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The Antibiotic Pipeline – Quick takes on novel agents

Over the past decade, several antibiotics with activity against bacteria deemed "serious" or "urgent" threats by the CDC have been developed. However, clinical management of patients with infections due to multidrug-resistant (MDR) bacteria remains challenging, especially those caused by resistant *Staphylococcus aureus* or carbapenem-resistant Enterobacteriaceae (CRE).

A recent study published in Diagnostic Microbiology and Infectious Disease found that hospitals in the southern United States typically adopt new antimicrobial agents the faster than other regions.[1] In fact, first use of new agents occurred up to twice as early compared to hospitals in the Northeast (2 years vs 4 years after FDA approval). Antibiotic stewardship for novel agents is therefore a priority for most hospitals within DASON.[1] In order to protect these agents and direct appropriate stewardship policies, it is critical to understand the therapeutic roles of each of these agents. This month's DASON newsletter will review four novel antibiotics that were recently approved for use in the United States.

Delafloxacin (Brand Name: Baxdela)

Delafloxacin (IV and PO) is a new fluoroquinolone that was approved for acute bacterial skin and skin structure infections (ABSSSI) in June of 2017.[2] It differs from other fluoroquinolones in that it has reliable activity against MRSA. While most fluoroquinolones bind to and inhibit either DNA gyrase *or* topoisomerase IV (and thus exhibit different spectra of activity), delafloxacin binds to and inhibits *both* enzymes with equal affinity and forms a complex.[3] This unique property allows for a wider spectrum of activity (including MRSA) and makes it an option for treatment of ABSSSI.

Delafloxacin received FDA-approval for ABSSSI on the basis of results from a phase III, randomized, blinded trial with 660 patients comparing delafloxacin with vancomycin and aztreonam. In this study, patients were treated for 5-14 days, and non-inferiority was assessed by a >20% reduction in erythema at 48 to 72 hours in combination with microbiologic and subjective outcome responses. The primary endpoint results were nearly identical in each arm. Delafloxacin is currently being studied for additional indications including community-acquired pneumonia (CAP), urinary tract infections (UTI), and treatment of *N. gonorrhoeae.*

Unfortunately, delafloxacin is similar to other fluoroquinolones in regards to side effects; therefore, caution with use is warranted due to known class-wide side effects including neuropathy, tendonitis, hypoglycemia, and psychiatric adverse events. Because it is so very broad spectrum, and has known class-wide side effects, we suggest that DASON hospitals limit its use to special scenarios where the benefit of an oral broad-spectrum agent outweighs the risks. In most cases of non-purulent ABSSI, use of a narrower, beta-lactam antibiotic is more appropriate, especially because *S. aureus* is an unlikely pathogen. Similarly, for most purulent ABSSSI, targeted therapy toward MRSA is adequate without broad gram-negative coverage. Well-established oral options for MRSA include doxycycline and TMP/SMX.

Eravacycline (Brand Name: Xerava)

Eravacycline (IV only) is a tetracycline derivative with broad Gram-negative activity approved for complicated intra-abdominal infections (cIAI) in August of 2018. It provides an extended spectrum compared to other tetracyclines and is active against resistant Gram-negatives including ESBL Enterobacteriaceae, CRE, carbapenem-resistant *Acinetobacter baumannii* (CRAB) as well as MRSA and VRE. Eravacycline lacks activity against *Pseudomonas spp*., however it may play an important role in therapy for mycobacterial species, though data is lacking and further research is needed.

Eravacycline received FDA-approval for cIAI after a 541 patient, blinded, randomized clinical trial demonstrated non-inferiority to ertapenem in the IGNITE1 Trial. The primary endpoint at the test-of-cure visit was met in 86.8% in the eravacycline group and 87.6% in the ertapenem group.[4] A second, similar study (IGNITE4) compared against meropenem and found similar results.[5] Importantly, eravacycline did not demonstrate non-inferiority to levofloxacin and ertapenem for treatment of complicated urinary tract infections (cUTI) in the IGNITE2 and IGNITE3 trials, and thus did not gain approval for UTI. Eravacycline may provide benefit compared with tigecycline in causing less nausea/vomiting side effects. We anticipate that eravacycline will have very limited use for treatment of MDR infections in patients with severe beta-lactam allergies or in cases where no other effective agents

exist. Most labs are unable to provide susceptibility information for this drug at this time.

Omadacycline (Brand Name: Nuzyra)

Omadacycline (IV and PO) is another tetracycline antibiotic approved for community-acquired bacterial pneumonia (CABP) and ABSSSI in October of 2018. Similar to other tetracyclines, omadacycline has activity against MRSA and MSSA, as well as *Streptococcus spp*. and atypical pathogens. Omadacycline also has anaerobic coverage and is active against VRE.

The FDA-approved indications for omadacycline came on the heels of a blinded, randomized clinical trial that assigned patients to either omadacycline or moxifloxacin in the treatment of CABP[6] as well as two randomized, controlled trials in ABSSSI.[7] In all three trials, omadacycline demonstrated non-inferiority to its counterparts with minimal adverse effects. The most common adverse events reported were gastrointestinal side effects.

