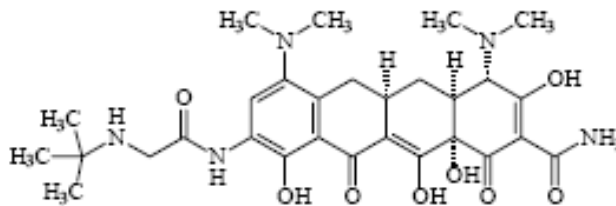


**Bon Secours Richmond**  
**Pharmacy and Therapeutics Committees**  
**Tigecycline (Tygacil®)**  
**9/2005**

**Recommendations:**

- Input from infectious disease specialists will be obtained to determine the proper formulary status of tigecycline and to guide the P&T recommendations. The following draft will be provided for ID review.
- Tigecycline use is restricted to infectious disease specialists and will be non-formulary at this time. Formulary status will be reevaluated in one year when sensitivity data is available.
- The microbiology department will obtain sensitivity panels and sensitivity testing is recommended for all patients receiving Tigecycline. Tigecycline will not be available for use until sensitivity testing can be performed. Note: The MIC range for numerous bacteria is above the breakpoint for tigecycline.
  - Antimicrobial therapy should be directed by culture and sensitivity results.
- Patients who become septic or develop septic shock have higher mortality rates when treated with tigecycline (1.5%) versus comparator agents (0.5%). Alternative agents are recommended.
- Tigecycline should not be used in neutropenic, immunosuppressed patients, or patients with endocarditis as it is bacteriostatic.
- Bactericidal agents are preferred for the treatment of serious, life threatening infections.
- Tigecycline is expensive, \$88 per day, and should be reserved for conditions where less expensive agents cannot be used. It is only available in an IV formulation.

The following represents the chemical structure of tigecycline:



Molecular Weight 586 daltons

**Findings:**

- Tigecycline is indicated for complicated skin and skin structure infections and complicated intra-abdominal infections.
- Tigecycline is a bacteriostatic analogue of minocycline with broad-spectrum antibiotic activity for parenteral use. It inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl-tRNA molecules into the A site of the ribosome.
- Tigecycline displays time dependent killing, the best measure pharmacokinetic/pharmacodynamic index associated with efficacy is the AUC/MIC ratio.
- Tigecycline is classified as a glycylicycline antimicrobial, which has gram-positive, and gram-negative activity. No cross-resistance has been observed between tigecycline and other antibiotics, tigecycline is not affected by two of the resistance mechanisms seen with other tetracyclines (ribosomal protection and active efflux).
- *Tigecycline is not active against P. aeruginosa, Proteus mirabilis; strains of Serratia marcescens, Acinetobacter species, Acinetobacter baumannii, Stenotrophomonas maltophilia, and Burkholderia cepacia due to active efflux.*
- *The MIC range is above the break point for Staph aureus (MRSA), coag negative staph, Enterococcus faecalis, Strep pneumoniae, and Strep viridans.*
- In Phase 3 clinical studies, infection related serious adverse events were more frequently reported for subjects treated with tigecycline (6.7%) vs comparators (4.6%). Significant differences in sepsis/septic shock with tigecycline (1.5%) vs comparators (0.5%) were observed.
- Tigecycline has demonstrated in vitro activity against: vancomycin resistant enterococci-, extended-spectrum beta-lactamase and methicillin-resistant Staphylococcus aureus-resistant phenotypes.
- Tigecycline demonstrates bacteriostatic activity against VRE, which may limit its use in serious VRE infections.

- The recommended dosage is: initial dose of 100mg followed by 50mg IV q12h for 5-14 days or 25 mg IV q12h for patients with severe hepatic impairment (Child Pugh C). Mixed in 0.9% NaCl or 5% D5W with a maximum concentration of 1 mg/ml. Stable for 6 hours room temperature or 24 hours in refrigerator.
- Comparative cost per day (ascending order):
  - Cefazolin 1 gm q6h plus metronidazole 0.5 mg q6h \$11
  - Ceftriaxone 1 gm q24h plus metronidazole 0.5 gm q6h \$26
  - Ceftazidime 1-2 gm q8H plus metronidazole 0.5 mg q6h \$22-\$48
  - Levofloxacin 750 mg q24h plus metronidazole 0.5 gm q6h \$22
  - Ampicillin/sulbactam 3.1 gm q6h \$41.20
  - Zosyn 3.375 gm q6h \$55.04
  - Tygacil 50 mg q12h \$87.89
  - Primaxin 500 mg q6h \$89.81
  - Nafcillin 2 gm q6h plus Levaquin 750 mg q24h plus clindamycin 600 mg q6 h \$94.78
  - Aztreonam 2 gm q12h plus vancomycin 1 gm q12h \$99.75
- In Vitro plasma protein binding of tigecycline ranges from approximately 71%-89%. Steady state volume of distribution of tigecycline averaged 500-700L. (7-9L/kg), which indicates that tigecycline is extensively distributed beyond plasma volume and into tissue.
- Tigecycline is not extensively metabolized. The primary route of elimination of Tigecycline is biliary excretion, 59%, with the majority being unchanged tigecycline. Secondary route of elimination is glucuronidation and renal excretion of unchanged drug 22%.
- No dosage adjustments are needed in regards to: age, race, mild to moderate hepatic dysfunction or in renally impaired patients.
- Tigecycline is not removed by hemodialysis due to large volume of distribution. No information is available on removal by high flux dialysis. Dosing after high flux hemodialysis is recommended.
- Compatibilities at Y-Site: dobutamine, dopamine, Lactated Ringer's, lidocaine, potassium chloride, ranitidine, and theophylline.
- Incompatibilities at Y-sites and IV administration include; amphotericin B, chlorpromazine, methylprednisolone, and voriconazole.
- Contraindications: tetracycline allergy
- Tigecycline may cause fetal harm when administered to pregnant women. **Pregnancy category D.** It is not known whether the drug is excreted in human milk (excreted readily in lactating rats), but the drug has limited oral bioavailability.
- Tigecycline use, as with other tetracyclines, during tooth development stages (last half of pregnancy, infancy and childhood up to age of 8 years) may cause permanent discoloration of the teeth. Other possible ADR are: photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic action (increase BUN, azotemia, acidosis, and hypophosphatemia)
- Most common adverse effects of Tigecycline are (mild or moderate) nausea, 29.5%, and vomiting 19.7%, which are twice the rate of the comparator medications. Discontinuation of tigecycline was most frequently associated with nausea and vomiting.

**Recommended Agents for Treatment of Community-acquired Complicated\* Intra-abdominal Infections, IDSA 2003**

<b>Single Agents</b>	Agents recommended for Mild to Moderate Infections	Agents recommended for High Severity Infections
Beta-lactam/Beta-Lactamase Inhibitor Combinations	Ampicillin/sulbactam 3 gm q6h (\$41), ticarcillin/clavulanic acid	Piperacillin/tazobactam 3.375 gm q6h \$52
Carbapenems	Ertapenem 1 gm q24h (\$43)	Imipenem/cilastatin 0.5 gm q6h \$90, meropenem 1 gm q8h \$91
<b>Combination Regimens</b>		
Cephalosporin Based	(Cefazolin 1 gm q6h \$6 or cefuroxime) plus metronidazole 0.5 gm q6h \$5	Third or Fourth Generation cephalosporin (cefotaxime, ceftriaxone 1 gm q24h \$21, ceftizoxime, ceftazidime 1 gm q8h \$22, cefepime 1-2 gm q8h \$47-\$95) plus metronidazole 0.5 gm q6h \$5
Fluoroquinolone Based	(Levofloxacin 750 mg q24 \$17, Ciprofloxacin 400 mg q12h \$49,) plus metronidazole 0.5 gm q6h \$5	
Monobactam Based		Aztreonam 2 gm q12-8h \$88-134 plus metronidazole 0.5 gm q6h \$5

\*Complicated intra-abdominal infections are defined as infections that extend beyond the hollow viscus of origin into the peritoneal space and that are associated either with abscess formation or peritonitis. These infections require either operative or percutaneous intervention to resolve.

\*\* Postoperative (nosocomial) infections are caused by more-resistant flora, which may include *Pseudomonas aeruginosa*, *Enterobacter* species, *Proteus* species, MRSA, enterococci, and *Candida* species. For these infections, complex multidrug regimens are recommended.

