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PHARMACY CONTINUING EDUCATION FROM WF PROFESSIONAL ASSOCIATES

"New Antimicrobials"

March 2016

Drug resistant infections are becoming more and more prevalent. In recent years, six new antimicrobials have been FDA-approved that have the potential to be used for these drug-resistant infections. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists & technicians in all practice settings. **The program ID # for this lesson is 707-000-16-003-H01-P for pharmacists & 707-000-16-003-H01-T for technicians.**

Participants completing this lesson by February 28, 2019 may receive full credit. Release date March 1, 2016.

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.
If you have any comments, suggestions or questions, contact us at the above address, or call 1-847-945-8050. **Please write your name, NABP eProfile (CPE Monitor®) ID Number & birthdate (MM/DD) in the indicated space on the quiz page.**

The objectives of this lesson are such that upon completion participants will be able to:

Pharmacists:

1. List the newly approved antimicrobials.
2. Describe indications for the new antimicrobials.
3. Discuss common side effects for each new antimicrobial.
4. Comment upon the usefulness of the new antimicrobials.

Technicians:

1. Name the newly approved antimicrobial drugs.
2. Describe indications for the new antimicrobials.

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INTRODUCTION

According to the United States Centers for Disease Control and Prevention (CDC), approximately 2 million people become infected with a pathogen that is resistant to antimicrobials each year, contributing to at least 23,000 deaths yearly.[1] New and novel antimicrobial agents are urgently needed to meet this unmet medical need. The Infectious Diseases Society of America (IDSA) has proposed legislative, regulatory, and funding incentives to address this crisis. In recent years, six new antimicrobials have been FDA-approved that have the potential to be used for drug-resistant infections:

1. dalbavancin,
2. oritavancin,
3. ceftolozane/tazobactam,
4. and ceftazidime/avibactam,
5. peramivir and
6. isavuconazonium

ISAVUCONAZONIUM

Increasing numbers of patients with chemotherapy-induced neutropenia and those undergoing transplantation has led to a greater incidence of invasive fungal infections (IFIs). Mortality rates associated with IFIs is particularly high, ranging from 30 to 90%.[3] Thus,

there is an urgent need for new antifungal agents with favorable pharmacokinetic profiles, adverse effect profiles and improved efficacy against *Aspergillus* spp. and *Zygomycetes* spp. Currently, broad-spectrum antifungal agents on the market include the triazoles (voriconazole and posaconazole) and amphotericin B liposomal. However, these agents are limited by considerable discontinuation rates due to adverse events, gaps in the spectrum of activity and drawbacks in pharmacokinetic properties. Isavuconazonium is an extended-spectrum triazole antifungal that was recently FDA-approved for the treatment of invasive aspergillosis and invasive mucomycosis. Isavuconazonium is a prodrug that is rapidly converted to its active moiety, isavuconazole. It has several pharmacokinetic advantages over the existing agents including: high prodrug water solubility (eliminating the need for cyclodextrin as the intravenous vehicle), high oral bioavailability (1:1 IV to PO conversion), and predictable linear pharmacokinetics with no relevant food effect and no requirement for serum concentration monitoring. Microbiological data revealed in vitro activity of isavuconazonium against *Aspergillus* spp. and variable activity against Mucorales.[4] Moreover, a head-to-head clinical trial versus voriconazole showed that isavuconazonium is safe and efficacious for the treatment of invasive aspergillosis. A randomized, double-blind, non-inferiority active controlled trial was conducted to evaluate the safety and efficacy of isavuconazonium versus voriconazole for primary treatment of invasive fungal disease caused by *Aspergillus* species or other filamentous fungi. Eligible patients had proven, probable, or possible invasive fungal infections per EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study group) criteria. Overall success at End-of-Treatment (EOT) in the subgroup of patients with proven or probable invasive aspergillosis was seen in 35% of isavuconazole-treated patients versus 38.9% of voriconazole-treated patients.

Although there are no head-to-head trials comparing isavuconazonium to posaconazole and amphotericin B liposomal for the treatment of invasive mucomycosis, an open-label non-comparative trial has demonstrated its safety and efficacy in patients who failed and discontinued previous antifungal therapy due to side effects. In addition, patients with invasive mucomycosis who failed posaconazole therapy and were intolerant of amphotericin B liposomal may benefit from treatment with isavuconazonium.

The safety of isavuconazonium has been assessed in 403 patients in two clinical trials.[4] The most frequently reported adverse reactions among these patients were nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), elevated liver function tests (16%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%) and back pain (10%). Isavuconazonium is a promising new drug for those patients intolerant to currently available therapy for invasive mucomycosis or aspergillosis. However, due to its high acquisition cost, it should remain only as an alternative treatment option for patients with refractory IFIs who are intolerant of first-line antifungal agents.

