Tigecycline (Tygacil®), the First in a New Class of Antibiotic
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Tigecycline is the first FDA-approved agent in a new class of antibiotics, glycylcyclines, a class closely related to the tetracyclines. Tigecycline was specifically developed to provide broad-spectrum coverage while overcoming two of the more common resistance mechanisms associated with tetracycline antibiotics: drug efflux and ribosomal protection. This combination of activity and lack of resistance allows tigecycline to be used for many infections that other antibiotics may not be able to address.

Tigecycline is unique among the small group of antibiotics used for multidrug-resistant Gram-positive infections because it also possesses activity against Gram-negative organisms. Tigecycline has activity against a number of Gram-positive organisms, including MRSA and Enterococcus faecalis, and Gram-negative organisms, including ESBL-producing bacteria, Acinetobacter spp., and Stenotrophomonas spp. Of note, tigecycline does not have antipseudomonal activity. Tigecycline also possesses antianaerobic activity.

Due to the very high volume of distribution, tigecycline achieves drug concentrations in the skin and soft tissues many times higher than that in the blood. For this reason, tigecycline is FDA-approved for treatment of complicated skin and skin-structure infections (cSSSI) as well as complicated intra-abdominal infections. Currently a Phase III trial is evaluating the use of tigecycline for the treatment of hospital-acquired pneumonia. Tigecycline should not be used for endovascular infections, such as primary bacteremia or endocarditis, due to this very high volume of distribution and low serum concentrations (approximately 0.6 mg/L).

Tigecycline is not indicated for use during pregnancy or in children under 8 years old as it may interfere with proper bone formation and cause permanent tooth discoloration. When considering use in these populations, all risks should be weighed against the potential benefits to the patient.

Adverse reactions that were reported in $\geq$10% of patients in clinical trials with tigecycline include; nausea (29.5%), vomiting (19.7%), and diarrhea (12.7%).

The recommended dose of tigecycline is 100 mg IV bolus followed by 50 mg IV every 12 hours to be delivered over 30 to 60 minutes. Usual duration of therapy is 5 – 14 days, although actual duration should be dictated by the site and severity of infection and the patient's overall clinical status. For those with severe hepatic disease (Child-Pugh C), dose should be initiated at 100 mg IV bolus followed by 25 mg IV every 12 hours for the duration of therapy. Use in this population should be done cautiously, with frequent monitoring for treatment response and toxicity.

Tigecycline does not require any specific monitoring except to determine if the infection is responding to therapy.

P&T Action: The Antimicrobial Subcommittee reviewed the request for addition of tigecycline to the inpatient formulary. In March, the P&T Committee accepted the recommendations of the antimicrobial subcommittee outlined below.

In order to make this medication available as a formulary agent for the general medical staff, to ensure appropriate usage, and to protect the medical staff from medical/legal considerations, the Antimicrobial Subcommittee has developed the following recommendations:
1. Add tigecycline to the inpatient formulary. Use of this drug, without Infectious Disease approval, is allowed for FDA-labeled indications only. (see above)
2. A written indication for use must accompany all tigecycline orders in the permanent medical record. Empiric orders should include site of infection and possible infecting organism(s).
3. Apply restrictions when tigecycline is ordered for off-label purposes.
3. a Any off-label use will require review and approval for continued use by the Infectious Disease (ID) Service. The ordering physician is responsible for contacting the ID service. Only the loading dose and first maintenance dose of tigecycline will be dispensed pending ID response; therefore, the review must occur within 24 hours of the original order.
3. b If off-label use is approved, the ID Service will relay this information to the ordering physician as well as to the pharmacy for continued administration of tigecycline. If tigecycline is thought to be inappropriate, the ID Service will provide alternative recommendations and communicate these recommendations to the physician originating the tigecycline order.

4. Monitor cost and outcomes to verify that tigecycline therapy results in evidence of satisfactory outcomes, shorter duration of therapy, and acceptable costs.