable population.

ADVERSE EFFECTS[1,4]

The most common adverse events reported in the Phase III clinical trial comparing meropenem-vaborbactam to piperacillin-tazobactam in adult

Table 3. Meropenem-vaborbactam Dosing

eGFR (mL/min/1.73m^2)	Vabomere Dose	Dosing Interval
≥ 50	4 g (meropenem 2 g and vaborbactam 2 g)	Q 8 hours
30-49	2 g (meropenem 1 g and |vaborbactam 1 g)	Q 8 hours
15-29	2 g (meropenem 1 g and vaborbactam 1 g)	Q 12 hours
< 15	1 g (meropenem 0.5 g and vaborbactam 0.5 g)	Q 12 hours

patients with cUT/acute pyelonephritis were headache (8.8%), phlebitis/infusion site reactions (4.4%), and diarrhea (3.3%). Adverse events led to study drug discontinuation in 2.6% of patients receiving meropenem-vaborbactam compared to 5.1% of patients who received piperacillin-tazobactam. The most common reason for discontinuation due to adverse effect was hypersensitivity (1.1%), followed by infusion-related reactions (0.7%). Death occurred in two patients in each arm.

DOSAGE AND ADMINISTRATION[1]

- Meropenem-vaborbactam is administered as an intravenous infusion over three hours.
- Dosing is expressed as total grams of the meropenem-vaborbactam combination in a 1:1 ratio (i.e., 2 g is 1 g meropenem and 1 g vaborbactam).
- Duration of use is up to 14 days.
- Dosing is affected by renal function as calculated by the Modification of Diet in Renal Disease (MDRD) formula.
- Administer after hemodialysis on dialysis days.
- Dose adjustment for hepatic impairment is not necessary.
- Further dilution in 0.9% sodium chloride is required prior to administration.

CONTRAINDICATIONS[1]

- Hypersensitivity to meropenem or vaborbactam or other drugs in the same class
- History of anaphylactic reactions to other β-lactam antibacterials

WARNINGS/PRECAUTIONS[1]

- Hypersensitivity reactions were reported in clinical trials. Risk is increased in patients with a history of sensitivity to multiple allergens and/or other β-lactam antibacterials.
- Neurologic adverse events, including seizures, have been reported with meropenem. Incidence is higher in patients with underlying neurologic disorders, bacterial meningitis, and/or renal impairment.
- Super-infections, including *Clostridium difficile*-associated diarrhea (CDAD), have been reported with prolonged use.
- Drug-drug interaction with meropenem and valproic acid may result in increased risk of breakthrough seizures due to subtherapeutic valproic acid concentrations that may not be possible to overcome by increasing valproic acid dose. The combination should be avoided; otherwise, alternative anticonvulsant therapy should be considered.
- Use caution with meropenem in patients with renal impairment, which may increase risk of neurologic adverse events and thrombocytopenia.

SIGNIFICANT DRUG INTERACTIONS[1]

- Valproic acid and meropenem (see Warnings/Precautions)
- Meropenem is a substrate of OAT1 and OAT3 renal transporters. Probenecid may increase meropenem mean systemic exposure by 56% and mean elimination half-life by 38% by competing for active tubular secretion.
- Vaborbactam has low potential for clinically significant drug-drug interactions as it is not a substrate or inhibitor of cytochrome P450 enzymes or hepatic/renal transporters based on in vitro studies.

CONCLUSION

Vaborbactam is a novel BLI that, when given in combination with meropenem, restores activity against some carbapenemase-producing *Enterobacteriaceae*. Meropenem-vaborbactam is the second beta-lactam/BLI combination available in the United States to have activity against *Klebsiella pneumoniae* carbapenemases (KPCs). However, similar to ceftazidime-avibactam, meropenem-vaborbactam lacks activity against Ambler class B MBLs. In Phase III studies in cUTI, meropenem-vaborbactam demonstrated superiority to piperacillin-tazobactam in the FDA primary endpoint of clinical cure or improvement and microbiological eradication at the end of IV treatment and appears to be well tolerated with a similar safety profile.

