Use of In Vitro Susceptibility and Pathogen Prevalence Data to Model the Expected Clinical Success Rates of Tigecycline and Other Commonly Used Antimicrobials for Empiric Treatment of Complicated Skin and Skin Structure Infections (cSSSI) in France, Germany and Italy

HS SADER, MG STILWELL, TR FRITSCHE, R MALLICK, A KUZNIK, RN JONES
JMI Laboratories, North Liberty, IA, USA; Wyeth Pharmaceuticals, Collegeville, PA, USA

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370,
fax 319.665.3371
ronald-jones@jmilabs.com

ABSTRACT

Background:
Tigecycline is a novel semisynthetic glycylcycline recently approved for parenteral treatment of cSSSI in the USA. We evaluated the antimicrobial spectrum of tigecycline and commonly used parenteral antimicrobials for empiric treatment of cSSSI.

Methods:
Consecutive, nonduplicate bacterial isolates collected from 2000 to 2005 from patients with documented cSSSI in 16 medical centers located in France (6), Germany (7), and Italy (3) were used to evaluate the frequency of pathogen occurrence and susceptibility rates of tigecycline and select parenteral antimicrobials. All isolates were tested using CLSI broth microdilution methods and interpretive criteria. Tigecycline breakpoints approved by the USA-FDA were used. By applying pathogen-specific susceptibility rates to the frequency of occurrence of pathogens in each country (as weights), we generated a (weighted average) measure of overall expected coverage for each antimicrobial.

Results:
The top 3 pathogens in France, Germany, and Italy were (frequency [%] by country): *S. aureus* (49.9, 35.1 and 39.6%, respectively), *P. aeruginosa* (8.3, 11.0 and 17.2%), and *E. coli* (8.0, 11.3 and 13.9%). Other frequently isolated pathogens included enterococci, ß-haemolytic streptococci, *Enterobacter* spp., coagulase-negative staphylococci, and *P. mirabilis,* with some intercountry variation. Tigecycline was highly active (>90% S) against the most common pathogens, except *P. aeruginosa* and *P. mirabilis.* Linezolid and vancomycin were also very active against Gram-positive but presumed to have no activity against Gram-negative organisms. The overall expected coverage of antimicrobials evaluated is summarized in the table:

	Overall expected coverage (% susceptible of all pathogens)		
Antimicrobial	France	Germany	Italy
Tigecycline	90.0	88.2	83.4
Vancomycin	74.4	66.6	65.6
Linezolid	74.4	66.6	65.8
Levofloxacin	82.9	88.3	71.2
Piperacillin/tazobactam	84.2	96.0	76.3
Imipenem	85.3	95.8	79.3

Conclusion:
Tigecycline was associated with the highest overall expected empiric coverage against cSSSI isolates collected in France and Italy, while levofloxacin, piperacillin/tazobactam and imipenem had equal or better expected coverage against cSSSI isolates from Germany, where *P. aeruginosa* was relatively more prevalent in relation to *S. aureus*. Our results suggest that tigecycline will be a viable option for empiric treatment of cSSSI in these European countries.

INTRODUCTION

Over 700,000 patients are hospitalized annually for complicated skin and skin structure infections (cSSSI; including deep cellulitis, major abscess, wound infections and infected ulcers) in the United States alone [HCUPnet, 2006]. The management of cSSSIs is often complicated by the potential microbiological spectrum of prevalent pathogens [Fluit et al., 2001; Fritsche et al., 2005]. In particular, cSSSIs are characterized by a fairly high prevalence of *Staphylococcus aureus*, including the emergence of methicillin-resistant *S. aureus* (MRSA) in both the hospital and community settings [Naimi et al., 2003]. In fact, up to 50% of cSSSIs are treated with a broad-spectrum antimicrobial usually combined with an anti-MRSA drug [Raghavan and Linden, 2004].

Tigecycline (formerly GAR-936) is the first in a new class of antimicrobial agents known as the glycylcyclines and is being initially developed as a parenteral agent targeting common pathogens responsible for cSSSI and intra-abdominal sepsis [Bradford, 2004]. The compound is a semisynthetic 9-t-butylglycylamido derivative of minocycline, whose action on bacterial ribosomes shows identical and overlapping binding sites when compared to tetracyclines. The position 9 substitution of tigecycline, however, provides additional steric hindrance features that result in a greater spectrum of activity [Bauer et al., 2004]. Tigecycline has been recently approved for parenteral treatment of cSSSI in the USA and Europe [Tygacil Package Insert, 2005].

In the present study, we evaluated the antimicrobial potency of tigecycline and commonly used parenteral antimicrobials for empiric treatment of cSSSI against recent clinical bacterial isolates collected through a global surveillance program in 3 countries – France, Germany, and Italy. In addition, we measured overall expected coverage or spectrum for tigecycline and other antimicrobials commonly used to treat cSSSI infections by applying pathogen-specific susceptibility rates to the frequency of organism occurrence by nation.