DALBAVANCIN AND ORITAVANCIN

Dalbavancin (Dalvance®) and oritavancin (Orbactiv®) are novel, semisynethic lipoglycopeptide antibiotics that are FDA-approved for the treatment of gram-positive acute bacterial skin and skin structure infections (ABSSSI), including: methicillin resistant *Staphylococcus aureus* (MRSA).[5] Both drugs are administered intravenously and possess extended half-lives, thus allowing for a significant reduction in the number of drug administrations.[6,7] Dalbavancin is given as a two-dose regimen over seven days. Oritavancin is given as a single dose regimen. See table 1 for dosing. Dalbavancin requires a dose adjustment for severe renal impairment without the use

of hemodialysis. No dose reduction is necessary with oritavancin.

These newer agents share a number of features with the glycopeptide, vancomycin, including: these drugs bind to the terminal D-Ala-D-Ala peptidoglycan chain which inhibits polymerization and cross-linkage in bacterial cell wall synthesis.[6,7] The spectrum of activity includes: *Staphylococcus aureus, Streptococcus pneumoniae* and susceptible *Enterococcus faecalis*. The primary added value in the newer agents lies in their prolonged half-life enabling a once weekly, two-dose regimen for dalbavancin and a single dose regimen for oritavancin.

In clinical trials, once weekly dalbavancin was determined to be non-inferior to twice daily vancomycin and linezolid in the treatment of ABSSSI.[6] Likewise, oritavancin was determined to be non-inferior to twice daily vancomycin for the same indication.[7] Both trials indicate similar rates of adverse events and no significant difference in safety. Due to the long half-life, there is concern for prolonged allergic reactions. Both drugs are reported to cause infusion-related reaction, "Red-man Syndrome", as seen with vancomycin.[5] Slower infusion reduces the risk and intensity of these reactions. Oritavancin is known to artificially elevate activated PTT levels, thus unfractionated heparin is contraindicated for 48 hours after administering oritavancin.[7] There is also a suggestion that patients with treatment failure may have an elevated risk of developing osteomyelitis. Thus, oritavancin should be avoided if osteomyelitis is considered likely.

Although neither drug is superior to vancomycin in terms of clinical efficacy or side effect profile, their appeal lies in their long half-life and convenient dosing regimen, allowing for avoidance of a central line and prolonged hospital stay. Given the very long half-life of both of these agents, some experts have expressed a concern regarding prolonged drug effect should a patient experience a serious adverse reaction. Additional data is required on whether the high cost of these medications ($3400 to $5300 per 14 day course) will offset the standard of care of vancomycin for skin and soft tissue infections.

PERAMIVIR

Peramivir is the third neuraminidase inhibitor (NAI) approved in December 2014 for the treatment of acute, uncomplicated influenza.[8] Peramivir was temporarily used prior to approval under the FDA's Emergency Use Authorization (EUA) during the 2009-2010 H1N1 influenza pandemic.[9,10] Other NAIs include orally administered oseltamivir and inhaled zanamivir. Peramivir is the first and only NAI that is administered by intravenous infusion. Peramivir possesses an extended half-life, thus allowing for treatment with a single dose. Dosing requires adjustment for renal impairment.

Clinical trials utilizing the FDA-approved, one-time dose were conducted in Japan in healthy volunteers with documented influenza. These studies showed that peramivir decreased time to recovery by approximately 21 hours when compared to placebo.[8] Trials comparing peramivir to oseltamivir showed non-inferiority. There was no significant difference between peramivir and oseltamivir in resumption of usual activity or influenza related complications. Time weighted change from baseline viral titer was greater in peramivir than that in oseltamivir. Peramivir was also well tolerated in all studies, with the most common adverse reaction being diarrhea and lab abnormalities. There is limited evidence for the use of peramivir in patients with severe influenza requiring hospitalization; however, safety reports from peramivir use through Emergency Investigational New Drug (eIND) and EUA demonstrated safety of peramivir in this population.