Carbapenems are considered the first-line treatment for multi-drug-resistant (MDR) gram-negative infections, including extended-spectrum β-lactamases. In a climate of increasing carbapenem resistance, meropenem-vaborbactam represents an important treatment option in the management of carbapenem-resistant *Enterobacteriaceae* (CRE). Given limited treatment experience, the role of meropenem-vaborbactam compared to current best available therapy for CRE remains to be seen, including any potential differences on clinical outcomes. Judicious use and further study of relative resistance thresholds also will be necessary, as breakthrough avibactam resistance already has been reported in patients treated

Table 4. Cost[5]

Medication	How Supplied	Average Wholesale Price	Usual Dose	Cost of Therapy per Day
Meropenem-vaborbactam	2 g vials	$198	4 g q8hr	$1,188
Ceftazidime-avibactam	2.5 g vials	$359.10	2.5 g q8hr	$1,077.30

with ceftazidime-avibactam. TANGO-2, a Phase III multi-center, open-label study comparing meropenem-vaborbactam to best available treatment in adults with serious infections due to known or suspected KPC-producing CRE has been completed but the results have not yet been published. Of note, researchers ended randomization to the comparator arm early after an interim analysis reported favorable efficacy and safety results with meropenem-vaborbactam.[6]

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COMMENTARY

Stewardship, Science, and Spirituality

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Awareness of a patient's and family's belief system might help physicians appropriately frame explanations about the importance of antimicrobial stewardship.

SOURCE: Stokes L. The promise and failure of antibiotics. *Christianity Today* 2017;61:58-61.

Emergency medicine specialist Lindsay Stokes laments the growing global problem of antimicrobial resistance. For several years, she has been following the 2004[1] (updated in 2013[2]) American Academy of Pediatrics' encouragement to promote "watchful waiting" for select children with otitis media, giving them a prescription but suggesting that they only start antimicrobial treatment if the child is not improving after two days of just symptomatic care. So far, every family given a prescription has started antibiotic treatment immediately.

Dr. Stokes is not alone. Others around the world have noted poor compliance with the "no antibiotic" treatment plan, even though it is medically sensible and cost effective.[3] Prior parental awareness of antimicrobial resistance and physician communication factors all influence the willingness of a family to withhold "treatment" for a crying child.[4,5]

"Stewardship" has become a buzzword for infectious disease specialists concerned with antimicrobial use. Stokes points out, though, that "stewardship" has long been a Christian term. (She is obviously writing mostly to Christians in a magazine called *Christianity Today* that is widely read by clergy and educated Protestants.) She explains to her readers that the World Health Organization is calling for a commitment to stewardship, emphasizing that we responsibly use what we have rather than seek new treatments. She notes that even microbes are part of creation and calls on her readers to accept the charge over creation to care for it. She urges that people who accept the "gift" of antibiotics also take care of them with gratitude to the creator.

Stokes reminds readers that they are to exercise stewardship over creation, according to biblical teaching. She explains that this biblical mandate makes them responsible for antimicrobial stewardship as well.

So, what does this mean for infectious disease physicians who might not read a Christian magazine and might not have considered what the Bible teaches about wise use of antimicrobial therapy? One relevant message might be that we should be aware of our patients' perspectives. When we notice that they claim a biblical, evangelical, or Christian faith, we can remind them that withholding antibiotics for likely viral infections and that targeting antimicrobial choices is all part of the stewardship to which physicians and Christian patients aspire. ■

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ABSTRACT & COMMENTARY

Etiology of Acute Liver Failure and Next-generation Sequencing

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: Metagenomic next-generation sequencing was applied to examine serum from 204 adult patients with acute liver failure (ALF). Researchers identified a potential viral etiology in eight of the 187 patients with ALF of indeterminate etiology. Potential pathogens identified in these included HSV-1, HBV, parvovirus B19, CMV, and HHV-7.