MATERIALS AND METHODS

Bacterial isolates
To assess the spectrum of activity and potency of tigecycline and antimicrobial agents used to treat cSSSI, recent clinical isolates submitted as part of global antimicrobial resistance surveillance programs were utilized [Fritsche et al., 2005]. A total of 1,608 isolates recovered from patients hospitalized with documented pyogenic cSSSI collected from 2000 to 2005 in 16 medical centers located in France (6 medical centers; 723 strains), Germany (7 medical centers; 547 strains), and Italy (3 medical centers; 338 strains) were processed.

Susceptibility testing
MIC values for tigecycline and other comparators were determined using validated, reference broth microdilution panels with cation-adjusted Mueller-Hinton medium (TREK Diagnostics Inc., Cleveland, OH). Testing, incubation and MIC interpretation were performed using the manufacturer's recommendations and/or Clinical and Laboratory Standards Institute guidelines [CLSI, 2006]. Tigecycline breakpoints approved by the United States Food and Drug Administration (US-FDA) were used [Tygacil Package Insert, 2005]. Quality control was performed using American Type Culture Collection (ATCC) strains including *Escherichia coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Streptococcus pneumoniae* ATCC 49619 and *Pseudomonas aeruginosa* ATCC 27853.

Evaluation of overall spectrum coverage
We developed a measure of overall expected coverage (success rate) for each antimicrobial by taking account of (i) the susceptibility rates of that antimicrobial when tested against pathogens isolated from cSSSI, and (ii) the prevalence of various pathogen as a cause of cSSSI. This was implemented as follows:

For each antimicrobial regimen *j* with respect to pathogen *i,* we first calculated a prevalence-adjusted susceptibility rate (PAS):

(1) $PAS_{ij} = 1 - [P_{i^*} (1 - S_{ij})]$,

Where P_i represents the prevalence of pathogen *i* (= 1, 2, ..., K) in the population of interest, and S_{ij} represents the susceptibility of pathogen *i* to antimicrobial *j*.

We then calculated the overall expected coverage (success rate) (EC_j) as the product of the prevalence-adjusted susceptibility rates of each antimicrobial against each of *i* (= 1, 2, …, K) possible pathogens, i.e.:

(2) $EC_j = (PAS_{1j^*} PAS_{1j^*} \ldots {}_* PAS_{Kj})$

For illustration, consider the following hypothetical example of two drugs (A,B) and a population of only two pathogens (X,Y).

Drug	Susceptibility against pathogen X	Prevalence of pathogen X	Susceptibility against pathogen Y	Prevalence of pathogen Y	Expected Coverage (Success Rate)
A	0%	10%	100%	90%	90%
B	100%	10%	0%	90%	10%

Drug A, which has excellent activity (100.0% susceptibility) against a highly prevalent (90.0%) pathogen, and no activity against a minimally prevalent (10.0%) pathogen, has a higher expected coverage (90%) than drug B (10%), which has good activity against a minimally prevalent pathogen but no activity when tested against a highly prevalent pathogen.

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RESULTS

- The eight most common cSSSI pathogens in each country are listed in Table 1. *S. aureus*, *P. aeruginosa* and *E. coli* were the 3 most frequently isolated pathogens in all three countries.
- Data from Italy revealed the highest MRSA rate and also the highest prevalence of *P. aeruginosa*, while data from Germany showed the lowest MRSA rate among the countries evaluated.

Table 1. Most frequently isolated pathogens from cSSSI in France, Germany and Italy (SENTRY Program, 2003-2005).

	Rank (No. of isolates/% of total)		
Organism	France	Germany[a]	Italy
S. aureus	1 (361 / 49.9%)	1 (192 / 35.1%)	1 (134 / 39.6%)
Oxacillin-susceptible	(261 / 36.1%)	(185 / 33.8%)	(91 / 26.9%)
Oxacillin-resistant	(100 / 13.8%)	(7 / 1.3%)	(43 / 12.7%)
P. aeruginosa	2 (60 / 8.3%)	3 (60 / 11.0%)	2 (58 / 17.2%)
E. coli	3 (58 / 8.0%)	2 (62 / 11.3%)	3 (47 / 13.9%)
ß-haemolytic streptococci	4 (57 / 7.9%)	9 (17 / 3.1%)	8 (3 / 0.9%)
Enterococci	5 (31 / 4.3%)	4 (35 / 6.4%)	5 (24 / 7.1%)
Enterobacter spp.	6 (28 / 3.9%)	10 (17 / 3.1%)	6 (17 / 5.0%)
P. mirabilis	7 (26 / 3.6%)	7 (22 / 4.0%)	7 (4 / 1.2%)
CoNS	8 (19 / 2.6%)	6 (28 / 5.1%)	4 (41 / 12.1%)

a. The 5th and 8th most frequently isolated pathogens were *Klebsiella* spp. (29 / 5.3%) and *Acinetobacter* spp. (21 / 3.8%), respectively.

