

DRUG UPDATE

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FORMULARY UPDATE

The following is a summary of the business conducted by the P&T Committee during the fourth quarter of 2007:

ADDED:

- ◆ Rosuvastatin (Crestor[®])
- ◆ Bortezomib (Velcade[®])
- ◆ Epoprostenol (Flolan[®])
- ◆ Tranexamic acid (Cyklokapron[®])

DELETED:

- ◆ Amprenavir (Agenerase[®])
- ◆ Aprotinin (Trasylol[®])

EVALUATED, NOT ADDED:

- ◆ Aliskerin (Tekturna[®])

Rosuvastatin (Crestor[®]) was added to the Shands Jacksonville *Formulary*. It joins the other statins in the *Formulary* atorvastatin, pravastatin, and simvastatin. Rosuvastatin is FDA-approved for the management of hypercholesterolemia, hypertriglyceridemia, hyperlipoproteinemia and to slow progression of atherosclerosis. All of the HMG-CoA reductase inhibitors share the same FDA-approved indications as rosuvastatin, but in addition the other statins have an indication for myocardial infarction and stroke prevention. Although rosuvastatin does not carry an indication for primary prevention, trial data suggest that rosuvastatin may have the same effect. Rosuvastatin is hydrophilic, like pravastatin, and due to

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Prescribing

Antibiotic resistance on the rise

According to the Centers for Disease Control (CDC), “antibiotic resistance has been called one of the world’s most pressing public health problems.” The number of bacteria resistant to antibiotics has increased over the past several years.¹ The Infectious Diseases Society of America (IDSA) reports that resistant pathogens have led to higher health care costs due to the need for more expensive agents and longer hospitalizations.² Antibiotic resistance was originally a problem with older generation antibiotics, but over the years there has been an emergence of resistance to newer antibiotics, including linezolid (Zyvox[®]), meropenem (Merrem[®]), moxifloxacin (Avelox[®]), and tigecycline (Tygacil[®]).

Linezolid is a synthetic antibacterial agent used in the treatment of complicated skin and soft tissue infections and nosocomial pneumonia caused by aerobic gram-positive bacteria. Linezolid has also been used for infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE). Linezolid binds to the bacterial 23S ribosomal RNA of the 50S subunit, which prevents the formation of a functional 70S initiation complex essential for bacterial translation.³ The mechanism of linezolid resistance is due to ribosomal target modification, characterized by decreased affinity for the ribosome due to mutations. The Zy-

vox Annual Appraisal of Potency and Spectrum Program (ZAAPS) monitored the occurrence of bacterial resistance to linezolid in 2002. It was found that linezolid had potent activity against all strains worldwide, except for four strains isolated in the United States (*S. aureus*, *S. epidermidis*, viridans group streptococci, and *E. faecium*). The MIC for these strains was > 8 mcg/mL. Of the four patients with resistant strains, two had received previous treatment with linezolid and two had no history of prior exposure to linezolid.⁴ The LEADER linezolid-surveillance program evaluated isolates with resistant phenotypes and emerging resistance patterns. In 2006, a total of 5374 strains from 50 medical centers were tested. Species included *Staphylococcus aureus*, coagulase-negative staphylococci (CoNSs), enterococci, *Streptococcus pneumoniae*, viridans group streptococci, and β -hemolytic streptococci. There were 27 linezolid-resistant isolates (1 *S. aureus*, 13 CoNSs, 3 *Enterococcus faecalis*, and 10 *Enterococcus faecium*). Overall, 99.55% of isolates remained susceptible to linezolid.^{4,5}

Meropenem is indicated for the treatment of skin and skin structure infections, intra-abdominal infections, and bacterial meningitis.⁶ Published reports indicate some resistance to gram-

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less interaction with CYP3A4, has fewer drug interactions compared to atorvastatin and simvastatin.