- Bowel injuries due to penetrating, blunt, or iatrogenic trauma that are repaired within 12 hours and intraoperative contamination of the operative field by enteric contents under other circumstances should be treated with antibiotics for  $\leq 24$  hours.
- Antibiotics used for empirical treatment of community acquired intra-abdominal infections should be active against enteric gram-negative aerobic and facultative bacilli and beta lactam susceptible gram-positive cocci. Coverage against obligate anaerobic bacilli should be provided for distal small bowel and colon-derived infections and for more proximal gastrointestinal perforations when obstruction is present.
- The expanded gram negative bacterial spectrum of some agents shown to be effective in clinical trials is not advantageous for patients with community acquired infections, and unnecessary use of such agents may contribute to the emergence of antimicrobial resistance. In particular, agents that are used to treat nosocomial infections in the ICU unit should not be routinely used to treat community-acquired infections.
- *Bacteroides fragilis* group demonstrate substantial resistance to clindamycin, cefotetan, cefoxitin, and quinolones.
- None of the above regimens has been consistently demonstrated to be superior or inferior.
- Completion of the antimicrobial course with oral forms of a quinolone plus metronidazole or with oral amoxicillin/clavulanic acid is acceptable for patients who are able to tolerate an oral diet.
- *Candida albicans* or other fungi are isolated from approximately 20% of patients with acute perforations of the GI tract. Even when fungi are recovered, antifungal agents are unnecessary, unless the patient has recently received immunosuppressive therapy for neoplasm, transplantation, or inflammatory disease or has postoperative or recurrent abdominal infections.

**Comparison of Tygacil® (tigecycline) vs. Zosyn®(piperacillin and tazobactam)**

	<b>Tygacil® (tigecycline)</b>	<b>Zosyn® (piperacillin and tazobactam)</b>
<b>Drug class</b>	Glycylcycline antibacterial Glycylamido moiety attached to the 9-position of minocycline.	Antibacterial combination product consisting of the semisynthetic antibiotic piperacillin sodium and the β-lactamase inhibitor tazobactam sodium for intravenous administration.
<b>Mechanism of Action</b>	Bacteriostatic activity; Inhibition of protein translation in bacteria by binding to 30S ribosomal subunit Not effected by two major tetracycline resistance mechanisms (ribosomal protection and efflux)	Bactericidal activity; Inhibition of septum formation and cell wall formation in susceptible bacteria
<b>Route of Elimination</b>	59% eliminated by biliary/fecal (mainly unchanged) 33% excreted in urine (22% unchanged)	Renal: via glomerular filtration and tubular secretion
<b>Clearance (L/hr)</b>	23.8 total 17.8 (Child Pugh A or B) 10.7 (Child Pugh C) 3.06 renal	
<b>Elimination half-life</b>	42.4 hours	0.7-1.2 hours not affected by dose or duration of infusion. T ½ increases with decreasing creatinine clearance.
<b>Protein Binding (in plasma)</b>	71%-89%	30% bound to plasma protein
<b>Volume of Distribution</b>	7-9 l/kg Extensively bound in tissues	
<b>Steady State Serum Levels (mcg/ml) for 50 mg q12h</b>	Cmax 0.63-0.87 Cmin 0.13	
<b>AUC 0-12 hours (mcg/hr/ml)</b>	Alveolar 134 Epithelial lining fluid 2.28 Serum 1.55 Skin Blister Fluid 25% of Serum	
<b>FDA approved indication(s)</b>	<p><b>*Complicated skin and skin structure infections caused by <i>E. coli</i>, <i>E. faecalis</i> (vancomycin susceptible isolates only), <i>S. aureus</i> (methicillin-susceptible and –resistant isolates), <i>S. agalactiae</i>, <i>S. anginosus</i> grp. (includes <i>Strep. anginosus</i>, <i>S. intermedius</i>, and <i>S. constellatus</i>) <i>S. pyogenes</i> and <i>B. fragilis</i>.</b></p> <p><b>* Complicated intra-abdominal infections caused by: <i>C. freundii</i>, <i>E. cloacae</i>, <i>E. coli</i>, <i>K. oxytoca</i>, <i>K. pneumoniae</i>, <i>E. Faecalis</i> (vancomycin-susceptible isolates only), <i>S. aureus</i> (methicillin-susceptible isolates only), <i>Strep. anginosus</i> grp. (includes <i>S. anginosus</i>, <i>S. intermedius</i>, and <i>S. constellatus</i>), <i>B. fragilis</i>, <i>B. thetaiotaomicron</i>, <i>B. uniformis</i>, <i>B. vulgatus</i>, <i>C. perfringens</i> and <i>Peptostreptococcus micros</i>.</b></p>	<p><b>*Uncomplicated and complicated skin and skin structure infections caused by piperacillin resistant, β-lactamase producing strains of <i>S. aureus</i>.</b></p> <p><b>*Appendicitis (complicated by rupture or abscess) and peritonitis caused by piperacillin-resistant, β-lactamase producing strains of <i>E. coli</i>, <i>B. fragilis</i> grp(includes <i>B. fragilis</i>, <i>B. ovatus</i>, <i>B. thetaiotaomicron</i> or <i>B. vulgatus</i>)</b></p> <p><b>* Also indicated for post partum endometritis or pelvic inflammatory disease caused by <i>E. coli</i>.</b></p> <p><b>*Nosocomial pneumonia caused by <i>S. aureus</i> <i>A. baumannii</i>, <i>H. influenzae</i>, <i>K. pneumoniae</i> and <i>P. aeruginosa</i> (<i>P. aeruginosa</i> should be treated in combination with an aminoglycoside)</b></p> <p><b>*Community –acquired pneumonia caused by <i>H. influenzae</i></b></p>
<b>Route of administration</b>	IV infusion over 30-60 minutes	IV infusion
<b>FDA Approved Dosage</b>	100mg Single Dose 50 mg q12h Multiple Dose, usual duration of treatment 5-14 days	4.5g q6h (+ aminoglycoside) 3.375g q6h duration of treatment usual (7-10d), guided by severity of infection and clinical/bacteriological progress)
<b>Geriatric Use</b>	No dosage adjustment is necessary.	No dosage adjustment is necessary.
<b>Pediatric Use</b>	Not established	Not established
<b>Renal Insufficiency Dose Adjustment</b>	No dosage adjustment is necessary in renal impairment or in hemodialysis.	Adjustment: decrease in dose to 2.25g q12h in all infections except nosocomial pneumonia( 2.25g q8h), additional 0.75g given to dialysis patients on dialysis days after treatment
<b>Hepatic Insufficiency Dose Adjustment</b>	No dosage adjustment is warranted in patients with mild to moderate hepatic impairment. Severe hepatic impairment the initial dose of Tygacil should be 100mg followed by a reduced maintenance dose of 25 mg q12h- use caution and monitor for treatment response	T ½ is ↓ 25% and 18% for piperacillin and tazobactam respectively, however no dosage adjustment is necessary

Table 5. Clinical Cure Rates from Two Pivotal Studies in Complicated Skin and Skin Structure Infections after 5 to 14 Days of Therapy

	TYGACIL <sup>a</sup> n/N (%)	Vancomycin/Aztreonam <sup>b</sup> n/N (%)
Integrated		
CE	365/422 (86.5)	364/411 (88.6)
c-mITT	429/538 (79.7)	425/519 (81.9)
Study 300		
CE	165/199 (82.9)	163/198 (82.3)
c-mITT	209/277 (75.5)	200/260 (76.9)
Study 305		
CE	200/223 (89.7)	201/213 (94.4)
c-mITT	220/261 (84.3)	225/259 (86.9)

<sup>a</sup> 100 mg initially, followed by 50 mg every 12 hours

<sup>b</sup> Vancomycin (1 g IV every 12 hours)/Aztreonam (2 g IV every 12 hours)

Table 6. Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Skin and Skin Structure Infections<sup>a</sup>

Pathogen	TYGACIL n/N (%)	Vancomycin/Aztreonam n/N (%)
<i>Escherichia coli</i>	27/32 (84.4)	26/30 (86.7)
<i>Enterococcus faecalis</i> (vancomycin-susceptible only)	13/17 (76.5)	24/29 (82.8)
Methicillin-susceptible <i>Staphylococcus aureus</i> (MSSA)	125/139 (89.9)	118/126 (93.7)
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	29/37 (78.4)	26/34 (76.5)
<i>Streptococcus agalactiae</i>	8/8 (100)	11/13 (84.6)
<i>Streptococcus anginosus</i> grp. <sup>b</sup>	16/20 (80.0)	9/10 (90.0)
<i>Streptococcus pyogenes</i>	31/33 (93.9)	24/27 (88.9)
<i>Bacteroides fragilis</i>	6/8 (75.0)	4/5 (80.0)

<sup>a</sup> Two cSSSI pivotal studies and one Phase 3 Resistant Pathogen study

<sup>b</sup> Includes *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*

Study exclusion criteria: necrotizing fasciitis, gangrene, osteomyelitis, plasmapheresis, hemoperfusion, neutropenia, severely impaired arterial blood supply, or any condition or medication that would impair the ability to eradicate infections.