Compared to the FDA's approved dose of single infusion for uncomplicated influenza, peramivir was used as repeated dosing with an average of duration of 5 days during the EUA with no significant adverse effects. If peramivir is used for hospitalized patients, the CDC recommends giving 5 days of treatment instead of the FDA approved one-time dose for uncomplicated influenza.[9]

Influenza A was the predominant virus identified in the clinical trials; thus, a limited number of subjects with influenza B have been studied. There is insufficient data to assess resistance of peramivir to various influenza strains, although studies seem to suggest that peramivir is effective against oseltamivir resistant H274Y mutant A/H1N1 virus. There are currently no studies comparing peramivir and zanamivir.[10]

Intravenous administration allows for the treatment of patients unable to take or tolerate oral agents. The CDC currently recommends using peramivir for patients who cannot tolerate or absorb oral or enterically-administered oseltamivir because of suspected or known gastric stasis, malabsorption, or gastrointestinal bleeding.[9]

The single dose regimen allows for ensured compliance compared to the 5-day treatment course of oseltamivir, but limited data is available for using peramivir in complicated, hospitalized patients with influenza. Additional data is required to justify its higher costs compared to the standard treatment, oseltamivir.

CEFTOLOZANE/TAZOBACTAM AND CEFTAZIDIME/AVIBACTAM

Ceftazidime/avibactam (Avycaz™) and ceftolozane/tazobactam (Zerbaxa™) are combination cephalosporin-class antibiotics with beta lactamase inhibitors indicated for the treatment of complicated intra-abdominal infection (cIAI) and complicated urinary tract infection (cUTI), including pyelonephritis. Both drugs were approved in February 2015 and December 2014, respectively. Both drugs have shown in vitro activity against Enterobacteriaceae and *P. aeruginosa*, even in the presence beta-lactamases such as TEM, SHV, CTX-M, and select oxacillinases (OXA). In vitro studies have demonstrated that the addition of avibactam to ceftazidime improves the activity against many resistant Enterobacteriaceae (*E.coli and Klebsiella spp.*) and *Pseudomonas aeruginosa*. Currently, there are no commercially available susceptibility testing methods for ceftazidime/avibactam or ceftolozane/tazobactam.

Ceftazidime/avibactam and ceftolozane/tazobactam are used in combination with metronidazole for cIAI. In cUTI, both drugs are used as monotherapy, dosed 2.5 g every 8 hours and 1.5 g every 8 hours, respectively.

Ceftazidime/avibactam was approved in February 2015 for the treatment of complicated intra-abdominal infections (used in combination with metronidazole) and complicated urinary-tract infections in patients with few or no other treatment options.[3] As of December 2015, the clinical phase III data for ceftazidime/avibactam had not yet been published. In Phase 2 clinical trials, ceftazidime/avibactam (plus metronidazole in cIAI) was shown to be safe and effective when compared to meropenem and imipenem/cilastatin for cIAI and cUTI, respectively. Phase 3 clinical trials for ceftazidime/avibactam have been completed but not yet published in a peer-reviewed journal. Preliminary reports for the Phase 3 cIAI trial report that ceftazidime/avibactam plus metronidazole compared to meropenem had increased mortality rates, 2.5% (13/529) versus 1.5% (8/529), respectively.

For ceftolozane/tazobactam (plus metronidazole in cIAI phase III trials), it was shown to be non-inferior to its comparator drugs, meropenem and levofloxacin for cIAI and cUTI, respectively. In the latter Phase 3 trial comparing ceftolozane/tazobactam and levofloxacin, 26.5% (212/800) of the pathogens were not susceptible to levofloxacin, which may account for the statistical significance found in the primary endpoint. In both phase III trials, clinical cure rates were lower in the ceftolozane/tazobactam patient groups with baseline renal impairment.[9] In the cIAI trial, the clinical cure rate was 85.2% in patients with normal renal function compared to 47.8% in patients with impaired renal function. The cUTI trial had a similar trend.

While ceftazidime/avibactam and ceftolozane/tazobactam both have proven safety and efficacy, neither agents have proven superiority over the comparator drugs. Ceftolozane/tazobactam provides an alternative option for complicated UTI and intra-abdominal infections when other options are unsuitable (such as when avoidance of carbapenem use is required for allergy or other considerations). Caution is advised in patients with renal impairment where clinical cure rates were found to be lower than in patients with normal renal function. Future studies will clarify the efficacy of ceftolozane/tazobactam in patients with ventilator-associated pneumonia.

CONCLUSION

After many years with very few new antimicrobials despite increasing prevalence of multi-drug resistant organisms, it is encouraging to see the approval of these six new antimicrobials. Dalbavancin and oritavancin have the potential to greatly simplify dose regimens for several gram-positive infections (especially those with MRSA). The two new agents for resistant, gram-negative organisms, ceftolozane/tazobactam and ceftazidime/avibactam, have broad antimicrobial spectra against resistant organisms. Peramivir provides an alternative for uncomplicated influenza. Isavuconazonium offers an alternative for invasive aspergillosis and mucomycosis. Taken together, these new antimicrobials significantly add to the clinician's armamentarium.