Omadacycline can be given as oral monotherapy for treatment of community-acquired pneumonia or skin/soft tissue infections and thus may be seen as an alternative to fluoroquinolones, especially for patients with severe beta-lactam allergy. It may play a future role in treatment of highly resistant *Acinetobacter*, non-tuberculous mycobacteria, or *Stenotrophonomas* spp. where first-line therapies are unavailable, although data for these indications are not yet available. Omadacycline avoids the typical resistance mechanisms of tetracyclines, although remains extremely broad spectrum. Thus, it should have limited use in favor of narrower agents whenever possible.

Imipenem/Cilastatin + Relebactam (Brand Name: Recarbrio)

Imipenem/cilastatin + relebactam (IV only) (hereafter shortened to imipenem-relebactam) is a carbapenem/beta-lactamase inhibitor combination recently approved for treatment of cUTI and cIAI on July 17, 2019.[8] Relebactam is a novel beta-lactamase inhibitor, which is active against the KPC enzyme that confers resistance for many CRE.[9] Similar to vaborbactam, relebactam is not active against organisms that produce metallo-beta-lactamases or OXA-48 enzymes. Relebactam does not provide added benefit for treatment of resistant *Acinetobacter baumannii.* However, relebactam may have activity against some resistant *P. aeruginosa* isolates, depending on the resistance mechanism.

Imipenem-relebactam received FDA-approval for cUTI and cIAI on the basis of the RESTORE-IMI 1 trial, a small, randomized, blinded trial that enrolled 47 patients and compared imipenem/cilastatin-relebactam vs colistin plus imipenem/cilastatin in patients with hospital-acquired or ventilator associated bacterial pneumonia, cIAI, or cUTI. The primary endpoint, favorable overall response in the population that had a qualifying baseline pathogen, was similar in the two groups (71.4% vs 70.0%); however, drug-related adverse events were far fewer in the imipenem-relebactam arm (16.1% vs 31.3%). Given these limited data, currently unavailable laboratory testing, and overlap in the niche with meropenem/vaborbactam for KPC-producing CRE, we expect that the role for this drug may be for treatment of MDR-P. aeruginosa or KPC-producing CRE where no other effective agents exist.

Take Home Points:

1. Several new, broad-spectrum agents to treat infections due to multi-drug resistant organisms have recently been approved. These agents are last lines of defense against MDRO and have limited availability of susceptibility testing. Thus, aggressive stewardship policies such as pre- authorization are warranted to maintain efficacy and ensure appropriate use.
2. Use of the agents detailed in this newsletter is nuanced and infectious disease consultation is recommended in all cases where available.
3. Delafloxacin is a new fluoroquinolone with broader activity than current fluoroquinolones, including MRSA and *Pseudomonas.* Approved for skin and soft tissue infections, use will likely expand to other infections due to the convenience of oral formulation. Delafloxacin will be a high priority stewardship target as it has similar side effect profile to other quinolones and broad spectrum.
4. Eravacycline will have very limited use for treatment of MDR infections in patients with severe beta-lactam allergies or in cases where no other effective agents exist. Eravacycline should be avoided for treatment of urinary tract infections.
5. Omadacycline was approved for treatment of community acquired pneumonia and skin soft tissue infection and may provide an alternative to fluoroquinolones. It should have limited use due to its broad-spectrum.
6. Imipenem-relebactam may have a future role for use in KPC-producing CRE or MDR-P. aeruginosa strains, but lack of available laboratory testing is a limiting factor.

Summary Table: Additional agents are added to the summary table for comparison. Please see prior DASON Newsletters for discussion of Meropenem-Vaborbactam (October 2017) and Plazomicin (July 2018).

Antibiotic	*Approved*	*MRSA*	*VRE*	*ESBL*	*CRE (KPC)*	*CRE (NDM1-OXA 48)*	*CRAB*	*CR-PsA*	*Notes*	*Approved for:*
Delafloxacin	Jun-2017	Yes	No	Mixed	Mixed	Mixed	Mixed	Mixed	Oral formulation available	ABSSSI
Eravacycline	Aug-2018	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor efficacy in complicated urinary tract infections.	Complicated Intra-Abdominal Infections
Omadacycline	Oct-2018	Yes	Yes	No	No	No	No	No	Oral formulation available	CABP and ABSSSI
Imipenem Relebactam	Jul-2019	No	No	Yes	Yes	No	No	Mixed	Does not inhibit metallo-beta-lactamases or OXA-48 carbapenemases.	Complicated UTI and complicated intra-abdominal infections
Meropenem-Vaborbactam	Aug-2017	No	No	Yes	Yes	No	Mixed	Mixed	Does not inhibit metallo-beta-lactamases or OXA-48 carbapenemases.	Complicated UTI
Plazomicin	Jun-2018	Possible, *in vitro* data.	No	Yes	Yes	Yes	No	Yes		Complicated UTI

MRSA= Methicillin resistant *Staphylococcus aureus*, VRE= Vancomycin resistant *Enterococcus*,
ESBL = Extended spectrum beta-lactamase, CRE = Carbapenem resistant *Enterobacteraciae*,
CRAB = Carbapenem resistant *Acinetobacter baumannii*, CR-PsA = Carbapenem resistant *Pseudomonas aeruginosa*
UTI = urinary tract infection, ABSSSI = acute bacterial skin/soft tissue structure infections,
CABP = community-acquired bacterial pneumonia

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