

# Potential role of tigecycline in the treatment of community-acquired bacterial pneumonia

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**Abstract:** Tigecycline is a member of the glycylcycline class of antimicrobials, which is structurally similar to the tetracycline class. It demonstrates potent in vitro activity against causative pathogens that are most frequently isolated in patients with community-acquired bacterial pneumonia (CABP), including (but not limited to) *Streptococcus pneumoniae* (both penicillin-sensitive and -resistant strains), *Haemophilus influenzae* and *Moraxella catarrhalis* (including  $\beta$ -lactamase-producing strains), *Klebsiella pneumoniae*, and ‘atypical organisms’ (namely *Chlamydomphila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*). Comparative randomized clinical trials to date performed in hospitalized patients receiving tigecycline 100 mg intravenous (IV)  $\times$  1 and then 50 mg IV twice daily thereafter have demonstrated efficacy and safety comparable to the comparator agent. Major adverse effects were primarily gastrointestinal in nature. Tigecycline represents a parenteral monotherapy option in hospitalized patients with CABP (especially in patients unable to receive respiratory fluoroquinolones). However, alternate and/or additional therapies should be considered in patients with more severe forms of CABP in light of recent data of increased mortality in patients receiving tigecycline for other types of severe infection.

**Keywords:** tigecycline, glycylcycline, community-acquired pneumonia

## Introduction

Community-acquired bacterial pneumonia (CABP) is a leading cause of morbidity and mortality in the United States.<sup>1–3</sup> An estimated 5–6 million cases per year result in hospitalization rates of ~20% and (among hospitalized patients) a mortality rate of 12%.<sup>1–3</sup> Organisms most commonly isolated in patients with CABP include *Streptococcus pneumoniae* (*S. pneumoniae*) (the most common), *Haemophilus influenzae*, *Moraxella catarrhalis* (*M. catarrhalis*), *Klebsiella pneumoniae* (*K. pneumoniae*), and ‘atypical organisms’ (namely *Chlamydomphila pneumoniae* (*C. pneumoniae*), *Mycoplasma pneumoniae* (*M. pneumoniae*), and *Legionella pneumophila* (*L. pneumophila*)).<sup>4–6</sup> Other Gram-negative bacilli and *Staphylococcus aureus* infrequently cause CABP, except in patients with severe disease and/or select underlying comorbidities.<sup>4,6</sup> Antimicrobial resistance among these organisms continues to be a growing concern. For example, rates of multidrug-resistant *S. pneumoniae* have been reported to be >30% worldwide, and the rates of  $\beta$ -lactamase-producing *H. influenzae* ranges from 12% to 27%.<sup>7–9</sup>

Current published guidelines for the empiric treatment of CABP in hospitalized patients not admitted to the intensive care unit (ICU) generally include

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either monotherapy with a respiratory fluoroquinolone (gemifloxacin, moxifloxacin, or levofloxacin) or a combination of a  $\beta$ -lactam (such as ceftriaxone or cefotaxime) in combination with a macrolide.<sup>4–6</sup> Alternative monotherapy options in such patients unable to receive a respiratory fluoroquinolone are lacking.

Tigecycline is a member of the glycylicycline class of antimicrobials, which is structurally similar to the tetracycline class.<sup>10</sup> It possesses favorable activity in vitro against a broad spectrum of aerobic Gram-positive, Gram-negative, anaerobic, and ‘atypical’ microorganisms, including those most frequently associated with CABP.<sup>10</sup> Previously published controlled clinical trials have established its effectiveness in the treatment of both complicated skin and skin structure infections (cSSSIs) and complicated intra-abdominal infections (cIAIs).<sup>11–14</sup> More recently, tigecycline has been studied for the treatment of CABP.<sup>15–17</sup> Our objective is to provide an overview of tigecycline’s activity, clinical efficacy, safety, and potential role in the treatment of CABP.

