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Evaluation of Expected Clinical Success Rates of Tigecycline and Other Commonly Used Antimicrobials for Empiric Treatment of Complicated Skin and Skin Structure Infections (cSSSI) in Germany, Spain and the United States

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AMENDED ABSTRACT

Objective:
To model the expected clinical success of tigecycline and commonly used antimicrobials for empiric treatment of cSSSI based on evaluation of antimicrobial susceptibility and frequency of pathogen occurrence from a global surveillance program. Tigecycline is a novel semisynthetic glycylcycline recently approved for parenteral treatment of cSSSI and intra-abdominal infections in the United States (US) and European countries.

Methods:
Consecutive, non-duplicate bacterial isolates collected between 2000 and 2005 from patients with documented cSSSI in 48 medical centers located in Germany (7), Spain (3), and the US (38) 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, we calculated the overall expected coverage for each antimicrobial agent or combination.

Results:
The top 3 pathogens identified in Germany and Spain were (frequency [%] by country): *S. aureus* (35.1 and 33.3%, respectively), *E. coli* (11.3 and 12.8%), and *P. aeruginosa* (11.0 and 12.6%). In the US, the top 3 pathogens identified were *S. aureus* (48.1%), *P. aeruginosa* (9.4%) and enterococci (8.8%). Other frequently isolated pathogens included ß-haemolytic streptococci, *Enterobacter* spp. and *Klebsiella* spp., with some inter-country variation. The rates of oxacillin-resistance (MRSA) varied from 3.6% in Germany to 17.3% in Spain and 43.5% in the US. Tigecycline was highly active (>90% S) against the most common pathogens, except *P. aeruginosa* and *P. mirabilis*. The overall expected coverage of cSSSI for the antimicrobials evaluated is summarized in the table:

	Overall expected coverage (% susceptible of all pathogens)		
Antimicrobial	Germany	Spain	United States
Tigecycline	87.8	85.1	90.6
Vancomycin	66.9	59.5	73.4
Linezolid	66.9	59.5	74.4
Levofloxacin	88.3	84.6	75.7
Piperacillin/tazobactam	93.1	85.5	74.5
Imipenem	92.9	87.7	73.2
Cefazolin	72.3	62.7	59.3
Ceftriaxone	78.4	71.8	63.0
Vancomycin & Piperacillin/tazobactam	98.2	95.8	95.7
Vancomycin & Levofloxacin	95.5	93.1	93.8

Conclusion:
Vancomycin in combination with piperacillin/tazobactam had the highest overall expected empiric coverage of cSSSI in the countries evaluated. Among monotherapies, tigecycline had the highest expected coverage rate in the US, where the prevalence of MRSA was relatively high. Piperacillin/tazobactam and imipenem had the highest expected coverage in Germany and Spain, where the prevalence of MRSA was relatively low. Our results suggest that tigecycline might be a viable option for empiric treatment of cSSSI in these countries, especially in settings with high MRSA rates.

INTRODUCTION

The management of complicated skin and skin structure infections (cSSSI) is often compromised by the potential microbiological diversity of prevalent pathogens. In particular, cSSSIs are characterized by a fairly high prevalence of *Staphylococcus aureus*, including the emergence of methicillin-(oxacillin) resistant *S. aureus* (MRSA) in both the hospital and community settings. Furthermore, in recent years serious cSSSI caused by multidrug-resistant pathogens, including non-fermentative Gram-negative bacilli and Enterobacteriaceae, have become more common, forcing the empirical use of broad-spectrum antimicrobials and anti-MRSA drugs.

The emergence and increased prevalence of resistant organisms as a cause of cSSSI has created the need for different therapeutic agents, such as linezolid, quinupristin/dalfopristin, daptomycin and tigecycline. Tigecycline (formerly GAR-936) is the first in a new class of antimicrobial agents known as the glycylcyclines which has been recently approved for parenteral treatment of cSSSI and intra-abdominal infections in the United States (USA) and Europe.

Results of surveillance programs documenting the frequency of occurrence and antimicrobial susceptibility patterns of organisms causing cSSSI can be very useful to guide empiric antimicrobial treatment. The SENTRY Antimicrobial Surveillance Program is a large multinational data source enabling longitudinal, global monitoring of predominant patterns in pathogen prevalence and antimicrobial susceptibility, including newly available antimicrobials.

In the present study, we evaluated the antimicrobial potency of tigecycline and commonly used parenteral agents for treatment of cSSSI against recent clinical bacterial isolates collected through the SENTRY Program in three countries – Germany, Spain and the USA. We also evaluated the overall expected coverage or spectrum for tigecycline and other antimicrobials commonly used to treat cSSSI infections, as calculated by applying pathogen-specific susceptibility rates to the frequency of organism occurrence in each nation.