SOURCE: Somasekar S, Lee D, Rule J, et al. Viral surveillance in serum samples from patients with acute liver failure by metagenomic next-generation sequencing. *Clin Infect Dis* 2017;65:1477-1485.

As part of the ongoing Acute Liver Failure Study Group (ALFSG), 204 sera samples collected between 1998 and 2010 were analyzed using traditional nucleic acid testing and metagenomic next-generation sequencing (mNGS). In this group were 187 patients who had acute liver failure (ALF) of indeterminate etiology and 17 controls (four cases each of hepatitis A and hepatitis B, three cases of acetaminophen toxicity, two cases of autoimmune hepatitis, three cases of drug-induced liver injury, and one case of hepatic ischemia).

A blinded analysis of mNGS data showed positive results for a potential viral pathogen in 27 patients. In the first group, seven of eight of the Hep A- or Hep B-positive controls were detected by mNGS. The one HBV+ control that was missed by mNGS had very low copy number of virus and was confirmed by conventional NAT. A second group of 11 cases tested positive by either serology or PCR or both but were considered indeterminate by the investigator. Eight of 11 of these cases were confirmed by mNGS. One case of HIV, one case of CMV (with co-infection with EBV), and one case of HBV (with HCV and HDV co-infection) were missed, but NAT for these viruses also were negative, suggesting that DNA or RNA in the sample had been degraded. In the last group, previously unrecognized viral infections were found in eight cases: HSV-1 alone in three cases, and one case each of HBV, parvovirus B19, HHV-7, CMV, and HPV-159, a cutaneous betapapillomavirus. (The latter virus is found commonly on the skin and may represent skin contamination of the sample at the time of phlebotomy.)

The parvovirus B19 case also was interesting, occurring in a previously healthy 75-year-old man. The HHV-7 case may have represented reactivation (rather than the cause of acute liver failure) in a very ill patient with a noninfectious cause of ALF, since > 90% of adults have evidence of previous infection with HHV-7.

■ COMMENTARY

This study shows that mNGS can be a powerful and useful tool to diagnose disease. Applied to

ALF in adults (where up to 20% of cases may be of indeterminate etiology by conventional clinical testing, especially in the developing world),[1] mNGS may be particularly useful. In addition to making the diagnosis of mixed viral infection in three cases in this series, the study also showed the importance of HSV-1, either as a single agent or co-infecting agent, as a cause of ALF. Four patients had previously unrecognized HSV-1 (subsequently confirmed by PCR). All four of these patients were immunocompetent, were quite ill, and the two with extremely high transaminase elevations died.

While further study of mNGS in ALF is important, this paper clearly shows the potential clinical utility of this powerful new diagnostic technique. Until mNGS is more readily available, the results of this study do suggest that initial workup of ALF include conventional NAT testing for HSV-1 and parvovirus B19 in addition to testing for hepatitis A-E viruses. ■

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PHARMACOLOGY UPDATE

Secnidazole Oral Granules (Solosec)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

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Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved the first oral single-dose treatment for bacterial vaginosis in adult women. Secnidazole is a next-generation 5-nitroimidazole prodrug that is activated after entry into bacterial cells. It was designated by the FDA as a Qualified Infectious Disease Product and was granted priority review. Secnidazole is marketed as Solosec.

INDICATIONS

Secnidazole is indicated for the treatment of bacterial vaginosis (BV) in adult women.[1]

DOSAGE

The recommended dose is a single 2-gram packet of granules once daily.[1] The granules should be sprinkled onto applesauce, yogurt, or pudding and taken within 30 minutes followed by a glass of water. It may be taken without regard to timing of meals.

Secnidazole is not intended to be dissolved in any liquid. It is available as 2-gram, unit-of-use, oral granules.