Table 7. Clinical Cure Rates from Two Pivotal Studies in Complicated Intra-abdominal Infections after 5 to 14 Days of Therapy

	TYGACIL <sup>a</sup> n/N (%)	Imipenem/Cilastatin <sup>b</sup> n/N (%)
Integrated		
ME	441/512 (86.1)	442/513 (86.2)
m-mITT	506/631 (80.2)	514/631 (81.5)
Study 301		
ME	199/247 (80.6)	210/255 (82.4)
m-mITT	227/309 (73.5)	244/312 (78.2)
Study 306		
ME	242/265 (91.3)	232/258 (89.9)
m-mITT	279/322 (86.6)	270/319 (84.6)

<sup>a</sup> 100 mg initially, followed by 50 mg every 12 hours

<sup>b</sup> Imipenem/Cilastatin (500 mg every 6 hours)

Table 8. Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Intra-abdominal Infections<sup>a</sup>

Pathogen	TYGACIL n/N (%)	Imipenem/Cilastatin n/N (%)
<i>Citrobacter freundii</i>	12/16 (75.0)	3/4 (75.0)
<i>Enterobacter cloacae</i>	14/16 (87.5)	16/17 (94.1)
<i>Escherichia coli</i>	281/329 (85.4)	298/343 (86.9)
<i>Klebsiella oxytoca</i>	19/20 (95.0)	18/20 (90.0)
<i>Klebsiella pneumoniae</i>	46/52 (88.5)	53/60 (88.3)
<i>Enterococcus faecalis</i> (vancomycin-susceptible only)	25/33 (75.8)	35/47 (74.5)
Methicillin-susceptible <i>Staphylococcus aureus</i> (MSSA)	26/29 (89.7)	22/24 (91.7)
<i>Streptococcus anginosus</i> grp. <sup>b</sup>	102/120 (85.0)	61/81 (75.3)
<i>Bacteroides fragilis</i>	67/87 (77.0)	60/74 (81.1)
<i>Bacteroides thetaiotaomicron</i>	36/41 (87.8)	31/36 (86.1)
<i>Bacteroides uniformis</i>	12/17 (70.6)	14/17 (82.4)
<i>Bacteroides vulgatus</i>	14/16 (87.5)	5/7 (71.4)
<i>Clostridium perfringens</i>	19/20 (95.0)	20/22 (90.9)
<i>Peptostreptococcus micros</i>	14/18 (77.8)	9/12 (75.0)

<sup>a</sup> Two cIAI pivotal studies

<sup>b</sup> Includes *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*

Selected exclusion criteria: neutropenia, bacterial isolated not susceptible, intraoperative antibacterial irrigants or peritoneal antibacterial agents

Susceptibility Testing From Package Insert			
	Sensitive (mcg/ml)	Intermediate (mcg/ml)	Resistant (mcg/ml)
<b>Staphylococcus aureus (including methicillin resistant isolates)</b>	<b>&lt;=0.5</b>		
<b>Streptococcus spp (other than S. pneumoniae)</b>	<b>&lt; 0.25</b>		
<b>Enterococcus faecalis (vancomycin-susceptible isolates)</b>	<b>&lt;0.25</b>		
<b>Enterobacteriaceae*</b>	<b>&lt;=2</b>	<b>4</b>	<b>&gt;= 8</b>
<b>Anaerobes</b>	<b>&lt;=4</b>	<b>8</b>	<b>&gt;=16</b>

\*Tigecycline has decreased in vitro activity against *Morganella* spp, *Proteus* spp. and *Providencia* spp.

	<b>Tygacil</b>	<b>Zosyn</b>
<b>Adverse Effects</b>	<p>May have similar adverse effects of tetracycline class antibiotics.</p> <p>May cause fetal harm when administered to pregnant a woman.</p> <p>Use during the last half of pregnancy, infancy and ages &lt;8 years old may cause permanent discoloration of the teeth.</p> <p>Pseudomembranous colitis may range from mild to life threatening; consider this diagnosis in patients who present with diarrhea after administration of antibiotic.</p> <p>Nausea, vomiting, allergic reaction, chills, abnormal stools, thrombophlebitis, bradycardia, tachycardia, vasodilation, anorexia, dry mouth, jaundice, injection site: inflammation, Pain, injection site reaction, injection site edema or phlebitis. Increased creatinine, hypocalcemia, hypoglycemia, hyponatremia, somnolence, taste perversion, eosinophilia, thrombocytopenia, vaginal moniliasis, vaginitis, leukorrhea</p>	<p>May have similar adverse effects of the penicillin class antibiotics.</p> <p>The most reported adverse effects are gastrointestinal disturbances (diarrhea, nausea, vomiting) hypersensitivity reactions and skin rashes.</p>
<b>Contraindications</b>	Tetracycline allergy	Pts with history of allergic reactions to penicillins, cephalosporins or $\beta$ -lactamase inhibitors
<b>Drug Interactions</b>	<p><b><u>Digoxin</u></b> (Cmax ↓ 13%, AUC or Clearance unchanged); No dosage adjustment is needed.</p> <p><b><u>Warfarin</u></b> ( Clearance↓ R-warfarin 40%, S-Warfarin 23%) SINGLE DOSE WARFARIN STUDY, No significant effects on INR; prothrombin time should be monitored when administered when tigecycline and warfarin are used together.</p> <p><b>In vitro studies in human liver microsomes indicate that tigecycline does not inhibit metabolism by the 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4 CYP450 enzymes.</b></p>	<p><b><u>Probenecid</u></b> given with Zosyn will prolong the t ½ of piperacillin by 21% and tazobactam by 71%</p> <p><b><u>Tobramycin</u></b> (AUC↓ 11%, renal clearance ↓ 32%, and urinary recovery ↓ 38%)</p> <p><b><u>Heparin</u></b>: coagulation parameters should be checked more frequently</p> <p><b><u>Methotrexate</u></b>: methotrexate concentrations and toxicity should be monitored more frequently.</p>
<b>Cost * see attachment 2</b>		

