New Antimicrobials

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Since 2010 the new antimicrobials introduced have activity against resistant Gram negative bacteria, long half-lives against Gram positive bacteria, better activity against *Clostridium difficile*, and safer antifungal properties. Limiting factors to using the new antimicrobials include lack of susceptibility testing, cost and reimbursement issues. This article describes the new antimicrobials an internist will have contact with.

Ceftaroline (trade name: Teflaro) is approved by the Food and Drug Administration (FDA) for therapy of skin and soft tissue infections and community acquired pneumonia. It is a cephalosporin with high affinity for PBP2a, the penicillin binding protein (PBP) associated with methicillin resistance. Ceftaroline is active against multi-drug resistant (MDR) *Streptococcus pneumoniae* and *Staphylococcus aureus*, including methicillin resistant (MRSA), vancomycin-intermediate resistant (VISA), vancomycin resistant (VRSA), linezolid resistant and daptomycin non-susceptible strains. Its activity against Enterobacteriaceae mirrors ceftazidime. It has good activity against oral anaerobes. Ceftaroline is dosed at 600mg intravenous (IV) every 12 hours and the dose must be adjusted for renal failure. It has been shown to be non-inferior to vancomycin in soft tissue infections and to ceftriaxone in community acquired pneumonia. Its safety profile is similar to that of comparator drugs in clinical trials with an adverse effect profile similar to other cephalosporins. Intramuscular (IM) administration does not cause significant pain. Ceftaroline is Category B for use in pregnancy and should be used with caution in nursing women. Its acquisition cost of about $80/day makes it comparable to other newer agents for the treatment of soft tissue infections and community acquired pneumonia, but it is more costly than IV vancomycin, other cephalosporins and fluoroquinolones. It is less expensive than newer agents used to treat MRSA – linezolid, daptomycin, or tigecycline.

Fidaxomicin (Dificid) is a nonabsorbed macrocyclic compound. It is the first antimicrobial agent approved in 25 years by the FDA for treating *Clostridium difficile* infections (CDI). Fidaxomicin is bactericidal and has been shown to be not inferior to vancomycin for treatment of CDI after 10 days of therapy. Fidaxomicin is superior to vancomycin for sustained response without recurrence 25 days after therapy completion. The indigenous fecal microbiota is relatively spared by fidaxomicin. It is Category B for use in pregnancy and should be used with caution in nursing women. Due to its high cost (10 day course ~ $4187.50) most hospitals and insurance companies place restrictions on its use, allowing it for the second or third recurrence of CDI after first line therapy.

Oritavancin (Orbactiv) and **Dalbavancin** (Dalvance) are long acting agents with excellent Gram-positive activity and chemical structures related to vancomycin. Oritavancin inhibits peptidoglycan cell wall synthesis and also disrupts bacterial cell membranes. It is highly active against MRSA, VISA, VRSA and vancomycin resistant enterococci (VRE). A single IV dose of 1200mg infused over 3 hours has a half-life of 393 hours, thus no repeat dosing is necessary to treat soft tissue infections. There is very slow elimination from tissue and no dosing adjustments are needed for renal or hepatic insufficiency. Trials have demonstrated noninferiority compared with vancomycin in the treatment of soft tissue infections. Adverse events are mostly similar to vancomycin except for liver enzyme elevation and the occurrence of osteomyelitis. Oritavancin is pregnancy risk factor C and the manufacturer recommends caution when given to nursing mothers. It could reduce outpatient infusion services and home care but its acquisition cost (~$2900) may ultimately limit its use. Also it is not a cost effective option for treatment of methicillin-sensitive Staphylococcus aureus (MSSA) infections, of which we see still plenty. Unfortunately it has yet to be assessed for treating bacteremia or bone infections. Dalbavancin has activity against virtually all important Gram-positive organisms with the exception of vanA-expressing VRE. Clinical trials have demonstrated its efficacy in treating skin and soft tissue infections. It has a prolonged half-life of 181 hours allowing for once-weekly dosing. It does not interact with the cytochrome p450 system making drug-drug interactions unlikely. No serious adverse events have been seen in clinical trials. Dalbavancin is pregnancy risk factor C and the manufacturer recommends caution when given to nursing mothers. Unfortunately there is no data to suggest clinical superiority over beta-lactam antibiotics or linezolid for infections due to susceptible organisms. Also, no sufficient data exists on its use in pneumonia or bone and joint infections. Also limiting its use is cost - a two dose course runs around $4470.