## Overview of tigecycline Pharmacology

Tigecycline acts by binding to the bacterial ribosomal subunit 30 S, resulting in inhibition of protein synthesis.<sup>11</sup> The resulting activity is time-dependent bacteriostatic against most organisms, although bactericidal activity has been observed with *S. pneumoniae* and *L. pneumophila* isolates.<sup>11</sup> The in vitro post-antibiotic effect of tigecycline against *Staphylococcus aureus*, *S. pneumoniae*, and Gram-negative organisms has ranged from >3 to 4.1, 8.9, and 2 to 5 h, respectively.<sup>11</sup>

Tigecycline’s in vitro activity appears unaffected by  $\beta$ -lactamase production, alterations in the target site, or target enzymes.<sup>11</sup> It also appears to be unaffected by most resistance mechanisms affecting the tetracyclines (such as ribosomal protection and select efflux pumps).<sup>18–25</sup> However, the most common mechanisms of resistance to tigecycline does appear to involve efflux pumps.<sup>11</sup> One particular type of efflux pump (known as the ‘resistance nodulation division’) has been noted in isolates of *Pseudomonas aeruginosa*, *Acinetobacter baumannii* (*A. baumannii*), *Serratia marcescens*, and *Enterobacter cloacae*.<sup>26–29</sup> Such efflux pumps, especially those found with *A. baumannii*, are associated with multidrug resistance.<sup>29</sup> Efflux pumps to tigecycline have also been observed in *Burkholderia* spp.<sup>30</sup> In *K. pneumoniae*, resistance to tigecycline expression of the mutant *ramR* gene resulted in alterations of the bacterial genome such as deletions, insertions, and point mutations that led to reduced susceptibility to tigecycline.<sup>31</sup>

## Microbiology

Tigecycline is a broad-spectrum antimicrobial agent that has in vitro activity against a variety of facultative aerobic Gram-positive, Gram-negative, and anaerobic bacteria (Table 1). According to the Clinical Laboratory Standards Institute, the minimum inhibitory concentration (MIC) considered susceptible to tigecycline is  $\leq 0.5$  mg/L for *Staphylococcus aureus* (including methicillin-resistant organisms),  $\leq 0.25$  mg/L for non-*Streptotoccus pneumoniae*, *Streptococcus* spp, and *Enterococcus faecalis* isolates.<sup>32,33</sup> For *S. pneumoniae*, the susceptibility MIC breakpoint is  $\leq 0.06$  mg/L.<sup>32,33</sup> The MIC considered susceptible for *Enterobacteraceae* and *H. influenzae* is  $\leq 2$  and  $\leq 0.25$  mg/L, respectively.<sup>32,33</sup> Anaerobes are deemed susceptible to tigecycline if the MIC is  $\leq 4$  mg/L.<sup>33,34</sup>

Tigecycline demonstrates potent activity in vitro data against most relevant Gram-positive organisms. Isolates of *Staphylococcus aureus* (n = 8765) displayed 99.4% susceptibility, with MIC<sub>90</sub> and ranges of 0.5 and  $\leq 0.016$ –1 mg/L, respectively.<sup>35</sup> In vitro susceptibilities of coagulase-negative *Staphylococcus* (n = 3570), *Enterococcus* spp (n = 3258),  $\beta$ -hemolytic *Streptotocci* (n = 769), and viridans group *Streptococci* (n = 378) were 97.5%, 92.7%, 99.7%, and 98.1%, respectively.<sup>35</sup> Of particular relevance to CABP, tigecycline displays potent in vitro activity against *S. pneumoniae*. A total of 92.7% of 605 isolates were susceptible to tigecycline, with MIC<sub>90</sub> and ranges of  $\leq 0.12$  and  $\leq 0.12$ –1 mg/L, respectively.<sup>35</sup> Tigecycline’s activity also includes penicillin-intermediate and penicillin-resistant *S. pneumoniae* organisms, with 90.2% (n = 1077) and 91.2% (n = 555) susceptibility, respectively, for North American isolates.<sup>36</sup> In addition, a tigecycline MIC of 0.12 mg/L was reported against a fluoroquinolone-resistant *S. pneumoniae*.<sup>37</sup> Although not common, community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) may cause CABP (most notably in patients with post-influenza bacterial pneumonia).<sup>38–40</sup> In such cases, mortality rates approach 30%.<sup>39</sup> CA-MRSA is often characterized by the presence of Pantone–Valentine leukocidin (PVL) cytotoxin, although its contribution to organism virulence is controversial.<sup>38</sup> Tigecycline exhibits favorable in vitro activity against CA-MRSA isolates (98.2% susceptibility rate) (n = 1989).<sup>41</sup> Tigecycline has also been reported to reduce the expression of the PVL gene, resulting in a 10-fold reduction in toxin production.<sup>41,42</sup>