	Attachment #1	In Vitro Activity
	Tygacil	Zosyn
<b>In Vitro Activity</b>	<p>Numerous pathogens including:  <b>In vitro and in Clinical Infections</b>  <u>Aerobic Facultative Gram(+) microorganisms:</u>            *<i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)            *<i>Staphylococcus aureus</i> (methicillin-susceptible and resistant isolates)            *<i>Streptococcus agalactiae</i>            *<i>Streptococcus anginosus</i> group.            (includes: <i>S. anginosus</i>, <i>S. intermedius</i>, and <i>S. constellatus</i>)</p> <p><u>Aerobic and facultative Gram(-) microorganisms:</u>            *<i>Citrobacter cloacae</i>            *<i>Enterobacter cloacae</i>            *<i>Escherichia coli</i>            *<i>Klebsiella oxytoca</i>            *<i>Klebsiella pneumoniae</i></p> <p><u>Anaerobic microorganisms:</u>            *<i>Bacteroides fragilis</i>            *<i>Bacteroides thetaiotaomicron</i>            *<i>Bacteroides uniformis</i>            *<i>Bacteroides vulgatus</i>            *<i>Clostridium perfringens</i>            *<i>Peptostreptococcus micros</i></p> <p>The following in vitro data are available, but their clinical significance is unknown.</p> <p><u>Aerobic and facultative Gram(+) microorganisms:</u>            *<i>Enterococcus avium</i>            *<i>Enterococcus casseliflavus</i>            *<i>Enterococcus faecalis</i> (vancomycin-resistant isolates)            *<i>Enterococcus faecium</i> (vancomycin-susceptible and –resistant isolates)            *<i>Enterococcus gallinarum</i>            *<i>Listeria monocytogenes</i>            *<i>Staphylococcus epidermidis</i> (methicillin susceptible and resistant isolates)            *<i>Staphylococcus haemolyticus</i></p> <p><u>Aerobic and facultative Gram(-) microorganisms:</u>            *<i>Acinetobacter baumannii</i>            *<i>Aeromonas hydrophila</i>            *<i>Citrobacter koseri</i>            *<i>Enterobacter aerogenes</i>            *<i>Pasteurella multocida</i>            *<i>Serratia marcescens</i>            *<i>Stenotrophomonas maltophilia</i></p> <p><u>Anaerobic microorganisms:</u>            *<i>Bacteroides diasonis</i>            *<i>Bacteroides ovatus</i>            *<i>Peptostreptococcus</i> spp.            *<i>Porphyromonas</i> spp.            *<i>Prevotella</i> spp.</p> <p><u>Other microorganisms:</u>            *<i>Mycobacterium abscessus</i>            *<i>Mycobacterium chelonae</i>            *<i>Mycobacterium fortuitum</i></p>	<p>Numerous pathogens including:</p> <p><u>Aerobic Facultative Gram(+) microorganisms:</u>            *<i>Staphylococcus aureus</i>(excluding methicillin and oxacillin-resistant isolates)</p> <p><u>Aerobic Facultative Gram(-) microorganisms:</u>            *<i>Acinetobacter baumannii</i>            *<i>Escherichia coli</i>            *<i>Haemophilus influenzae</i> (excluding <math>\beta</math>-lactamase negative, ampicillin-resistant isolates)            *<i>Klebsiella pneumoniae</i>            *<i>Pseudomonas aeruginosa</i> ( given in combination with an aminoglycoside to which the isolate is susceptible)</p> <p>The following in vitro data are available, but their clinical significance is unknown. Mic <math>\leq</math> the susceptible breakpoint for piperacillin/tazobactam.</p> <p><u>Aerobic and Facultative Gram (+) microorganisms:</u>            *<i>Enterococcus faecalis</i>(ampicillin or penicillin-susceptible isolates only)            * <i>Staphylococcus epidermidis</i> (excluding methicillin and oxacillin resistant isolates)            *<i>Streptococcus agalactiae</i>†            *<i>Streptococcus pneumoniae</i>† (penicillin-susceptible isolates only)            *<i>Streptococcus pyogenes</i>†            *<i>Viridans group streptococci</i>†</p> <p>†These are not <math>\beta</math>-lactamase producing bacteria and, therefore, are susceptible to piperacillin alone.</p> <p><u>Aerobic and facultative Gram(-) microorganisms:</u>            *<i>Citrobacter koseri</i>            *<i>Moraxella catarrhalis</i>            *<i>Morganella morganii</i>            *<i>Neisseria gonorrhoeae</i>            *<i>Proteus mirabilis</i>            *<i>Proteus vulgaris</i>            *<i>Serratia marcescens</i>            *<i>Providencia stuartii</i>            *<i>Providencia rettgeri</i>            *<i>Salmonella enterica</i></p> <p><u>Gram(+) anaerobes:</u>            *<i>Clostridium perfringens</i></p> <p><u>Gram(-) anaerobes:</u>            *<i>Bacteroides distasonis</i>            *<i>Prevotella melaninogenica</i></p>

Cost comparison of Antibiotics Attachment # 2

Drug	Tygacil	Zosyn	Primaxin	Merrem	Vancocin	Zyvox	Cubicin
Dose	50mg q12h	3.375g q6h	0.5 gm q6h	1g q8h	1g q12h	600mg q12h	500mg q24h
Cost per Day	\$87.90	\$55.04	\$89.81	\$91.53	\$11.62	\$132.84	\$138.51

Diagn Microbiol Infect Dis. 2005 Jul;52(3):163-164.

**Antimicrobial activity and pharmacokinetics/pharmacodynamics of the novel glycylicycline, tigecycline.**

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Int J Infect Dis. 2005 Aug 11; [Epub ahead of print]

**Efficacy and safety of tigecycline monotherapy compared with vancomycin plus aztreonam in patients with complicated skin and skin structure infections: Results from a phase 3, randomized, double-blind trial.**

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**OBJECTIVES::** To compare the effect of tigecycline monotherapy, a first-in-class, expanded broad spectrum glycylicycline, with the combination of vancomycin and aztreonam (V+A) in the treatment of complicated skin and skin structure infections (cSSSI). **METHODS::** A phase 3, double-blind study conducted in 8 countries enrolled adults with cSSSI who required intravenous (IV) antibiotic therapy for  $\geq 5$  days. Patients were randomly assigned (1:1) to receive either tigecycline or V+A for up to 14 days. Primary endpoint was the clinical cure rate at the test-of-cure visit. Secondary endpoints included microbiologic efficacy and in vitro susceptibility to tigecycline of bacteria that cause cSSSI. Safety was assessed by physical examination, laboratory analyses, and adverse event reporting. **RESULTS::** A total of 596 patients were screened for enrollment, 573 were analyzed for safety, 537 were included in the clinical modified intent-to-treat (c-mITT) population, 397 were clinically evaluable (CE), and 228 were microbiologically evaluable (ME). At test-of-cure, cure rates were similar between tigecycline and V+A groups in the CE population (82.9% versus 82.3%, respectively) and in the c-mITT population (75.5% versus 76.9%, respectively). Microbiologic eradication rates (subject level) at test-of-cure in the ME population were also similar between tigecycline and V+A. Frequency of adverse events was similar between groups, although patients receiving tigecycline had higher incidence of nausea, vomiting, dyspepsia, and anorexia, while increased ALT/SGPT, pruritis, and rash occurred significantly more often in V+A-treated patients. **CONCLUSIONS::** This study demonstrates that the efficacy of tigecycline monotherapy for the treatment of patients with cSSSI is statistically noninferior to the combination of V+A.

Clin Infect Dis. 2005 Sep 1;41 Suppl 5:S354-67.

**The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data.**

[Babinchak T](#), [Ellis-Grosse E](#), [Dartois N](#), [Rose GM](#), [Loh E](#); [Tigecycline 301 Study Group](#); [Tigecycline 306 Study Group](#).

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This pooled analysis includes 2 phase 3, double-blind trials designed to evaluate the safety and efficacy of tigecycline, versus that of imipenem-cilastatin, in 1642 adults with complicated intra-abdominal infections. Patients were randomized to receive either tigecycline (initial dose of 100 mg, followed by 50 mg intravenously every 12 h) or imipenem-cilastatin (500/500 mg intravenously every 6 h) for 5-14 days. The primary end point was the clinical response at the test-of-cure visit (12-42 days after therapy) in the co-primary end point microbiologically evaluable and microbiological modified intent-to-treat populations. For the microbiologically evaluable group, clinical cure rates were 86.1% (441/512) for tigecycline, versus 86.2% (442/513) for imipenem-cilastatin (95% confidence interval for the difference, -4.5% to 4.4%;  $P < .0001$  for noninferiority). Clinical cure rates in the microbiological modified intent-to-treat population were 80.2% (506/631) for tigecycline, versus 81.5% (514/631) for imipenem-cilastatin (95% confidence interval for the difference, -5.8% to 3.2%;  $P < .0001$  for noninferiority). Nausea (24.4% tigecycline, 19.0% imipenem-cilastatin [ $P = .01$ ]), vomiting (19.2% tigecycline, 14.3% imipenem-cilastatin [ $P = .008$ ]), and diarrhea (13.8% tigecycline, 13.2% imipenem-cilastatin [ $P = .719$ ]) were the most frequently reported adverse events. This pooled analysis demonstrates that tigecycline was efficacious and well tolerated in the treatment of patients with complicated intra-abdominal infections.

Clin Infect Dis. 2005 Sep 1;41 Suppl 5:S341-53.

**The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam.**

[Ellis-Grosse EJ](#), [Babinchak T](#), [Dartois N](#), [Rose G](#), [Loh E](#); [Tigecycline 300 cSSSI Study Group](#); [Tigecycline 305 cSSSI Study Group](#).

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Two phase 3, double-blind studies in hospitalized adults with complicated skin and skin-structure infections (cSSSI) determined the safety and efficacy of tigecycline versus that of vancomycin-aztreonam. Patients received tigecycline (100 mg, followed by 50 mg intravenously twice daily) or vancomycin (1 g intravenously twice daily) plus aztreonam (2 g intravenously twice daily) for up to 14 days. Populations were as follows: 1116 patients (566 treated with tigecycline, and 550 treated with vancomycin-aztreonam) constituted the modified intent-to-treat (mITT) population, 1057 patients (538 treated with tigecycline, and 519 treated with vancomycin-aztreonam) constituted the clinical mITT (c-mITT) population, and 833 patients (422 treated with tigecycline, and 411 treated with vancomycin-aztreonam) constituted the clinically evaluable population. Clinical responses to tigecycline and vancomycin-aztreonam at test-of-cure were similar: c-mITT, 79.7% (95% confidence interval [CI], 76.1%-83.1%) versus 81.9% (95% CI, 78.3%-85.1%) (P = .4183); and clinically evaluable, 86.5% (95% CI, 82.9%-89.6%) versus 88.6% (95% CI, 85.1%-91.5%) (P = .4233). Adverse events were similar, with increased nausea and vomiting in the tigecycline group and increased rash and elevated hepatic aminotransferase levels in the vancomycin-aztreonam group. Tigecycline monotherapy is as safe and efficacious as the vancomycin-aztreonam combination in treating patients with cSSSI.