MATERIALS AND METHODS

Bacterial isolates
To assess the spectrum of activity and potency of tigecycline and selected antimicrobial agents commonly used to treat cSSSI, recent clinical isolates submitted as part of a global antimicrobial resistance surveillance program were utilized. A total of 5,690 consecutive, clinically significant, isolates recovered from unique patients hospitalized with documented pyogenic cSSSI collected from 2000 to 2005 in 48 medical centers located in Germany (seven medical centers; 547 strains), Spain (three medical centers; 469 strains), and the USA (38 medical centers; 4674 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. Tigecycline susceptible breakpoints approved by the USA Food and Drug Administration (FDA) were used as follows: ≤2 mg/L for Enterobacteriaceae, ≤0.5 mg/L for staphylococci, and ≤0.25 mg/L for streptococci and enterococci. 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 empiric coverage
The overall expected empiric coverage for each monotherapy regimen was calculated by incorporating the observed susceptibility rate of each antimicrobial in relation to the prevalence of each pathogen. Based on the observed susceptibility of each pathogen *i* (= 1, 2, …..,) to each agent *j* (*j=A, B, C,…),* a prevalence-adjusted susceptibility rate of the pathogen to the antimicrobial regimen *j* (PAS_{ij}) was calculated as follows:

(1) $PAS_{ij} = 1 - [P_i \cdot (1 - S_{ij})]$,

where P_i represents the prevalence of pathogen *i* in the population of interest, and S_{ij} represents the observed susceptibility of pathogen *i* to antimicrobial *j*.

The overall expected empiric coverage (EC_j) was calculated as the product of the prevalence-adjusted susceptibility rates of each antimicrobial agent tested against each pathogen *i*, i.e.:

(2) $EC_j = (PAS_{1j} \cdot PAS_{2j} \cdot PAS_{3j} \cdot \ldots\ldots\ldots)$

For combination regimens, susceptibility rates were calculated as the prevalence of strains susceptible to either one of the agents in the combination. These prevalence-adjusted susceptibility rates for combination therapies were then used as previously described by equation (2), to calculate the corresponding expected empiric coverage rates for the combination therapies.

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RESULTS

- *S. aureus* was the most frequently isolated pathogen in all countries (33.3 - 48.1%). *E. coli* (11.3-12.8%) and *P. aeruginosa* (11.0 -12.6%) were the second and third most common pathogens in Germany and Spain, while *P. aeruginosa* (9.4%) ranked second and enterococci (8.8%) third in the USA (Table 1).
- The prevalence of MRSA as a cause of cSSSI varied significantly among the countries evaluated. While in Germany only 1.2% of all SSSI were caused by MRSA, this pathogen was responsible for 20.9% of the cases from the USA (Table 1).
- The highest rate of MRSA was observed in the USA (43.5%); while Germany was characterized by the lowest MRSA rate (3.6%) among the three countries evaluated.
- Tigecycline, vancomycin and linezolid were the most active compounds against Gram-positive pathogens, which represented over 60% of pathogens evaluated. More than 99% of staphylococci (including MRSA) and streptococci were susceptible to these three antimicrobials (Table 2).
- Tigecycline and imipenem were the most potent compounds against *E. coli.* Tigecycline was active against most Gram-negative pathogens except *P. aeruginosa* (9.4 - 12.6% of cSSSI pathogens across the three countries) and *P. mirabilis* (2.7 - 6.2%).
- Piperacillin/tazobactam (75.9 - 96.7% susceptibility) and imipenem (72.4 - 93.3%) were the most active antimicrobials when tested against *P. aeruginosa.*
- The expected coverage of vancomycin plus imipenem or vancomycin plus piperacillin/tazobactam were the highest among all eleven potential empiric regimens in all three countries evaluated (>95%; Table 3).
- Among the eight monotherapy regimens evaluated, tigecycline emerged with the highest overall expected empiric coverage in the USA (90.6%) and also showed excellent results in Germany (87.8%) and Spain (85.1%; Table 3). Tigecycline, like in the USA, demonstrated the highest overall expected empiric coverage in France (90.0%) and Italy (83.4%) in a previous study (data not shown).
- The overall expected empiric coverage of monotherapy regimens was significantly influenced by the frequency of occurrence (prevalence) of the pathogens. Piperacillin/tazobactam and imipenem showed the highest overall expected empiric coverage against cSSSI isolates in Germany (92.9 - 93.1%) and Spain (85.5 - 87.7%), where *P. aeruginosa* prevalence was relatively high (11.0 - 12.6%) and the corresponding MRSA rates were low (3.6 - 17.3%).