Tigecycline also exhibits potent in vitro activity against many Gram-negative organisms, with notable exceptions including *Proteus* and *Pseudomonas* spp.<sup>35</sup> In one

**Table 1** In vitro activity of tigecycline against common CABP respiratory pathogens<sup>a</sup>

Bacteria	No. of isolates	MIC <sub>90</sub>	MIC range (in mg/L)	References
Typical pathogens				
<i>S. pneumoniae</i>	6456	0.06	≤0.008–1	95
<i>S. pneumoniae</i> , penicillin-intermediate susceptible	1077 <sup>b</sup>	0.06	NR	36
<i>S. pneumoniae</i> , penicillin resistant	891	0.06	≤0.008–0.25	95
<i>H. influenzae</i>	6070	0.5	≤0.008–2	95
<i>H. influenzae</i> , β-lactamase positive	1346	0.5	≤0.008–2	95
<i>Klebsiella pneumoniae</i>	10,644	2	≤0.008–16	95
<i>Moraxella catarrhalis</i>	2314	0.5	≤0.06–4	43
Atypical pathogens				
<i>Chlamydia pneumoniae</i>	10	0.125	0.125–0.25	51
<i>Legionella</i> spp <sup>c</sup>	100	8	0.5–8	52,53
<i>Mycoplasma pneumoniae</i>	30	0.25	0.06–0.25	50

**Notes:** <sup>a</sup>According to the Clinical Laboratory Standards Institute (CLSI), the MICs considered susceptible are as follows: *S. pneumoniae* ≤ 0.06 mg/L, *H. influenzae* ≤ 0.25 mg/L, and Enterobacteriaceae ≤ 2 mg/L; <sup>b</sup>Data from North American isolates; <sup>c</sup>Isolates (n = 50) of *Legionella pneumophila* are represented.

**Abbreviations:** CABP, community-acquired bacterial pneumonia; MIC, minimum inhibitory concentration; NR, not reported; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*.

intercontinental study involving over 26,000 isolates, many Gram-negative organisms displayed over 95% susceptibility to tigecycline.<sup>35</sup> This included *Escherichia coli* (*E. coli*) (n = 3217; 0.25 and 0.03–4 mg/L), *Enterobacter* spp (n = 801; 2 and 0.06–8 mg/L), and *Klebsiella* spp (n = 1503; 1 and 0.06–8 mg/L) for isolate numbers, MIC<sub>90</sub>, and range, respectively.<sup>35</sup> Other Gram-negative organisms that are often susceptible to tigecycline include *Serratia* spp (n = 294, 94.6% susceptible), *Stenotrophomonas maltophilia* (n = 203, 93.1% susceptible), and *Acinetobacter* spp (n = 326, 94.5% susceptible).<sup>35</sup> Of relevance to Gram-negative pathogens causing CABP, tigecycline displays potent in vitro activity against *H. influenzae* (including resistant isolates such as β-lactamase producers) and *M. catarrhalis*.<sup>36,43</sup> In one study of respiratory tract organisms, *M. catarrhalis* isolates (n = 2314) demonstrated tigecycline MIC<sub>90</sub> and ranges of 0.5 and ≤0.06–4 mg/L.<sup>43</sup> In another study, North American *H. influenzae* isolates had MIC<sub>90</sub> and ranges of 0.5 and ≤0.008–2 mg/L for β-lactamase-producing *H. influenzae* (n = 904) and 0.5 and 0.015–2 mg/L for β-lactamase negative, ampicillin-resistant *H. influenzae* isolates (n = 34), respectively.<sup>36</sup> While generally not of concern as etiologic agents in CABP, tigecycline displays favorable in vitro activity against extended-spectrum β-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae*.<sup>44,45</sup> For example, 90.7% of 150 isolates of ESBL-producing *K. pneumoniae* were considered susceptible to tigecycline.<sup>46</sup> A regional study examined ESBL-producing *E. coli* isolates and reported susceptibilities of 94.7% (n = 19), 89.2% (n = 65), and 95.5% (n = 22) in the East North Central, Middle Atlantic, and South Atlantic regions of the USA, respectively.<sup>47</sup>