Clin Infect Dis. 2005 Sep 1;41 Suppl 5:S315-32.

**In vitro activity of tigecycline against isolates from patients enrolled in phase 3 clinical trials of treatment for complicated skin and skin-structure infections and complicated intra-abdominal infections.**

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The in vitro activity of tigecycline was evaluated against 4913 baseline pathogens isolated from 1986 patients enrolled in 4 pivotal phase 3 clinical trials. The trials, which were conducted in 38 countries worldwide, involved patients with complicated skin and skin-structure infections or complicated intra-abdominal infections. Tigecycline was active against the most prevalent pathogens for each infection type, including gram-positive and gram-negative strains of both aerobic and anaerobic bacteria (MICs, < or =2 microg/mL for most pathogens). The spectrum of activity of tigecycline included important pathogens, such as *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*. A few genera, such as *Pseudomonas aeruginosa* and members of the tribe Proteaceae, were generally less susceptible to tigecycline than were other gram-negative pathogens. The susceptibility of the pathogens to tigecycline was similar for isolates obtained from patients enrolled in the studies of complicated skin and skin-structure infection or of complicated intra-abdominal infection. For most pathogens, the susceptibility to tigecycline was similar across all geographic regions. The excellent expanded broad-spectrum activity of tigecycline demonstrated in vitro against clinical isolates confirmed its potential utility for pathogens associated with complicated skin and skin-structure infections or complicated intra-abdominal infections.

J Antimicrob Chemother. 2005 Jul 15; [Epub ahead of print]

**Penetration, efflux and intracellular activity of tigecycline in human polymorphonuclear neutrophils (PMNs).**

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**OBJECTIVES:** To evaluate the penetration, efflux and intracellular activity of tigecycline in human polymorphonuclear neutrophils (PMNs). **METHODS:** PMNs were isolated from fresh whole blood and tested for viability and purity prior to use. Tigecycline drug uptake was evaluated by incubating  $5 \times 10^6$  cells/mL at 37 degrees C up to 3 h at tigecycline concentrations of 1, 2, 5 and 10 mg/L. Drug efflux from PMNs was determined following a 2 h incubation with tigecycline at 10 mg/L. Its intracellular activity against *Staphylococcus aureus* was evaluated following tigecycline extracellular exposures of 1 mg/L. **RESULTS:** Tigecycline uptake was rapid and achieved high concentrations within PMNs with maximal penetration noted at 1 h of incubation. At 1 h, dose-dependent intracellular concentrations ranged from 15.83 +/- 11.09 mg/L to 264 +/- 54.60 mg/L at tigecycline 1 and 10 mg/L, respectively. At these exposures, intracellular drug concentrations were approximately 20 and 30 times higher at 1 h than extracellular concentrations. By 3 h, tigecycline displayed sustained high intracellular exposures. Tigecycline cell efflux followed first order kinetics with a half-life of 1.39 h. Tigecycline was bacteriostatic against intracellular *S. aureus*. **CONCLUSIONS:** Tigecycline rapidly achieved high intracellular concentrations

in PMNs and exhibited static activity against *S. aureus* supporting its potential clinical utilization.

J Antimicrob Chemother. 2005 Aug;56(2):349-52. Epub 2005 Jun 10.

**In vitro activity of tigecycline against Bacteroides species.**

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**OBJECTIVES:** To ascertain the current susceptibility patterns of members of the *Bacteroides fragilis* group in our hospital and to assess the in vitro activity of tigecycline against these organisms. **METHODS:** A total of 400 non-duplicate clinical isolates of the *B. fragilis* group collected from 2000 to 2002 were studied. Susceptibility testing was performed according to the reference agar dilution method described by the NCCLS. The following antimicrobials were tested: tigecycline, clindamycin, metronidazole, chloramphenicol, cefoxitin, imipenem, amoxicillin-clavulanate and piperacillin-tazobactam. **RESULTS:** All strains were susceptible to metronidazole and chloramphenicol. For clindamycin and cefoxitin, the overall susceptibility rates were 59.5% and 83%, respectively. Imipenem and piperacillin-tazobactam were the most active beta-lactam agents tested. Tigecycline inhibited 89.8% of the strains at a concentration of 8 mg/L with an MIC range of  $\leq 0.01$  to  $>16$  mg/L. By comparing the MIC<sub>50</sub> and MIC<sub>90</sub> values of tigecycline among the various species of the group, *B. fragilis*, *Bacteroides thetaiotaomicron* and *Bacteroides vulgatus* were the most susceptible (MIC<sub>50</sub>/MIC<sub>90</sub>s of 0.5-1/8 mg/L). **CONCLUSIONS:** Tigecycline exhibited activity against most isolates of the *B. fragilis* group tested. These results indicate that tigecycline may be useful in the treatment and prophylaxis of infections involving these organisms.

Int J Antimicrob Agents. 2005 Jun;25(6):523-9.

**Steady-state serum and intrapulmonary pharmacokinetics and pharmacodynamics of tigecycline.**

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The steady-state serum and intrapulmonary pharmacokinetic and pharmacodynamic parameters of tigecycline were determined after intravenous administration in 30 subjects. Tigecycline was administered as a 100mg loading dose followed by six 50mg doses given every 12h and was measured using HPLC/mass spectrometry. Ratios of tigecycline maximum serum concentration and area under the serum concentration-time curve to 90%-minimum inhibitory concentrations (C(max)/MIC(90); AUC/MIC(90)), and percentage time above MIC(90) were calculated for common respiratory pathogens (*Streptococcus pneumoniae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae*). The C(max) (mean $\pm$ S.D.), AUC and half-life for serum were 0.72 $\pm$ 0.24 microg/mL, 1.73 $\pm$ 0.64 microg\*h/mL and 15.0 $\pm$ 1.10h; for lung epithelial lining fluid (ELF) the values were 0.37 microg/mL, 2.28 microg\*h/mL and 39.1h; and for alveolar cells (AC) were 15.2 microg/mL, 134 microg\*h/mL and 23.7h. Tigecycline was concentrated in AC: C(max)/MIC(90) ratios ranged from 30.4 (*H. influenzae*) to 507 (*S. pneumoniae*); AUC/MIC(90) ratios ranged from 268 (*H. influenzae*) to 4467 (*S. pneumoniae*); and percentage dose interval above MIC(90) was 100% for the five respiratory pathogens. The C(max)/MIC(90), AUC/MIC(90) ratios, T<sub>></sub>MIC(90) and extended serum and intrapulmonary half-lives following the regimen used in this study are favourable for the treatment of tigecycline-susceptible pulmonary infections.

Antimicrob Agents Chemother. 2005 Apr;49(4):1636-8.

**Presence of tetracycline resistance determinants and susceptibility to tigecycline and minocycline.**

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No relation between the presence of tetracycline resistance determinants tet(A) to tet(E) and the MICs of tigecycline was observed for Enterobacteriaceae, although tetracycline-susceptible isolates were more susceptible overall to tigecycline, whereas the presence of tet(M) in *Staphylococcus aureus* was associated with higher MICs of minocycline.

Antimicrob Agents Chemother. 2005 Apr;49(4):1629-32

**Pharmacokinetic profile of tigecycline in serum and skin blister fluid of healthy subjects after multiple intravenous administrations.**

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The pharmacokinetics of tigecycline, when given as a 100-mg loading dose followed by 50 mg every 12 h, were determined in serum and blister fluid. The peak tigecycline concentration and half-life in serum were greater than those in blister fluid. Tigecycline penetrates into blister fluid well, with a mean penetration rate of 74%.

Int J Antimicrob Agents. 2005 Mar;25(3):185-92.

**Tigecycline: clinical evidence and formulary positioning.**

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Tigecycline, is a novel broad-spectrum glycylycylcline antibiotic, which has activity against a broad range of Gram-positive, Gram-negative, atypical, anaerobic and antibiotic-resistant bacteria. This includes activity against MRSA, VRE and penicillin resistant *Streptococcus pneumoniae*. Whilst exhibiting antibacterial activities typical of earlier tetracyclines, it has more potent activity against tetracycline-resistant organisms. Although a bacteriostatic compound in vitro, its effectiveness in clinical trials suggests that traditional laboratory thinking about using bacteriostatic drugs in serious infections needs to be revised. Unlike existing tetracyclines, tigecycline is only available as an intravenous preparation, is administered twice daily although its long half life and post-antibiotic effect may make once daily dosing possible, appears to have good tissue penetration (e.g. skin) and requires no adjustment in the presence of renal or hepatic diseases. It is efficacious in complicated skin and soft tissue infections and in intra-abdominal infections. In three trials, it was well tolerated despite increased frequency of nausea and vomiting. In the light of these early clinical data and the likelihood that this agent will become available for clinical use within the next 12-24 months, this review aims to summarise the key clinical data and potential formulary considerations for the future use of this agent, subject to further clinical trials and publication of clinical human data.