Table 1. Prevalence of the most commonly isolated SSSI bacterial pathogens in each country evaluated.

	Rank (No. of isolates/% of total)		
Organism	Germany[a]	Spain	USA
S. aureus	1 (192 / 35.1%)	1 (156 / 33.3%)	1 (2,248 / 48.1%)
Oxacillin-susceptible	(185 / 33.8%)	(129 / 27.5%)	(1,269 / 27.2%)
Oxacillin-resistant	(7 / 1.2%)	(27 / 5.8%)	(979 / 20.9%)
E. coli	2 (62 / 11.3%)	2 (60 / 12.8%)	4 (307 / 6.6%)
P. aeruginosa	3 (60 / 11.0%)	3 (59 / 12.6%)	2 (440 / 9.4%)
Enterococci	4 (35 / 6.4%)	8 (19 / 4.1%)	3 (412 / 8.8%)
Klebsiella spp.	5 (29 / 5.3%)	6 (24 / 5.1%)	7 (186 / 4.0%)
CoNS[b]	6 (28 / 5.1%)	7 (21 / 6.2%)	9 (99 / 2.1%)
P. mirabilis	7 (22 / 4.0%)	5 (29 / 6.2%)	8 (127 / 2.7%)
ß-haemolytic streptococci	9 (17 / 3.1%)	-	6 (195 / 4.2%)
Enterobacter spp.	10 (17 / 3.1%)	4 (40 / 8.5%)	5 (219 / 4.7%)
Total[c]	547	469	4,674

a. *Acinetobacter* spp. was the eighth most frequently isolated pathogen in Germany (21 / 3.8%).
b. CoNS = coagulase-negative staphylococci.
c. Total number of strains analyzed in each nation.

Table 3. Expected coverage/success rate of select antimicrobial regimens commonly used for empiric treatment of cSSSI.

	Overall expected coverage (%)		
Antimicrobial regimens	Germany	Spain	USA
Tigecycline	87.8	85.1	90.6
Vancomycin	66.9	59.5	73.4
Linezolid	66.9	59.5	74.4
Levofloxacin	88.3	84.6	75.7
Piperacillin/tazobactam	93.1	85.5	74.5
Imipenem	92.9	87.7	73.2
Cefazolin	72.3	62.7	59.3
Ceftriaxone	78.4	71.8	63.0
Vancomycin plus piperacillin/tazobactam	98.2	95.8	95.7
Vancomycin plus levofloxacin	95.5	93.1	93.8
Vancomycin plus imipenem	98.0	98.3	97.5

CONCLUSIONS

- *S. aureus* represented the leading cause of cSSSI in all countries monitored, but with a substantial variation of the MRSA rate (range, 3.6% in Germany to 43.5% in the USA).
- Our results revealed that tigecycline, with broad spectrum coverage against both Gram-positive and most Gram-negative organisms, provides excellent empiric coverage for cSSSI.
- Among all evaluated antimicrobial regimens, combination therapy (including vancomycin and agents with broad-spectrum against Gram-negative pathogens, such as imipenem and piperacillin/tazobactam) emerged consistently with the highest levels of expected coverage.
- Better knowledge of expected empirical coverage based on local microbiological trends and susceptibility patterns can provide important guidance for the selection of empiric antimicrobial therapy and greatly influence clinical outcomes.

Table 2. Antimicrobial susceptibilities of prevalent bacterial pathogens from SSSI when testing tigecycline and selected antimicrobials.

	% Susceptible[a] (no. tested)		
Pathogen/pathogen group	Germany	Spain	USA
Oxacillin-susceptible *S. aureus*	(185)	(129)	(1,269)
Tigecycline[b]	99.4	99.2	99.5
Piperacillin/tazobactam	100.0	100.0	99.9
Oxacillin	100.0	100.0	100.0
Cefazolin	100.0	100.0	99.7
Ceftriaxone	100.0	100.0	99.4
Ceftazidime	87.6	95.3	92.6
Levofloxacin	89.7	96.9	94.7
Clindamycin	94.1	99.2	95.7
Linezolid	100.0	100.0	100.0
Vancomycin	100.0	100.0	100.0
Imipenem	100.0	100.0	100.0
Oxacillin-resistant *S. aureus*[c]	(7)	(27)	(979)
Tigecycline[b]	100.0	100.0	99.1
Levofloxacin	28.6	3.7	29.1
Clindamycin	14.3	74.1	50.7
Linezolid	100.0	100.0	100.0
Vancomycin	100.0	100.0	100.0
P. aeruginosa	(60)	(59)	(440)
Tigecycline[d]	7.1[d]	5.3[d]	24.5[d]
Piperacillin/tazobactam	91.7	93.2	90.2
Cefazolin	0.0	0.0	0.0
Ceftriaxone	5.0	6.8	5.2
Ceftazidime	86.7	88.1	89.1
Imipenem	83.3	89.8	90.2
Levofloxacin	70.0	84.7	76.1
Gentamicin	86.7	86.4	89.3
Enterococcus spp.	(35)	(19)	(412)
Tigecycline[b]	93.9	78.9	88.1
Piperacillin/tazobactam[e]	88.6[e]	100.0[e]	84.2[e]
Ampicillin	88.6	100.0	84.2
Levofloxacin	74.3	84.2	53.2
Linezolid	100.0	100.0	99.8
Vancomycin	100.0	100.0	84.2