Bortezomib (Velcade®) is the first FDA-approved proteasome inhibitor, and represents a new alternative for the treatment of refractory multiple myeloma and mantle cell lymphoma. Clinical trials have shown its efficacy in increasing time to progression, response rates, and overall survival.

Epoprostenol (Flolan®) is a prostacyclin analog that is FDA-approved for IV administration for the treatment of primary pulmonary hypertension and diagnosis secondary to the scleroderma spectrum of disease in refractory NYHA Class III and IV patients. Data from clinical trials demonstrate benefits related to exercise capacity, quality of life, and survival compared to conventional therapy. This drug is

administered through a central line, and it has limited stability. This addition is intended only for inpatient use and will be restricted to the Division of Pulmonology.

Tranexamic acid (Cyklokapron®) is an FDA-approved treatment for hemophilia, but was added to the *Formulary* for its off-label use to prevent hemostasis during cardiac surgery in patients with a high risk for bleeding. **Aprotinin (Trasylol®)**, which was originally used for this indication, is now unavailable. Aprotinin is associated with an increased incidence of renal dysfunction and mortality in patients undergoing cardiac artery bypass grafting compared to placebo and tranexamic acid. Subsequently, aprotinin was deleted from the *Formulary*. Tranexamic acid use is restricted to the Division of Cardiothoracic Surgery and Cardiac Anesthesiology.

Amprenavir (Agenerase®) was deleted from the *Formulary* since it was discontinued by the manufacturer. Amprenavir is a protease inhibitor used for the treatment of HIV. **Fosamprenavir (Lexiva®)** is listed in the *Formulary*, it is the prodrug of amprenavir and has less pill burden.

Aliskiren (Tekturna®) is the first approved direct renin inhibitor. It is FDA-approved for the treatment of hypertension as monotherapy or in combination with other agents such as angiotensin receptor blockers (ARBs) and diuretics. Trial data show aliskiren decreases systolic and diastolic blood pressure similarly to valsartan and ramipril. The adverse effect profile of aliskiren is similar to ARBs (i.e., monitor potassium, avoid use during pregnancy, low risk for cough). Because of the limited data available regarding this agent and its lack of mortality data, the P&T Committee did not add aliskiren to the *Formulary*.

Formulary

Linezolid (Zyvox) Criteria for Use

Linezolid was added to the *Formulary* in May 2005. At that time, Criteria for Use were also approved by the Pharmacy and Therapeutics Committee. All Criteria for Use are available on the Infonet in the Department of Pharmacy Inpatient Formulary link: http://intrashands1.umc.ufl.edu/pharmacy/formulary/Inpatient_Formulary_12-07r.xls

Periodically, criteria for use will be published in the *Drug Update* as a reminder for all prescribers.

INDICATIONS:

1. Treatment of complicated skin and skin structure infection (excluding osteomyelitis), or pneumonia with or without concurrent bacteremia caused by documented, susceptible, vancomycin-resistant *Enterococci* infection.
2. Second-line therapy for bacteremia,

complicated skin and skin structure infection (excluding osteomyelitis), or pneumonia caused by documented susceptible methicillin-resistant staphylococcal infections (*Staphylococcus aureus* (MRSA) or coagulase-negative staphylococci) in patients who:

- CANNOT tolerate vancomycin therapy due to allergy, or documented intolerance (not related to infusion rate)
- Have failed to respond clinically to an adequate trial of vancomycin

NOTE: Avoid treating patients colonized with MRSA without signs and symptoms of clinical infection.

3. As a second-line alternative to vancomycin, for the treatment of MRSA-induced ventilator-associated pneumonia in renally-impaired patients (CrCL < 50 mL/min).

NOTE: Linezolid is not FDA-

approved for the treatment of catheter-related bloodstream infections, catheter-site infections, or for the treatment of infections caused by Gram negative bacteria. If infection with Gram-negative bacteria is known or suspected, appropriate therapy should be started immediately.