Clin Ther. 2004 May;26(5):704-14.

**Results of a multicenter, randomized, open-label efficacy and safety study of two doses of tigecycline for complicated skin and skin-structure infections in hospitalized patients.**

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**BACKGROUND:** Tigecycline is a broad-spectrum glycylycylcline antibiotic being investigated for the treatment of serious infections in hospitalized patients. Tigecycline has been shown to be efficacious against serious infections in animals, and preliminary studies in healthy adults have shown that tigecycline has an acceptable tolerability profile. **OBJECTIVE:** This study compared the clinical and microbiological efficacy, pharmacokinetic properties, and tolerability of 2 doses of tigecycline in hospitalized patients with a complicated skin and skin-structure infection (cSSSI). **METHODS:** This Phase II, randomized, open-label study was conducted between September 1999 and March 2001 at 14 investigative centers across the United States. Patients were randomized to receive tigecycline 25 or 50 mg IV q12h for 7 to 14 days. The primary efficacy end point was the clinically observed cure rate among clinically evaluable (CE) patients at the test-of-cure visit. Secondary end points were the clinical cure rate at the end of treatment and bacteriologic response in microbiologically evaluable (ME) patients. Also, in vitro tests of susceptibility to tigecycline were performed for selected pathogens known to cause skin infections, including methicillin-resistant and methicillin-susceptible *Streptococcus pyogenes*, *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis*, and *Enterococcus faecium*. Tolerability assessments also were conducted. **RESULTS:** A total of 160 patients received  $\geq 1$  dose of tigecycline; 109 patients were CE, and 91 were ME. The majority of patients (74%) were men, and the mean (SD) age was 49.0 (14.8) years. At the test-of-cure visit, the clinical cure rate in the 25-mg group was 67% (95% CI, 53.3%-79.3%) and in the 50-mg group was 74% (95% CI, 60.3%-85.0%). In the 25-mg group, 56% of the patients had eradication (95% CI, 40.0%-70.4%) of the pathogens compared with 69% (95% CI, 54.2%-82.3%) in the 50-mg group. Values for the minimum concentration of tigecycline that is inhibitory for 90% of all isolates ranged from 0.06 to 0.50 microg/mL for the selected pathogens. Both tigecycline doses were generally well tolerated. Nausea and vomiting were the most common adverse events. **CONCLUSIONS:** In this study, tigecycline appeared efficacious and showed a favorable pharmacokinetic profile and an acceptable safety profile in the treatment of hospitalized patients with cSSSI. In patients who received 50-mg doses of tigecycline q12h, the clinical cure rates and microbial eradication rates were 74% and 70%, respectively, and were 67% and 56% in patients who received 25-mg doses.

Antimicrob Agents Chemother. 2004 Jun;48(6):2179-84.

**Effects of efflux transporter genes on susceptibility of Escherichia coli to tigecycline (GAR-936).**

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The activity of tigecycline, 9-(t-butylglycylamido)-minocycline, against Escherichia coli KAM3 (acrB) strains harboring plasmids encoding various tetracycline-specific efflux transporter genes, tet(B), tet(C), and tet(K), and multidrug transporter genes, acrAB, acrEF, and bcr, was examined. Tigecycline showed potent activity against all three Tet-expressing, tetracycline-resistant strains, with the MICs for the strains being equal to that for the host strain. In the Tet(B)-containing vesicle study, tigecycline did not significantly inhibit tetracycline efflux-coupled proton translocation and at 10 microM did not cause proton translocation. This suggests that tigecycline is not recognized by the Tet efflux transporter at a low concentration; therefore, it exhibits significant antibacterial activity. These properties can explain its potent activity against bacteria with a Tet efflux resistance determinant. Tigecycline induced the Tet(B) protein approximately four times more efficiently than tetracycline, as determined by Western blotting, indicating that it is at least recognized by a TetR repressor. The MICs for multidrug efflux proteins AcrAB and AcrEF were increased fourfold. Tigecycline inhibited active ethidium bromide efflux from intact E. coli cells overproducing AcrAB. Therefore, tigecycline is a possible substrate of AcrAB and its close homolog, AcrEF, which are resistance-modulation-division-type multicomponent efflux transporters.

Drugs. 2004;64(1):63-88.

**The glycylicyclines: a comparative review with the tetracyclines.**

[Zhanel GG](#), [Homenuik K](#), [Nichol K](#), [Noreddin A](#), [Vercaigne L](#), [Embil J](#), [Gin A](#), [Karlowsky JA](#), [Hoban DJ](#).

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The tetracycline class of antimicrobials exhibit a broad-spectrum of activity against numerous pathogens, including Gram-positive and Gram-negative bacteria, as well as atypical organisms. These compounds are bacteriostatic, and act by binding to the bacterial 30S ribosomal subunit and inhibiting protein synthesis. The tetracyclines have been used successfully for the treatment of a variety of infectious diseases including community-acquired respiratory tract infections and sexually transmitted diseases, as well in the management of acne. The use of tetracyclines for treating bacterial infections has been limited in recent years because of the emergence of resistant organisms with efflux and ribosomal protection mechanisms of resistance. Research to find tetracycline analogues that circumvented these resistance mechanisms has led to the development of the glycylicyclines. The most developed glycylicycline is the 9-tert-butyl-glycylamido derivative of minocycline, otherwise known as tigecycline (GAR-936). The glycylicyclines exhibit antibacterial activities typical of earlier tetracyclines, but with more potent activity against tetracycline-resistant organisms with efflux and ribosomal protection mechanisms of resistance. The glycylicyclines are active against other resistant pathogens including methicillin-resistant staphylococci, penicillin-resistant Streptococcus pneumoniae, and vancomycin-resistant enterococci. Tigecycline is only available in an injectable formulation for clinical use unlike currently marketed tetracyclines that are available in oral dosage forms. Tigecycline has a significantly larger volume of distribution (> 10 L/kg) than the other tetracyclines (range of 0.14 to 1.6 L/kg). Protein binding is approximately 68%. Presently no human data are available describing the tissue penetration of tigecycline, although studies in rats using radiolabelled tigecycline demonstrated good penetration into tissues. Tigecycline has a half-life of 36 hours in humans, less than 15% of tigecycline is excreted unchanged in the urine. On the basis of available data, it does not appear that the pharmacokinetics of tigecycline are markedly influenced by patient gender or age. The pharmacodynamic parameter that best correlates with bacteriological eradication is time above minimum inhibitory concentration. Several animal studies have been published describing the efficacy of tigecycline. Human phase 1 and 2 clinical trials have been completed for tigecycline. Phase 2 studies have been conducted in patients with complicated skin and skin structure infections, and in patients with complicated intra-abdominal infections have been published as abstracts. Both studies concluded that tigecycline was efficacious and well tolerated. Few human data are available regarding the adverse effects or drug interactions resulting from tigecycline therapy; however, preliminary data report that tigecycline can be safely used, is well tolerated and that the adverse effects experienced were typical of the tetracyclines (i.e. nausea, vomiting and headache). Tigecycline appears to be a promising new antibacterial based on in vitro and pharmacokinetic/pharmacodynamic activity; however more clinical data are needed to fully evaluate its potential.

J Antimicrob Chemother. 2003 Jun;51 Suppl 3:iii23-30.

**Therapeutic and preventative options for the management of vancomycin-resistant enterococcal infections.**

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Enterococci are naturally resistant to a wide range of antimicrobial agents. In addition, some enterococci, known as vancomycin-resistant enterococci (VRE) have become resistant to glycopeptide antibiotics. The therapeutic options for VRE infections are therefore very limited. New antimicrobials have been developed that are active against VRE, such as linezolid and quinupristin/dalfopristin. Others, e.g. tigecycline, daptomycin and oritavancin, are in the later stages of development. However, resistance has already been detected to some of these agents. Some success has been enjoyed through the application of older antibiotics against VRE. The lack of therapeutic options has led to the consideration of measures to prevent infection with VRE. In addition to standard infection control procedures such as isolation and hand washing, decolonization of the gastrointestinal tract has been investigated as a method for the prevention of VRE infection in vulnerable patient groups. Several decolonization regimens have been investigated. These include the use of ramoplanin, a new glycolipopeptide antibiotic that has features that particularly suit it for decolonization. Ramoplanin is not absorbed from the gastrointestinal tract, has potent bactericidal activity against Gram-positive organisms and limited side effects. These features and current clinical evidence suggest that ramoplanin may have a role in future gastrointestinal decolonization regimens.