	% Susceptible[a] (no. tested)		
Pathogen/pathogen group	Germany	Spain	USA
E. coli	(62)	(60)	(307)
Tigecycline[b]	100.0	100.0	100.0
Piperacillin/tazobactam	98.4	93.3	95.1
Cefazolin	91.9	71.7	83.1
Ceftriaxone	100.0	85.0	93.8
Ceftazidime	98.4	88.3	93.8
Amoxicillin/clavulanate	79.0	71.7	75.9
Levofloxacin	91.9	70.0	83.4
Imipenem	100.0	100.0	100.0
Enterobacter spp.	(17)	(40)	(219)
Tigecycline[b]	100.0	100.0	94.0
Piperacillin/tazobactam	94.1	95.0	84.9
Cefazolin	0.0	5.0	4.2
Ceftriaxone	94.1	94.1	83.1
Ceftazidime	100.0	95.0	80.8
Amoxicillin/clavulanate	0.0	0.0	5.0
Imipenem	100.0	100.0	99.1
Levofloxacin	100.0	100.0	95.9
Gentamicin	100.0	100.0	92.2
ß-haemolytic streptococci	(3)		(195)
Tigecycline[b]	100.0	-	100.0
Piperacillin/tazobactam[f]	100.0[f]	-	100.0f
Penicillin	100.0	-	100.0
Clindamycin	100.0	-	92.8
Levofloxacin	100.0	-	99.5
Linezolid	100.0	-	100.0
Vancomycin	100.0	-	100.0

	% Susceptible[a] (no. tested)		
Pathogen/pathogen group	Germany	Spain	USA
Klebsiella spp.	(29)	(24)	(186)
Tigecycline[b]	100.0	100.0	95.2
Piperacillin/tazobactam	96.6	83.3	90.9
Cefazolin	82.8	87.5	75.8
Ceftriaxone	96.6	100.0	91.4
Ceftazidime	100.0	100.0	88.7
Amoxicillin/clavulanate	89.7	79.2	86.0
Imipenem	100.0	100.0	98.9
Levofloxacin	100.0	100.0	89.8
Gentamicin	96.6	100.0	90.9
P mirabilis	(22)	(29)	(127)
Tigecycline[b]	64.7	66.7	76.5
Piperacillin/tazobactam	100.0	100.0	99.2
Cefazolin	81.8	82.8	92.1
Ceftriaxone	95.5	100.0	100.0
Ceftazidime	95.5	100.0	100.0
Amoxicillin/clavulanate	90.9	100.0	97.6
Levofloxacin	95.5	93.1	88.2
Imipenem	95.5	100.0	100.0
Gentamicin	95.5	93.1	92.1
CoNS[g]	(28)	(21)	(99)
Tigecycline[b]	96.3	95.2	98.7
Imipenem	96.4	90.5	86.9
Oxacillin	35.7	14.3	25.3
Levofloxacin	67.9	61.9	51.5
Clindamycin	78.6	90.5	66.7
Linezolid	100.0	100.0	100.0
Vancomycin	100.0	100.0	100.0

a. Utilizing CLSI (2006) breakpoints, where available.
b. Based on USA-FDA breakpoints (Package Insert, 2005).
c. Oxacillin-resistant (MRSA) strains were considered resistant to cefazolin, ceftazidime, ceftriaxone, imipenem, and piperacillin/tazobactam.
d. According to USA-FDA breakpoints established for Enterobacteriaceae.
e. Susceptibility predicted by ampicillin results.
f. Susceptibility predicted by penicillin results.
g. Susceptibility rates to cefazolin, ceftazidime, ceftriaxone, imipenem and piperacillin/tazobactam were predicted by oxacillin results.