The in vitro activity of tigecycline against anaerobes has been studied, and tigecycline displayed excellent potency against *Clostridium perfringens*, *Peptostreptococcus micros*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, and *Bacteroides uniformis*.<sup>48</sup> While not frequent causes of CABP, anaerobic pathogens may be of concern in cases of aspiration.<sup>49</sup>

Organisms such as *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila* have also been reported as etiologies to CABP.<sup>50–53</sup> The MIC<sub>90</sub> and ranges for tigecycline were 0.125 and 0.125–0.25 mg/L for *C. pneumoniae* (n = 10), 8 and 0.5–8 mg/L for *Legionella* spp (n = 100), and 0.25 and 0.06–0.25 mg/L for *M. pneumoniae*.<sup>50–53</sup>

## Pharmacokinetics/pharmacodynamics

Tigecycline exhibits linear kinetics, with a two-compartment model following intravenous (IV) administration.<sup>54,55</sup> Data from healthy volunteers (n = 103) receiving tigecycline 100 mg as a loading dose followed by 50 mg every 12 h demonstrated a maximum plasma concentration (C<sub>max</sub>) of 0.63 μg/mL after a 60-min infusion and a minimum plasma concentration (C<sub>min</sub>) of 0.13 μg/mL.<sup>11,54</sup> The area under the plasma concentration–time curve from 0 to 24 h (AUC<sub>0–24</sub>) was 4.7 μg·h/mL.<sup>54</sup> Similar pharmacokinetic parameters have been noted in phase III clinical studies of patients with cSSSIs and cIAIs.<sup>56,57</sup>

Tigecycline is highly protein bound (71%–89%) at plasma drug concentrations of 0.1–1.0 μg/mL and exhibits a large volume of distribution (Vd) at steady state of 7–9 L/kg in healthy volunteers.<sup>11,54</sup> Animal and human studies have demonstrated that tigecycline can distribute into various tissues and body fluids (such as the lungs, skin, peritoneal fluid, gallbladder, colon, heart, liver, meninges, and bone).<sup>11,58–64</sup> In a study of adult patients (n = 104) undergoing medical

or surgical procedures, tigecycline concentrations were evaluated 4 h after the administration of 100 mg over 30 min.<sup>63</sup> The highest concentration of tigecycline was found in the bile. The mean ratio of tigecycline in the tissue to serum (expressed as  $AUC_{0-24}$ ) was 537 in the bile, 23 in the gallbladder, 2.6 in the colon, 2.0 in the lung, 0.41 in bone, 0.31 in synovial fluid, and 0.11 in cerebrospinal fluid.

Lung penetration of tigecycline has been evaluated in healthy adults ( $n = 30$ ) after receiving a loading dose of 100 mg of tigecycline followed by six doses of 50 mg every 12 h.<sup>60</sup> The  $AUC_{0-12}$  was  $1.73 \mu\text{g} \cdot \text{h/mL}$  in the serum,  $134 \mu\text{g} \cdot \text{h/mL}$  in the alveolar cells (ACs), and  $2.28 \mu\text{g} \cdot \text{h/mL}$  in the epithelial lining fluid (ELF). The corresponding  $C_{\text{max}}$  was 0.72, 15.2, and  $0.37 \mu\text{g/mL}$ , respectively. In adult critically ill mechanically ventilated patients ( $n = 3$ ), mean tigecycline concentrations 4 h following the infusion were  $0.36 \pm 0.20$ ,  $0.02 \pm 0.01$ , and  $8.96 \pm 0.15 \text{ mg/L}$  in the plasma, ELF, and ACs, respectively, after receipt of 100 mg followed by 50 mg every 12 h.<sup>65</sup> The ratios of ELF and AC concentrations relative to plasma concentrations were  $0.06 \pm 0.02$  and  $34.3 \pm 7.8$ , respectively. Although plasma, ELF, and AC concentrations are comparable to healthy volunteers, the penetration of tigecycline into the extracellular lung compartment of these critically ill patients with underlying pulmonary pathology (as noted by the ELF to plasma ratio) was low.<sup>60,66</sup> Although ELF is an intrapulmonary site, concentrations within this fluid are believed to be important in reflecting potency against extracellular organisms (such as *S. pneumoniae* and *K. pneumoniae*).<sup>65,66</sup>