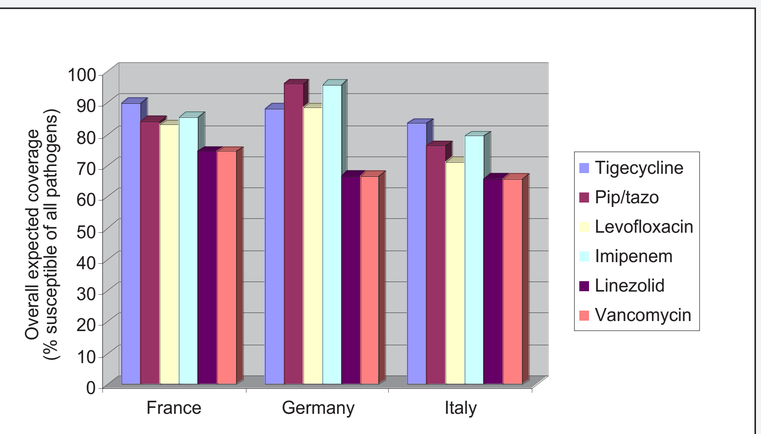
Table 2. Antimicrobial susceptibility of the most frequently isolated organism from skin and skin structure infections.

	% Susceptible (no. tested)		
Organism	France	Germany	Italy
Oxacillin-susceptible *S. aureus*	(261)	(185)	(91)
Tigecycline	100.0	99.4	100.0
Piperacillin/tazobactam	100.0	100.0	100.0
Oxacillin	100.0	100.0	100.0
Levofloxacin	95.8	89.7	100.0
Clindamycin	95.8	94.1	97.8
Linezolid	100.0	100.0	100.0
Vancomycin	100.0	100.0	100.0
Oxacillin-resistant *S. aureus*	(100)	(7)	(43)
Tigecycline	98.9	100.0	100.0
Piperacillin/tazobactam	0.0[a]	0.0[a]	0.0[a]
Oxacillin	0.0	0.0	0.0
Levofloxacin	11.0	28.6	4.7
Clindamycin	47.0	14.3	27.9
Linezolid	100.0	100.0	100.0
Vancomycin	100.0	100.0	100.0
E. coli	(58)	(62)	(47)
Tigecycline	100.0	100.0	100.0
Piperacillin/tazobactam	89.7	98.4	93.6
Cefazolin	82.8	91.9	91.5
Amoxicillin/clavulanate	77.6	79.0	89.4
Levofloxacin	84.5	91.9	89.4
Imipenem	100.0	100.0	100.0
ß-haemolytic streptococci	(57)	(3)	(17)
Tigecycline	97.4	100.0	100.0
Piperacillin/tazobactam	100.0[b]	100.0[b]	100.0[b]
Penicillin	100.0	100.0	100.0
Clindamycin	84.2	100.0	100.0
Levofloxacin	100.0	100.0	100.0
Linezolid	100.0	100.0	100.0
Vancomycin	100.0	100.0	100.0
Enterococcus spp.	(31)	(35)	(24)
Tigecycline	100.0	93.9	90.5
Piperacillin/tazobactam	96.8[c]	88.6[c]	70.8[c]
Ampicillin	96.8	88.6	70.8
Levofloxacin	87.1	74.3	66.7
Linezolid	100.0	100.0	100.0
Vancomycin	100.0	100.0	95.8
CoNS	(19)	(28)	(41)
Tigecycline	100.0	96.3	100.0
Piperacillin/tazobactam	42.1[a]	35.7[a]	22.0[a]
Oxacillin	42.1	35.7	22.0
Levofloxacin	84.2	67.9	29.3
Clindamycin	94.7	78.6	65.9
Linezolid	100.0	100.0	100.0
Vancomycin	100.0	100.0	100.0

a. Susceptibility predicted by oxacillin results [CLSI, 2006].
b. Susceptibility predicted by penicillin results [CLSI, 2006].
c. Susceptibility predicted by ampicillin results [CLSI, 2006].

- Antimicrobial susceptibilities of the six most frequently isolated pathogens are summarized in Table 2. Tigecycline, linezolid and vancomycin were the most active compounds against Gram-positive pathogens, which represented 58.3% of pathogens evaluated.
- Tigecycline and imipenem were the most active against *E. coli* (10.4% of pathogens evaluated). Tigecycline was also highly active against most Gram-negative pathogens except *P. aeruginosa* (11.1% of pathogens) and *P. mirabilis* (3.2% of pathogens).
- Piperacillin/tazobactam and imipenem were the most active compounds when tested against *P. aeruginosa.*
- Tigecycline was associated with an overall expected coverage ranging from 90.0% (France) to 83.4% (Italy; Figure 1).

Figure 1. Overall expected coverages for the empiric treatment of cSSSI of tigecycline and comparator antimicrobials.



CONCLUSIONS

- Tigecycline was associated with the highest overall expected empiric coverage against cSSSI isolates collected in France and Italy, while levofloxacin, piperacillin/tazobactam and imipenem had equal or better overall expected coverage against cSSSI isolates from Germany, where *P. aeruginosa* was relatively more prevalent and the MRSA rate was low (3.6%).
- The overall expected coverages of broad-spectrum ß-lactams were compromised by the high prevalence of MRSA in France and Italy.
- Our results suggest that tigecycline is expected to represent a viable option for empiric treatment of cSSSI in these European countries given its broad spectrum of activity against the most frequently isolated pathogens.

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