Tedizolid (Sivextro), an oxazolidinone like Linezolid, is active against a wide range of Gram-positive pathogens and is dosed daily. It is approved to treat skin and soft tissue infections and a 6 day course has been shown to be non-inferior to a 10 day course of Linezolid. Some advantages over linezolid include less gastrointestinal and hematological side effects and lack of interactions with selective serotonin reuptake inhibitors. Tedizolid is pregnancy risk factor C and the manufacturer recommends caution when given to nursing mothers. Its pricing per dose is comparable to brand name Linezolid but can be used for 6 instead of 10 days for soft tissue infections.

Gram-negative organisms have developed many resistance mechanisms to antibiotics. Algorithms have been published to predict a patient's likelihood of having a resistant Gram-negative infection looking at risk factors such as prior infection, days hospitalized, indwelling catheter, antibiotic exposure and age. Two novel beta-lactam/beta-lactamase combination antibiotics, **Ceftolozane/tazobactam** (Zerbaxa) and **Ceftazidime/avibactam** (Avycaz), are available to help treat MDR Gram-negatives, including *Pseudomonas aeruginosa*. Both are intravenously dosed three times a day in patients with normal renal function. In clinical trials, they were noninferior to comparators in the treatment of complicated urinary tract infections and complicated intra-abdominal infections (with metronidazole). Studies on pneumonia are currently being conducted. Antimicrobial stewardship will be essential to preserving their activity. There are no adequate and well controlled studies of Avycaz, ceftazidime, or avibactam in pregnant women. Ceftolozane/tazobactam is pregnancy class B. Caution is recommended with both these agents when administering to nursing women. Ceftazidime/avibactam has

activity against *Klebsiella pneumoniae* carbapenemase producing organisms (KPC) whereas Ceftolozane/tazobactam does not. Neither inactivates metallo-β-lactamases such as the New Delhi metallo-β-lactamases.

For all the above mentioned antibiotics except Ceftaroline, no commercial sensitivity testing is currently available so surrogate markers or research-use-only disks can be used to help predict susceptibility of isolated pathogens.

Peramavir (Rapivab) is a single IV dose neuraminidase inhibitor with a similar mechanism of action as oseltamivir and zanamavir. It is approved for adults with acute uncomplicated influenza. In the clinical trial for licensure, Peramavir resulted in recovery from fever 12 hours sooner than placebo, similar to the other neuraminidase inhibitors. No benefit was seen in serious flu infection in severely ill hospitalized patients. It is pregnancy risk factor C and a risk benefit decision should be made if considering use in nursing women. Potential indications include use in patients with nausea and vomiting, those requiring IV hydration or medications, patients wanting single dose therapy, or patients who otherwise cannot be prescribed oral or inhaled multi-dose therapies.

Isavuconazole (Cresemba) is an extended spectrum triazole with activity against yeasts, molds, and dimorphic fungi. It is approved for treatment of invasive aspergillosis and mucormycosis and experience is being gained in the treatment of other fungal infections. Desirable properties include availability of a water-soluble IV formulation, excellent oral bioavailability, and predictable pharmacokinetics. It inhibits fungal cell membrane ergosterol synthesis with great avidity for a cell wall forming protein, killing pathogens resistant to other azoles. It cannot be used with rifampin, carbamazepine and long-acting barbiturates as these lead to increased levels of isavuconazole. Sirolimus, tacrolimus and cyclosporine levels should be monitored as isavuconazole raises their level. Overall, when compared to voriconazole and posaconazole, isavuconazole seems to have fewer drug-drug interactions. It is relatively safe and well tolerated and has none of the side effects of voriconazole – visual disturbances, hallucinations, or photosensitivity. Liver enzymes should be monitored. There have been cases of infusion reactions in a few patients; it is recommended an in-line filter be used for infusion. Isavuconazole is pregnancy risk factor C and breast-feeding is not recommended by manufacturer.

As described, these antibiotics have some unique and specific indications that can help justify their formulary inclusion despite high cost. Antibiotic stewardship is crucial to preserve their activity against MDR pathogens. Thankfully several new antibiotics with novel mechanisms of action are in the development pipeline.

Suggested reading:

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