Tigecycline is minimally metabolized to nonactive metabolites of glucuronide, its epimer M1 and M2, and *N*-acetyl-9-aminomincycline (M6).<sup>11,67,68</sup> The primary route of elimination of tigecycline is as unchanged drug and metabolites through the feces (59%) and biliary tract.<sup>67</sup> Renal excretion (33%) and glucuronidation are secondary routes of elimination. Tigecycline has a terminal half-life of 37–67 h and a total systemic clearance of 0.2–0.3 L/h/kg.<sup>54</sup>

The pharmacokinetic profile of tigecycline has been evaluated in several different special patient populations. No differences have been noted based on age (18 to >75), gender, or race.<sup>69,70</sup> Patients with renal insufficiency (creatinine clearance  $\leq 30 \text{ mL/min}$ ) and dependent on hemodialysis also did not demonstrate alterations in their pharmacokinetic profiles.<sup>71</sup> Tigecycline is not significantly removed with hemodialysis.<sup>71</sup> Patients with severe hepatic impairment (Child–Pugh class C) demonstrated a 43% increase in half-life and a 55% decrease in tigecycline clearance.<sup>72</sup> It is recommended that the

maintenance dose of tigecycline should be reduced to 25 mg every 12 h in these individuals.<sup>11,72,73</sup> In contrast, no adjustment in doses are necessary for patients with mild to moderate (Child–Pugh class A or Child–Pugh class B) hepatic impairment.<sup>11,72</sup>

Based on animal and the clinical data, the AUC to MIC ratio (AUC/MIC) is most likely to be the best predictor of efficacy with tigecycline.<sup>37,69,74</sup> Studies in cSSSIs and cIAIs have suggested that the  $AUC_{0-24}/\text{MIC}$  of  $\geq 17.9$  and  $\geq 6.96$ , respectively, were predictive of favorable clinical response and microbiological eradication.<sup>74,75</sup> In two phase III CABP studies ( $n = 68$ ), patients receiving a loading dose of 100 mg followed by 50 mg every 12 h had a median  $AUC_{0-24}/\text{MIC}$  of 55.5 (5.2–179.5) with the MICs ranging from 0.03 to 1.0 mg/L for mono- and poly-microbial *S. pneumoniae* infections.<sup>76</sup> Due to the low incidence of clinical and microbiological failures, the authors felt that a clear pharmacokinetics/pharmacodynamics relationship could not be established. However, a Classification and Regression Tree (CART)-derived AUC/MIC breakpoint of 64 was predictive of time to fever resolution, since the median time to fever resolution for AUC/MIC of  $\geq 64$  and  $< 64$  were 12 and 24 h, respectively ( $P = 0.05$ ). In contrast, evaluation of a phase III hospital-acquired pneumonia (HAP) study ( $n = 61$ ) in which patients received standard doses of tigecycline, a CART-derived AUC/MIC breakpoint of 5.75 was significantly associated with clinical success in patients ( $P \leq 0.02$ ).<sup>76</sup> Only 43.2% (7/16) patients with an AUC/MIC of  $< 5.75$  achieved clinical success, while 80% (36/45) of patients with an AUC/MIC of  $\geq 5.75$  achieved clinical success ( $P = 0.011$ ).

In regards to the treatment of bacteremia, low  $C_{\text{max}}$  concentrations obtained after standard dosing of tigecycline are concerning, since it approaches the MICs of organisms most commonly encountered.<sup>77</sup> Furthermore, tigecycline concentrations rapidly decline once the  $C_{\text{max}}$  is reached. Animal models in neutropenic mice have demonstrated that unbound serum concentrations of tigecycline need to be above the MIC of the organism for at least 50% of the dosing interval in order to achieve maximum effectiveness.<sup>63,69,78,79</sup> Therefore, organisms would need to have a relatively low MIC to tigecycline in order to achieve this pharmacodynamic target in bacteremia.<sup>60,80</sup> To address this issue, case reports with higher dosing schemes of tigecycline (200–400 mg as the loading dose followed by 100–200 mg every 24 h) have reported success in the treatment of multidrug-resistant *K. pneumoniae* and *A. baumannii* with higher dosing schemes in order to maximize the AUC/MIC.<sup>80–82</sup>