Antimicrob Agents Chemother. 2003 Mar;47(3):972-8.

**Efflux-mediated resistance to tigecycline (GAR-936) in *Pseudomonas aeruginosa* PAO1.**

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*Pseudomonas aeruginosa* strains are less susceptible to tigecycline (previously GAR-936; MIC, 8 micro g/ml) than many other bacteria (P. J. Petersen, N. V. Jacobus, W. J. Weiss, P. E. Sum, and R. T. Testa, Antimicrob. Agents Chemother. 43:738-744, 1999). To elucidate the mechanism of resistance to tigecycline, *P. aeruginosa* PAO1 strains defective in the MexAB-OprM and/or MexXY (OprM) efflux pumps were tested for susceptibility to tigecycline. Increased susceptibility to tigecycline (MIC, 0.5 to 1 micro g/ml) was specifically associated with loss of MexXY. Transcription of *mexX* and *mexY* was also responsive to exposure of cells to tigecycline. To test for the emergence of compensatory efflux pumps in the absence of MexXY-OprM, mutants lacking MexXY-OprM were plated on medium containing tigecycline at 4 or 6 micro g/ml. Resistant mutants were readily recovered, and these also had decreased susceptibility to several other antibiotics, suggesting efflux pump recruitment. One representative carbenicillin-resistant strain overexpressed OprM, the outer membrane channel component of the MexAB-OprM efflux pump. The *mexAB-oprM* repressor gene, *mexR*, from this strain contained a 15-bp in-frame deletion. Two representative chloramphenicol-resistant strains showed expression of an outer membrane protein slightly larger than OprM. The *mexCD-OprJ* repressor gene, *nfxB*, from these mutants contained a 327-bp in-frame deletion and an IS element insertion, respectively. Together, these data indicated drug efflux mediated by MexCD-OprJ. The MICs of the narrower-spectrum semisynthetic tetracyclines doxycycline and minocycline increased more substantially than did those of tigecycline and other glycylicyclines against the MexAB-OprM- and MexCD-OprJ-overexpressing mutant strains. This suggests that glycylicyclines, although they are subject to efflux from *P. aeruginosa*, are generally inferior substrates for *P. aeruginosa* efflux pumps than are narrower-spectrum tetracyclines.

Antimicrob Agents Chemother. 2003 Feb;47(2):665-9

**AcrAB multidrug efflux pump is associated with reduced levels of susceptibility to tigecycline (GAR-936) in *Proteus mirabilis*.**

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Tigecycline has good broad-spectrum activity against many gram-positive and gram-negative pathogens with the notable exception of the PROTEAE: A study was performed to identify the mechanism responsible for the reduced susceptibility to tigecycline in *Proteus mirabilis*. Two independent transposon insertion mutants of *P. mirabilis* that had 16-fold-increased susceptibility to tigecycline were mapped to the *acrB* gene homolog of the *Escherichia coli* AcrRAB efflux system. Wild-type levels of decreased susceptibility to tigecycline were restored to the insertion mutants by complementation with a clone containing a PCR-derived fragment from the parental wild-type *acrRAB* efflux gene cluster. The AcrAB transport system appears to be associated with the intrinsic reduced susceptibility to tigecycline in *P. mirabilis*.

Antimicrob Agents Chemother. 2003 Jan;47(1):216-22.

**Activity and diffusion of tigecycline (GAR-936) in experimental enterococcal endocarditis.**

[Lefort A](#), [Lafaurie M](#), [Massias L](#), [Petegnief Y](#), [Saleh-Mghir A](#), [Muller-Serievs C](#), [Le Guludec D](#), [Fantin B](#).  
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The activity of tigecycline (GAR-936), a novel glycylicycline, was investigated in vitro and in experimental endocarditis due to the susceptible *Enterococcus faecalis* JH2-2 strain, its VanA type transconjugant BM4316, and a clinical VanA type strain, *E. faecium* HB217 resistant to tetracycline. MICs of GAR-936 were 0.06 micro g/ml for the three strains. In vitro pharmacodynamic studies demonstrated a bacteriostatic effect of GAR-936 that was not enhanced by increasing concentrations to more than 1 micro g/ml and a postantibiotic effect ranging from 1 to 4.5 h for concentrations of 1- to 20-fold the MIC. Intravenous injection of [(14)C]GAR-936 to five rabbits with enterococcal endocarditis sacrificed 30 min, 4 h, or 12 h after the end of the infusion evidenced a lower clearance of GAR-936 from aortic vegetations than from serum and a homogeneous diffusion of GAR-936 into the vegetations. In rabbits with endocarditis, GAR-936 (14 mg/kg of body weight twice a day [b.i.d.]) given intravenously for 5 days was bacteriostatic against both strains of *E. faecalis*. Against *E. faecium* HB217, bacterial counts in vegetations significantly decreased during therapy ( $P < 0.01$ ), and the effect was similar with GAR-936 at 14 mg/kg b.i.d., 14 mg/kg once a day (o.d.), and 7 mg/kg o.d., which provided concentrations in serum constantly above the MIC. Mean serum elimination half-life ranged from 3.3 to 3.6 h. No GAR-936-resistant mutants were selected in vivo with any regimen. We concluded that the combination of prolonged half-life, significant postantibiotic effect, and good and homogeneous diffusion into the vegetations may account for the in vivo activity of GAR-936 against enterococci susceptible or resistant to glycopeptides and tetracyclines, even when using a o.d. regimen in rabbits.

Pharmacotherapy. 2002 Dec;22(12):1517-23.

**Antimicrobial activity of tigecycline (GAR-936) against *Enterococcus faecium* and *Staphylococcus aureus* used alone and in combination.**

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**STUDY OBJECTIVE:** To evaluate the antimicrobial properties of tigecycline, both alone and in combination with other antibiotics, against multidrug-resistant strains of *Enterococcus faecium* and *Staphylococcus aureus*. **DESIGN:** In vitro study. **SETTING:** University laboratory. **MEASUREMENTS AND MAIN RESULTS:** Tigecycline, both alone and in combination with other antimicrobial agents, was evaluated against two strains of vancomycin-resistant *E. faecium* (VREF), three glycopeptide-intermediately resistant *S. aureus* strains, and one methicillin-resistant *S. aureus* strain. Tigecycline's activity was compared with that of vancomycin, gentamicin, rifampin, and doxycycline, using time-kill studies and analysis of minimum inhibitory concentrations and minimum bactericidal concentrations. Tigecycline also was evaluated in combination with vancomycin, gentamicin, rifampin, and doxycycline in time-kill studies. The number of log<sub>10</sub> colony-forming units/ml at 24 hours was compared among treatment groups and growth control by analysis of variance. All isolates were susceptible to tigecycline, regardless of their susceptibilities to vancomycin or doxycycline. In time-kill studies, tigecycline significantly inhibited the bacterial inoculum of all isolates ( $p < 0.05$ ). Although none of the tigecycline combinations studied had enhanced killing activity against VREF, when gentamicin was combined with tigecycline, improved effects were found against both strains. Against three of the *S. aureus* strains tested, the combination of gentamicin and tigecycline demonstrated enhanced or improved activity independently of each strain's susceptibility to gentamicin. **CONCLUSION:** The multidrug-resistant, gram-positive bacteria tested, including doxycycline-resistant isolates, were susceptible to tigecycline. The combination of tigecycline and gentamicin may have improved or enhanced activity against strains of vancomycin-resistant enterococci and *S. aureus*.

Drug Resist Updat. 2002 Jul-Aug;5(3-4):119-25.

**New developments in tetracycline antibiotics: glycylicyclines and tetracycline efflux pump inhibitors.**

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The tetracyclines, discovered in the 1940s, are a well-established class of antibiotics that still have a role in treating microbial infections in man. However, the widespread emergence of bacterial resistance due to efflux and ribosomal protection mechanisms has severely limited their effectiveness. A new generation of tetracyclines, the glycylicyclines, has been developed to overcome resistance to earlier tetracyclines. One of the new glycylicyclines, 9-t-butylglyclamido-minocycline (GAR-936, tigecycline) is currently undergoing clinical trials. This review considers the current status of glycylicyclines and the possibility that resistance to these agents might arise in the future. Other approaches are also being taken to address the emergence of resistance to tetracyclines. Recently, a number of tetracycline efflux pump inhibitors have been discovered that might be used in combination with earlier tetracyclines to restore their activity against resistant organisms. However, the development of tetracycline efflux pump inhibitors is complicated by the occurrence of several efflux pump sub-families and by the presence of both efflux and ribosomal protection mechanisms in the same organism, especially in naturally occurring, Gram-positive clinical isolates.