DOSAGE/ADMINISTRATION:

1. Adults (≥ 12 years): 600 mg intravenously or orally every 12 hours.
2. Pediatrics (birth to 11 years): 10 mg/kg intravenously or orally every 8 hours
3. Neonates (< 7 days, gestational age < 34 weeks): 10 mg/kg intravenously or orally every 12 hours: (*dosing should be increased to 10 mg/kg intravenously or orally every 8 hours by 7 days of life or if sub-optimal clinical response is suspected)

MONITORING PARAMETERS/PRECAUTIONS:

1. Linezolid has been associated with myelosuppression (e.g., anemia, leukopenia, thrombocytopenia, pancytopenia)

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negative organisms, including *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Acinetobacter species*, *Proteus species*, *Serratia marcescens*, *Enterobacter species*, and *Klebsiella pneumoniae*. Resistance to carbapenems occurs either through bacterial production of β -lactamase enzymes or through porin changes in the bacterial cell wall that reduces the permeability of the drug into the organism.⁷ The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program is an international resistance surveillance network of over 100 medical centers throughout the world monitoring susceptibility of bacterial pathogens. In the 2006 MYSTIC update, 7124 isolates from 40 European centers were evaluated and compared to the 2002 results. There has been little change in the susceptibility in gram-positive organisms compared with the 2002 results; the carbapenems still have > 90% susceptibility rating. The study also showed that the carbapenems have demonstrated slight losses of activity compared to the 2002 results among the extended-spectrum beta-lactamase (ESBL) and AmpC beta-lactamase producing organisms. However, there was a significant decrease in the susceptibility of *Acinetobacter* spp. when compared to the 2002 data. In 2002, there was approximately 84% susceptibility; however, in 2006 susceptibility was reported to be approximately 56%.^{6,8} Additionally, ESBL resistance to carbapenems has been detected. *Klebsiella pneumoniae* carbapenemases, or KPCs have been reported in North Florida and in other parts of the country. KPCs have similar resistance profiles to ESBLs with added resistance to the carbapenems. Treatment options for KPCs may include the polymyxins, tigecycline and possibly the aminoglycosides or tetracyclines.¹⁴

Although not as common, antimicrobial resistance has been documented with moxifloxacin, a non-formulary agent at Shands Jacksonville, and tigecycline. Moxifloxacin is a

broad spectrum antibacterial agent indicated for use in a variety of infections, including community acquired pneumonia, skin and skin structure infections, chronic bronchitis, and intra-abdominal infections. In the most recent surveillance data, *Streptococcus pneumoniae* resistance was reported in less than 1% of isolates collected in the United States between 1994 and 2003. There is very little resistance for gram-positive and gram-negative organisms, but there has been documented resistance for anaerobic organisms.⁹ Tigecycline is a synthetic derivative of minocycline and is the first marketed glycylcycline. Tigecycline is indicated for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections. Gram-negative bacterial resistance to

The susceptibility for Enterococcus to linezolid (at Shands Jacksonville) is 86%; the majority of the 14% considered non-susceptible had intermediate susceptibility.

tigecycline has been documented by in vitro data. The most common mechanism of resistance, suggested by in vitro studies, is mediated by the non-specific multidrug efflux pump system.¹⁰

To date, no cases of linezolid resistant *Staphylococcus aureus* have been reported at Shands Jacksonville. However, the susceptibility for *Enterococcus* to linezolid is 86%; the majority of the 14% considered non-susceptible had intermediate susceptibility. The majority of gram-negative organisms are 100% susceptible to meropenem, except for *Acinetobacter* spp. (97%), *Enterobacter cloacae* (99%), and *Pseudomonas* spp. (88%). Currently, hospital susceptibility data is not available for tigecycline and moxifloxacin. Shands Jacksonville's antibiogram information is available on the Infonet at [\[intrahands1.umc.ufl.edu/lab/default-new.htm\]\(http://intrahands1.umc.ufl.edu/lab/default-new.htm\) scroll down the right hand column and click on *Empiric antibiotic recommendations/Antibiogram*. Any questions regarding susceptibility testing should be directed to the Shands Jacksonville Microbiology Laboratory at 904-244-6063.¹³](http://</p></div><div data-bbox=)