## Effectiveness of tigecycline in the treatment of CABP

Results of two noninferiority, randomized, double-blind, multinational, phase III studies have been published, which compared the safety and efficacy of tigecycline in comparison with levofloxacin.<sup>15–17</sup> Febrile, hospitalized adults with CABP (confirmed by chest radiograph and at least two of the following: symptoms consistent with a bacterial respiratory infection, leukocytosis, or hypoxemia) who required IV antibiotics were included. Those who failed outpatient fluoroquinolones previously, were recently hospitalized, resided in a long-term care facility (within 14 days), required ICU admission, or had known or suspected infections (*P. aeruginosa*, *Legionella pneumoniae*, or active tuberculosis) were excluded. Patients were randomized to receive either tigecycline (100 mg IV  $\times$  1, then 50 mg IV twice daily thereafter) or levofloxacin (500 mg IV daily (one of the trials also had the option for 500 mg IV twice daily at the discretion of the investigator)). In one of the two trials, patients in either group could be switched to oral levofloxacin at the discretion of the investigator after 3 days of IV antibiotics. The total duration of antimicrobial treatment was 7–14 days in both of these studies. The primary end points were clinical response at the test of cure (TOC) in both the clinical modified intent-to-treat (c-mITT) and the clinically evaluable (CE) populations. In these studies, ‘cure’ required the improvement or resolution of clinical signs and symptoms attributable to CABP, improvement or no change on chest radiograph, and no additional antimicrobials.<sup>15–17</sup>

Of the 859 patients included in the intent-to-treat (ITT) population, 797 and 574 were included in the c-mITT and CE populations, respectively. For the tigecycline group, the mean age was 52.6 years ( $\pm$ 18) with 57.3% male patients; the levofloxacin group’s mean age was 51.9 years ( $\pm$ 18.7) with 62.8% male patients. Fine pneumonia severity index scores and confusion, urea nitrogen, respiratory rate, blood pressure (CURB-65) criteria were similar among the groups, with 80% of the population having scores of I–III for Fine and 92% having scores of 0–2 for CURB-65. Concomitant diseases (including chronic obstructive pulmonary disease, diabetes, liver and renal disease, heart failure and cerebrovascular diseases, as well as cancer) were also comparable among the two treatment groups. In one of the studies, 90% and 88% of the tigecycline and levofloxacin groups were switched to oral antibiotics after a median of 3.9 and 3.3 days, respectively.<sup>15–17</sup> In the first of the trials, a clinical cure rate for the CE and c-mITT populations were 90.6% versus 87.2% (absolute difference 3.4% (95% confidence interval (95% CI): –4.4% to 11.2%)) and 78.0% versus

77.8% (absolute difference 0.2% (95% CI: 8.5%–8.9%)) for tigecycline and levofloxacin treatments, respectively. Similar observations were made in the second trial. Success rates in the CE and c-mITT populations were 88.9% versus 85.3% (absolute difference 3.6% (95% CI: –4.5% to 11.8%)) and 83.7% versus 81.5% (absolute difference 2.0% (95% CI: –5.5% to 9.6%)) in tigecycline and levofloxacin groups, respectively. No differences were noted in clinical cure rates among respiratory pathogens, including both typical and atypical organisms. To be considered noninferior, the lower limit of the 95% CI could not exceed –15% for the absolute difference. Thus, tigecycline was considered noninferior to levofloxacin in both studies.<sup>15,16</sup>

The safety and efficacy of tigecycline has also been compared to other therapies (such as imipenem–cilastatin) in other patient populations with pneumonia, most notably HAP (including ventilator-associated pneumonia (VAP) patients).<sup>83</sup> In this phase III, multicenter, multinational, double-blind randomized trial, tigecycline failed to meet the prespecified noninferiority criteria (the lower limit of the 95% CI could not exceed –15% for the absolute difference) for the coprimary endpoints of clinical response rates at the TOC in the CE (67.9% vs 78.2%, absolute difference –10.4% (95% CI: –17.8% to –3%)) and c-mITT (62.7% vs 67.6%, absolute difference –4.8% (95% CI: –11.0% to 1.3%)) in the tigecycline and imipenem groups, respectively. In the VAP subgroup, there were lower cure rates (47.9% vs 70.1%), and higher rates of mortality (19.1% vs 12.3%) were seen in tigecycline patients relative to those receiving imipenem–cilastatin. (See further discussion of mortality in the safety and tolerability section.) Patients with VAP and bacteremia at baseline had significantly greater mortality with 50% (9/18) in the tigecycline population versus 7.7% (1/13) in the comparator group.<sup>83</sup> Until further studies are performed, tigecycline should not be recommended for these types of patients. As of May 2010, this was an added component of the ‘Warnings and Precaution’ section of the Tygacil® package insert.<sup>11</sup>