Table 1. Key Points for Six New Antimicrobial Agents

Drug, Dose	FDA approved indications	Average Wholesale Price per day	Precautions
Ceftazidime/ avibactam (Avycaz®). 2.5g IV q8h.	Complicated intraabdominal infections. Complicated UTI when no other option available.	$684	• Dose adjustment required for renal dysfunction. • Phase 2 data increased mortality compared to meropenem.
Ceftolozane/ tazobactamn (Zerbaxa®). 1.5g IV q8h.	Complicated intraabdominal infections. Complicated UTI.	$298	• Dose adjustment required for renal dysfunction.

Drug, Dose	FDA approved indications	Average Wholesale Price per day	Precautions
Dalbavancin (Dalvance®). 1000 mg IV; 500 mg IV one week later.	Acute bacterial skin & skin structure infections.	$383. (Averaged from $5364 per 14 day course).	• Red Man's Syndrome. • Unable to remove exposure in the event of adverse reaction.
Isavuconazonium (Cresemba®). 372mg IV/PO q8h x 2days; then 372mg daily.	Invasive mucomycosis & aspergillosis.	IV: $286.00 per 372mg vial. PO: $84 per 186mg tablet.	• Drug interactions.
Oritavancin (Orbactiv®). 1200 mg IV once.	Acute bacterial skin & skin structure Infections.	$244 (averaged from $3420 per 14 day course).	• Avoid in likely osteomyelitis. • Artificial elevation of PTT. • Unable to remove exposure in the event of adverse reaction.
Peramivir (Rapivab®). One time dose.	Uncomplicated influenza.	$950	• Not studied in hospitalized patients. • Dose adjustment required for renal dysfunction. • Additional information found at http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Topics for 2016

Annual Pharmacy Law Lesson
New FDA-Approved Drugs
Prescription Adherence
Update: Gout
Hyperlipidemia
Validation of Pain Medication Rxs
Pharmacy Considerations Regarding the Opioid Crisis of Abuse
Pharmacogenetics
Vaccines---Truths, Myths, Hesitancy, Controversies
Update *C. diff*---do probiotics and/or yogurt help?

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12. Ceftazidime-avibactam (Avycaz™) Package Insert, Actavis. February 2015.

13. Ceftolozane/tazobactam (Zerbaxa™) Package Insert, Cubist Pharmaceuticals. December 2014.

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Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?

Describe the Newly approved antimicrobials	YES	NO
List the FDA approved indications for the new antimicrobials	YES	NO
Describe common side effects for each antimicrobial	YES	NO
Comment upon the usefulness of the new antimicrobials	YES	NO

2. Was the program independent & non-commercial YES NO

	Low Relevance						Very Relevant
3. Relevance of topic	1	2	3	4	5	6	7

4. What did you like most about this lesson?_____

5. What did you like least about this lesson?_____

Please Mark the Correct Answer(s)

1. **Isavuconazonium is FDA-approved for:**
   A. Invasive candidiasis B. Invasive aspergillosis
   C. Invasive mucomycosis D. B and C

2. **The most common side effects with isavuconazonium include:**
   A. Diarrhea
   B. Nausea
   C. Abnormalities in liver function tests
   D. Headaches
   E. All of these

3. **Dalbavancin & oritavancin have a mechanism of action similar to:**
   A. Linezoid B. Vancomycin
   C. Voriconazole D. All of these

4. **Common side effects & precautions with oritavancin are:**
   A. False elevations of PTT
   B. Red Man's Syndrome
   C. Nephrotoxicity
   D. A & B

5. **Peramivir is FDA-approved for which of these virus(es)?**
   A. Influenza A and B B. Coronavirus
   C. SARS D. Rotavirus
   E. None of these

6. **Dalbavancin & oritavancin cover these organisms:**
   A. *E. coli* B. *Staph. aureus*
   C. *Strep. pyogenes* D. B & C
   D. All of these

7. **Ceftolozane/tazobactam & ceftazidime/avibactam are FDA-approved for:**
   A. Intra-abdominal infections
   B. Complicated urinary tract infections
   C. Skin & soft tissue infections
   D. A & B

8. **Which of these do not require dose adjustment of renal dysfunction?**
   A. Ceftolazane/tazobactam
   B. Ceftazidime/avibactam
   C. Peramivir
   D. Isavuconazonium

9. **Ceftolozane/tazobactam covers which of these organisms?**
   A. *E. coli* B. *Pseudomonas*
   C. *S. aureus* D. A & B

10. **Which antimicrobial is given with ceftolozane/tazobactam or ceftazidime/avibactam for Intraabdominal infections?**
    A. Metronidazole B. Clindamycin
    C. Vancomycin D. Daptomycin
    E. None of these

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