Since resistance continues to be a growing problem, various strategies have been developed to minimize the emergence of resistance. These include antimicrobial stewardship, the introduction of the Strategies to Address Antimicrobial Resistance (STAAR) Act, and the CDC's Campaign to Prevent Antimicrobial Resistance. Antimicrobial stewardship includes the appropriate selection, dosing, route, and duration of antimicrobial therapy. The primary goal is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including the emergence of resistance.¹¹ The STAAR Act, endorsed by multiple medical and infectious disease organizations, calls for an Office of Antimicrobial Resistance in the Department of Health and Human Services. The Act will stress the importance of federal antimicrobial resistance surveillance, antimicrobial resistance prevention and control, and future research for newer antibiotics.²

Lastly, the CDC developed a Campaign to Prevent Antimicrobial Resistance, which focuses on preventing antimicrobial resistance in health-care settings. The Campaign developed tools for clinicians to prevent antimicrobial resistance in hospitalized adults, dialysis patients, surgical patients, hospitalized children, and long-term care patients. These can be found at <http://www.cdc.gov/drugresistance/healthcare/default.htm>.¹²

Antimicrobial resistance continues to be an evolving problem both in the health-care setting and in the community. It is important for healthcare professionals to be aware of the growing resistance to the newer antibiotics. Healthcare professionals have a re-

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- penia); therefore, complete blood cell counts should be monitored on a weekly basis, especially in patients-receiving greater than two weeks of linezolid therapy with pre-existing myelosuppression, receiving other myelosuppressive drugs, and with chronic infection who have received previous or concomitant antibiotic therapy.
- Linezolid should be discontinued in those who develop or experience worsening myelosuppression. Pyridoxine (Vitamin B6) 50 mg once daily has been suggested as a means to reduce the incidence of myelosuppression related to linezolid therapy.
 - Linezolid is a reversible, non-selective monamine oxidase inhibitor (MAOI) and may result in a significant pressor response in patients who consume large quantities of foods or beverages with high tyramine content (greater than 100 mg tyramine per meal). Examples of foods high in tyramine include those that have been aged, pickled, smoked or fermented.
 - Similarly, due to linezolid's MAOI activity, elevations in blood pressure may also occur with concomitant administration of adrenergic agents (e.g., pseudoephedrine, dopamine, epinephrine).
 - Patients receiving concomitant serotonergic agents (e.g., fluoxetine, nefazodone, paroxetine, sertraline) may

be at increased risk for development of serotonin syndrome (confusion, tremor, delirium, flushing, diaphoresis, hyperpyrexia) while receiving linezolid due to its MAOI activity.

- The most common adverse effects associated with linezolid therapy include diarrhea (3-11%), headache (1-11%), and nausea (3-20%). Patients receiving linezolid should also be monitored for development of lactic acidosis.
- Peripheral and optic neuropathy (i.e., changes in visual acuity, changes in color vision, blurred vision, visual field defect) have been reported in patients receiving linezolid for greater than 28 days. Patients who experience these symptoms should receive prompt medical evaluation.
- Caution is recommended in phenylketonurics as the oral suspension of linezolid contains phenylalanine (20 mg/5 mL).

OUTCOME:

- Eradication of vancomycin resistant *Enterococcus faecium* infection and methicillin-resistant *Staphylococcus aureus* infections in specified patient populations.
- Absence of fever.
- White blood cell count within normal limits.

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sponsibility to help control the emergence of resistant pathogens. This requires adherence to infection control guidelines, awareness of local resistance patterns, and appropriate use of antimicrobial agents.

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