Case reports of tigecyclines effectiveness in the treatment of pneumonia by various organisms including *Mycobacterium chelonae*,<sup>84</sup> multidrug-resistant *Stenotrophomonas maltophilia*,<sup>85</sup> and carbapenemase-producing *K. pneumoniae*<sup>86</sup> have been documented. However, until further data are available, tigecyclines routine use against these organisms cannot be recommended.

## Safety and tolerability of tigecycline

Overall, tigecycline was well tolerated in phase III clinical studies for the treatment of CABP and was comparable to

those studies performed with tigecycline in the treatment of cSSSIs and cIAIs. The most common adverse effect reported was nausea (20.8% in community-acquired pneumonia (CABP) studies; 34.5% in cSSSIs studies; 24.4% in cIAIs studies) and vomiting (13.2% in CABP studies; 19.6% in cSSSIs studies; 19.2% in cIAIs studies).<sup>12–17,87</sup> Using the National Cancer Institute Common Toxicity Criteria, the nausea and vomiting was characterized as mild to moderate in severity in most patients in the CABP studies, and only led to discontinue therapy in 14 patients.<sup>17</sup> Factors that have been shown to be associated with a higher incidence of nausea and vomiting secondary to tigecycline therapy include female gender, <65 years of age, and non-European descent.<sup>11</sup> Furthermore, altering the infusion rate and the use of antiemetics have not been beneficial in prevention of such reactions.<sup>11,54</sup> Administration with food may improve tolerability.<sup>11</sup>

Pooled data from the CABP studies utilizing the mITT population (n = 846) reported more drug-related adverse events with tigecycline compared to the levofloxacin (47.9% vs 37.4%, respectively ( $P < 0.01$ )).<sup>15–17</sup> The most common adverse effects noted in the studies were nausea (20.8% vs 6.6%) and vomiting (13.2% vs 3.3%) in tigecycline- and levofloxacin-treated patients, respectively ( $P < 0.001$ ).<sup>17</sup> Levofloxacin had a higher incidence of alanine aminotransferase (6.4% versus 2.6%) and aspartate amino transferase (5.9% vs 2.1%) elevations relative to tigecycline, respectively ( $P < 0.01$ ).<sup>17</sup> Other adverse events such as diarrhea, phlebitis, and headache were statistically similar among treatment groups.<sup>17</sup> Serious adverse events resulting in extended hospitalizations, readmission to the hospital or life-threatening effects (9.9% vs 10.9%), drug discontinuation secondary to adverse effects (6.1% vs 8.1%), and the incidence of death not related to study drug (2.8% vs 2.6%) were comparable between tigecycline and levofloxacin groups, respectively.<sup>17</sup> Only one case of *Clostridium difficile* infection was reported in the tigecycline arm.<sup>17</sup> Other more commonly reported adverse effects with tigecycline include diarrhea (7.5%), phlebitis (4%), and headache (3.5%).<sup>17</sup> Other additional adverse effects reported with tigecycline from postmarketing surveillance since its food and drug administration (FDA) approval include anaphylaxis and anaphylactoid reactions, acute pancreatitis, elevated liver function tests, hyperbilirubinemia, jaundice, and hepatic cholestasis.<sup>11,88–90</sup>

Recent, pooled analysis from 13 phase III and IV clinical studies evaluating the use of tigecycline (n = 3788) versus other antibiotics (n = 3646) in the treatment of various serious