POTENTIAL ADVANTAGES

Secnidazole offers a single-dose oral treatment for BV. Current treatments recommended by the CDC are oral metronidazole twice daily for seven days, metronidazole vaginal gel once daily for five days, or clindamycin cream intravaginally once daily for seven days.[2]

Alternative regimens include oral tinidazole or clindamycin for two to seven days. Secnidazole does not produce a significant drug-drug interaction with oral contraceptives containing ethinyl estradiol and norethindrone.[1]

POTENTIAL DISADVANTAGES

Secnidazole treatment may result in vulvovaginal candidiasis.[1] In clinical trials, the frequency was 9.6% compared to 2.9% for placebo. This is the most frequently reported adverse reaction. Breastfeeding is not recommended during treatment and for 96 hours after administration.[1]

COMMENTS

The efficacy of secnidazole was evaluated in two randomized, placebo-controlled studies in subjects with BV.[1,3] Diagnosis of BV was defined as: the presence of an off-white (milky or gray), thin homogeneous vaginal discharge; vaginal pH ≥ 4.7; presence of clue cells ≥ 20% of the total epithelial cell on microscopic examination of the vaginal saline wet mount; a positive "whiff" test (detection of fishy odor on addition of 10% potassium hydroxide solution to a sample of vaginal discharge); and a Nugent score (gram stain scoring system) ≥ 4.[1,4] Efficacy endpoints were clinical response (defined as normal vaginal discharge); negative "whiff" test and clue cells < 20%, Nugent score cure (score of 0-3); and therapeutic response, clinical response, and Nugent score cure.

At 21-30 days after randomization, clinical response rates were 67.7% for study 1 and 53.3% for study 2, with corresponding placebo rates of 17.7% and 19.3%, respectively. Nugent score cures were 40.3% and 43.9% vs. 6.5% and 5.3%, respectively. Therapeutic response rates were 40.3% and 34.6% vs. 6.5% and 3.5%. Currently, there are no comparative studies with other antibacterial agents. The results were similar to a study

of oral metronidazole and oral tinidazole. For subjects with a baseline Nugent score > 7 and evaluated at the one-month follow-up visit, Nugent score cures were 35.9% for metronidazole (500 mg twice daily for seven days) and 38.1% for tinidazole (500 mg twice daily for seven days).[3]

CLINICAL IMPLICATIONS

BV is a polymicrobial clinical syndrome caused by replacement of *Lactobacillus* spp in the vagina with anaerobic bacteria (e.g., *Gardnerella vaginalis*, *Prevotella* spp, and *Mobiluncus* spp).[2] It is the most prevalent cause of vaginal discharge. Typical treatment is oral or intravaginal treatment for seven and five days, respectively. Secnidazole is the first single-dose treatment for this common condition. It appears to have similar effectiveness to metronidazole and is well tolerated.

Cost is not available as the drug is expected to be available in the first quarter of 2018. ■

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CME QUESTIONS

1. Which of the following is correct regarding Lyme disease in the United States from 2008 to 2015?

a. The incidence increased in the 14 states with the highest incidence.

b. The incidence increased in eight of the 11 states neighboring the high-incidence states.

c. The peak incidence occurred in individuals 15-25 years of age.

d. The geographic extent shrank.

2. Based on data from recent mumps outbreaks, which of the following statements is true?

a. All children should receive three MMR vaccines.

b. Immigrant children should receive three MMR vaccines.

c. University students in settings of a mumps outbreak should receive a third MMR vaccine.

d. University students in settings of a mumps outbreak should receive a third MMR vaccine if it has been more than five years since their last dose.

3. Which of the following is correct?

a. Vaborbactam inhibits serine proteases, such as KPC.

b. Vaborbactam inhibits metallo-beta-lactamases.

c. Vaborbactam routinely enhances the activity of meropenem against *Pseudomonas aeruginosa*.

d. Vaborbactam routinely enhances the activity of meropenem against *Acinetobacter baumannii*.

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.