**In vitro and in vivo activities of tigecycline (GAR-936), daptomycin, and comparative antimicrobial agents against glycopeptide-intermediate Staphylococcus aureus and other resistant gram-positive pathogens.**

Antimicrob Agents Chemother. 2002 Aug;46(8):2595-601.

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Tigecycline (GAR-936) and daptomycin are potent antibacterial compounds in advanced stages of clinical trials. These novel agents target multiply resistant pathogenic bacteria. Daptomycin is principally active against gram-positive bacteria, while tigecycline has broad-spectrum activity. When tested by the standard protocols of the National Committee for Clinical Laboratory Standards in Mueller-Hinton broth II, tigecycline was more active than daptomycin (MICs at which 90% of isolates tested are inhibited, 0.12 to 1 and 0.5 to 16 microg/ml, respectively) against staphylococcal, enterococcal, and streptococcal pathogens. Daptomycin demonstrated a stepwise increase in activity corresponding to an increase in the supplemental concentration of calcium. When tested in base Mueller-Hinton broth supplemented with 50 mg of calcium per liter, daptomycin demonstrated improved activity (MIC(90)s, 0.015 to 4 microg/ml). The activity of daptomycin, however, equaled that of tigecycline against the glycopeptide-intermediate Staphylococcus aureus (GISA) strains only when the test medium was supplemented with excess calcium (75 mg/liter). Tigecycline and daptomycin demonstrated in vivo efficacies against GISA, methicillin-resistant S. aureus, and methicillin-susceptible S. aureus strains in an intraperitoneal systemic murine infection model. These data suggest that tigecycline and daptomycin may offer therapeutic options against clinically relevant resistant pathogens for which current alternatives for treatment are limited.

Antimicrob Agents Chemother. 2000 Apr;44(4):943-9.

**In vivo pharmacodynamic activities of two glycylyclines (GAR-936 and WAY 152,288) against various gram-positive and gram-negative bacteria.**

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The in vivo pharmacodynamic activities of two glycylyclines (GAR-936 and WAY 152,288) were assessed in an experimental murine thigh infection model in neutropenic mice. Mice were infected with one of several strains of Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli, or Klebsiella pneumoniae. Most infections were treated with a twice-daily dosing schedule, with administration of 0.75 to 192 mg of GAR-936 or WAY 152,288 per kg of body weight. A maximum-effect dose-response model was used to calculate the dose that produced a net bacteriostatic effect over 24 h of therapy. This dose was called the bacteriostatic dose. More extensive dosing studies were performed with S. pneumoniae 1199, E. coli ATCC 25922, and K. pneumoniae ATCC 43816, with doses being given as one, two, four, or eight equal doses over a period of 24 h. The dosing schedules were designed in order to minimize the interrelationship between the various pharmacokinetic and pharmacodynamic parameters studied. These parameters were time above 0.03 to 32 times the MIC, area under the concentration-time curve (AUC), and maximum concentration of drug in serum (C(max)). The bacteriostatic dose remained essentially the same, irrespective of the dosing frequency, for S. pneumoniae 1199 (0.3 to 0.9 mg/kg/day). For E. coli ATCC 25922 and K. pneumoniae ATCC 43816, however, more frequent dosing led to lower bacteriostatic doses. Pharmacokinetic studies demonstrated dose-dependent elimination half-lives of 1.05 to 2.34 and 1.65 to 3.36 h and serum protein bindings of 59 and 71% for GAR-936 and WAY 152,288, respectively. GAR-936 and WAY 152,288 were similarly effective against the microorganisms studied, with small differences in maximum effect and 50% effective dose. The glycylyclines were also similarly effective against tetracycline-sensitive and tetracycline-resistant bacteria. Time above a certain factor (range, 0.5 to 4 times) of the MIC was a better predictor of in vivo efficacy than C(max) or AUC for most organism-drug combinations. The results demonstrate that in order to achieve 80% maximum efficacy, the concentration of unbound drug in serum should be maintained above the MIC for at least 50% of the time for GAR-936 and for at least 75% of the time for WAY 152,288. The results of these experiments will aid in the rational design of dose-finding studies for these glycylyclines in humans.

**In vitro activity of tigecycline against 3989 Gram-negative and Gram-positive clinical isolates from the United States Tigecycline Evaluation and Surveillance Trial (TEST Program; 2004).**

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The Tigecycline Evaluation and Surveillance Trial (TEST Program) determined the in vitro activity of tigecycline over a

large population of organisms from geographically diverse sites. Tigecycline was compared to amikacin, ampicillin, amoxicillin/clavulanic acid, imipenem, cefepime, ceftazidime, ceftriaxone, levofloxacin, minocycline, piperacillin/tazobactam, linezolid, penicillin, and vancomycin against 3989 commonly encountered clinical Gram-negative and Gram-positive pathogens collected from sites in the United States during 2004. The tigecycline activity was equivalent to imipenem against Enterobacteriaceae. Tigecycline inhibited extended-spectrum beta-lactamase and AmpC phenotypes at MIC(90) values (minimum inhibitory concentration) of  $\leq 2$   $\mu\text{g}/\text{mL}$ . In vitro results for tigecycline were similar to other broad-spectrum antimicrobial agents against nonfermenters with MIC(90) results of 2  $\mu\text{g}/\text{mL}$  against *Acinetobacter* spp. and  $>16$   $\mu\text{g}/\text{mL}$  against *Pseudomonas aeruginosa*. Tigecycline demonstrated potent activity against *Staphylococcus aureus* (MIC(90), 0.25  $\mu\text{g}/\text{mL}$ ) and enterococci (MIC(90), 0.12  $\mu\text{g}/\text{mL}$ ) regardless of methicillin or vancomycin susceptibility. Tigecycline MIC values were unaffected by penicillin nonsusceptibility and beta-lactamase production among fastidious respiratory pathogens (*Streptococcus pneumoniae* [MIC(90), 0.5  $\mu\text{g}/\text{mL}$ ] and *Haemophilus influenzae* [MIC(90), 0.25  $\mu\text{g}/\text{mL}$ ]). Tigecycline offers excellent activity against most of the commonly encountered nosocomial and community-acquired bacterial pathogens.

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**In vitro activity of tigecycline against Bacteroides species.**

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**OBJECTIVES:** To ascertain the current susceptibility patterns of members of the *Bacteroides fragilis* group in our hospital and to assess the in vitro activity of tigecycline against these organisms. **METHODS:** A total of 400 non-duplicate clinical isolates of the *B. fragilis* group collected from 2000 to 2002 were studied. Susceptibility testing was performed according to the reference agar dilution method described by the NCCLS. The following antimicrobials were tested: tigecycline, clindamycin, metronidazole, chloramphenicol, cefoxitin, imipenem, amoxicillin-clavulanate and piperacillin-tazobactam. **RESULTS:** All strains were susceptible to metronidazole and chloramphenicol. For clindamycin and cefoxitin, the overall susceptibility rates were 59.5% and 83%, respectively. Imipenem and piperacillin-tazobactam were the most active beta-lactam agents tested. Tigecycline inhibited 89.8% of the strains at a concentration of 8 mg/L with an MIC range of  $\leq 0.01$  to  $>16$  mg/L. By comparing the MIC<sub>50</sub> and MIC<sub>90</sub> values of tigecycline among the various species of the group, *B. fragilis*, *Bacteroides thetaiotaomicron* and *Bacteroides vulgatus* were the most susceptible (MIC<sub>50</sub>/MIC<sub>90</sub>s of 0.5-1/8 mg/L). **CONCLUSIONS:** Tigecycline exhibited activity against most isolates of the *B. fragilis* group tested. These results indicate that tigecycline may be useful in the treatment and prophylaxis of infections involving these organisms.

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**Presence of tetracycline resistance determinants and susceptibility to tigecycline and minocycline.**

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No relation between the presence of tetracycline resistance determinants tet(A) to tet(E) and the MICs of tigecycline was observed for Enterobacteriaceae, although tetracycline-susceptible isolates were more susceptible overall to tigecycline, whereas the presence of tet(M) in *Staphylococcus aureus* was associated with higher MICs of minocycline.