infections have demonstrated an increased risk with the use of tigecycline for all-cause mortality (4% vs 3%, (adjusted risk difference based on a random effects model stratified by trial weight 0.6; 95% CI: 0.1, 1.2)).<sup>11,91</sup> The increase in mortality was particularly noted for cSSSIs, cIAIs, diabetic foot infections, and in HAP patients with VAP. Although mortality rates in these infections individually did not reach statistical significance, the incidence was higher for each infection in the tigecycline group and when pooled, there was a statistically significant difference. In patients with CABP, all-cause mortality rates of 2.8% in the tigecycline arm (12/424) compared to 2.6% in the alternate treatment arm (11/422) (risk difference 0.3 (95% CI: -2.0, 2.4)). In patients with HAP, the incidence of all-cause death was 14.1% (66/467) in the tigecycline arm versus 12.2% (57/467) in the comparator arm (risk difference 0.60.2 (95% CI: -2.4, 6.3)). Mortality rates in patients with VAP were 19.1% (25/131) versus 12.3% (15/122) for tigecycline and the comparator arm, respectively (risk difference: 6.8; 95% CI: -2.1, 15.7). It has been speculated that this increased incidence of mortality in the tigecycline arms may have been due to progression of infection while on therapy, possibly secondary to the static nature of the drug; however, there is limited data currently to support that bactericidal drugs are more efficacious than bacteriostatic drugs.<sup>92</sup>

Tigecycline should be avoided in pregnant women (pregnancy category D) and in growing children due to an accumulation of the drug in bones; thus resulting a delay in ossification.<sup>11,58,63</sup> Additionally, similar to tetracyclines, teeth discoloration during tooth development may occur from the use of tigecycline and should, therefore, be avoided in children below the age of eight.<sup>11</sup>

## Drug interactions

Tigecycline is neither metabolized nor does it cause alterations to the cytochrome P450 system; thus, drug interactions mediated through this system have not been identified and significant drug interactions have not been reported.<sup>11</sup> Although studies in healthy volunteers administered tigecycline concomitantly with digoxin failed to detect any significant drug interactions, the clearance of the R and S enantiomers of warfarin were decreased.<sup>11,93,94</sup> Therefore, the international normalized ratio and signs and symptoms of bleeding should be monitored if patients are receiving tigecycline concurrently with warfarin.<sup>11,94</sup> Additionally, similar to other antibiotics, concurrent administration of tigecycline with oral contraceptives may reduce the efficacy of these agents.<sup>11</sup>

## Health care resource utilization perspective

In an analysis of health care resource utilization data from CABP patients receiving either tigecycline ( $n = 393$ ) or levofloxacin ( $n = 403$ ), no difference was reported between the groups in terms of mean length of hospital stay (9.8 days for each group;  $P = 0.883$ ) or mean duration of study antibiotic (9.8 days tigecycline vs 10 days levofloxacin group;  $P = 0.511$ ). Additionally, there was no difference between groups in the rate of rehospitalization, admission to the ICU or emergency room, use of home health, or admission to the nursing home. The need for concurrent antibiotics during or after discharge was lower in the tigecycline group compared to the levofloxacin group (5.6% vs 11.7% ( $P = 0.002$ ), respectively).<sup>17</sup>

## Patient-focused perspective/conclusion

Initial empiric treatment of CABP in hospitalized patients often involves the use of broad-spectrum antibiotics, and combination therapy is frequently indicated (especially in treatment options excluding respiratory fluoroquinolones). With its broad spectrum of activity against most common respiratory pathogens causing CABP, tigecycline offers an antibiotic option that can be used as monotherapy. Patients with a history of  $\beta$ -lactam or quinolone allergy, or patients with organisms resistant to alternate therapies may also benefit from the use of tigecycline. Although patients failing therapy with alternative agents might be considered for therapy with tigecycline, data in this population is sparse.

With the possible exception of gastrointestinal intolerance, tigecycline was reasonably well tolerated in this patient population.<sup>17</sup> Tigecycline is only available in an IV formulation. Therefore, its use for CABP would likely be limited largely to patients requiring hospitalization. Alternate therapy would be required for conversion to oral therapy. Data for the treatment of *Staphylococcus aureus* and MRSA pneumonias are somewhat limited. Recent concerns have emerged regarding tigecycline use in patients with severe forms of CABP related to data obtained in patients with other forms of severe infection, including HAP.

## Disclosure

Richard H. Drew MS, Pharm.D., BCPS:

Commercial Astellas (consultant), Cubist (research, speaker), Ortho-McNeil (consultant), Wyeth/Pfizer (consultant), Merck/Schering-Plough (consultant, research, speaker), UpToDate (publication royalties) Non-commercial CustomID (development team), Moses Cone Health System (speaker),

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