

Re-defining tigecycline therapy

Francesco G. De Rosa¹, Silvia Corcione¹, Giovanni Di Perri¹, Francesco Scaglione²

¹Department of Medical Sciences, University of Turin, Infectious Diseases at Amedeo di Savoia Hospital, Italy;

²Department of Biotechnology and Translational Medicine, University of Milan, Italy

SUMMARY

Tigecycline, the first member of the glycylicyclines, has been approved for complicated skin and soft tissue infections (cSSTIs) and complicated intra-abdominal infections (cIAIs). It has a wide range of activity against Gram-positive and Gram-negative bacteria, including anaerobes. Since its approval, the worldwide clinical use of tigecycline has been heterogeneous, either as a monotherapy or as a part of combination therapy, almost exclusively at the standard dosage, in patients with community-acquired (CA) infections as well as health-care associated (HCA) or nosocomial infections (HA), including infections caused by multidrug-resistant (MDR) bacteria. In recent years, issues and warnings of an increased mortality in these heterogeneous patients treated with tigecycline have been raised by meta-analyses and by regulatory agencies.

Re-defining tigecycline therapy is a proposal, based on epidemiological, clinical, microbiological and pharmacological considerations, to distinguish patients who may be treated with monotherapy, according to the official indications and dosages, from those treated with combination treatment, mostly with high dosages in the setting of nosocomial IAIs, possibly caused by MDR bacteria or as a carbapenem-sparing strategy. Whilst available clinical data and guidelines suggest caution with monotherapy in severe infections, experience worldwide indicates that combination treatment with high-dosage tigecycline is increasingly used.

KEY WORDS: Tigecycline, Complicated skin and soft tissue infections, Complicated intra-abdominal infections, Glycylicyclines, Broad-spectrum antibacterial therapy.

Received January 23, 2015

Accepted March 1, 2015

INTRODUCTION

Tigecycline, the first member of the glycylicyclines, has been approved for complicated skin and soft tissue infections (cSSTIs) and complicated intra-abdominal infections (cIAIs) (European Medicine Agency, 2014). Tigecycline has a wide range of activity against Gram-positive and Gram-negative bacteria, including anaerobes, has a wide volume of distribution and a peculiar mechanism of action, inhibiting bacterial protein synthesis by binding to the 30S ribosomal subunit with five times higher affini-

ty than the tetracyclines (Pankey, 2005; Greer, 2006; Batthacharya *et al.*, 2009).

Notwithstanding the official indications, clinical use of tigecycline has been heterogeneous, including pulmonary and bloodstream infections as well as infections by multi-drug resistant (MDR) bacteria since patients do not fit into clinical protocols (Dryden, 2013; De Pascale *et al.*, 2014). Confusion has been generated by its administration in official indications as well as in complicated respiratory or bloodstream infections, as a monotherapy or as a part of combination therapy, at the standard dosage of 50 mg twice daily or at high dosages (HD) of 100 mg twice daily, in patients with community-acquired (CA) infections as well as health-care associated (HCA) or nosocomial infections (HA). As a consequence, issues and warnings of increased mortality have been raised by meta-analyses calculated on heterogeneous patients with ventilator-associated

Corresponding author

Prof. Francesco G. De Rosa, MD
Department of Medical Sciences
Infectious Diseases at Amedeo di Savoia Hospital
University of Turin
Corso Svizzera, 164 - 10149 Torino, Italy
E-mail: francescogiuseppe.derosa@unito.it

pneumonia (VAP), hospital-acquired pneumonia (HAP), diabetic foot infections, infections by MDR bacteria and shock not better defined (FDA, 2010; European Medicine Agency, 2011; European Medicine Agency, 2014).

In Europe, the benefit/risk evaluation of the European Medicines Agency's (EMA) Committee stated that the benefits of tigecycline treatment continue to outweigh its risks, but recommended that the product information be changed to ensure appropriate use by making prescribers aware of an increased mortality in clinical studies (Dryden, 2013; European Medicine Agency, 2014). Subsequently, the FDA conducted another meta-analysis in September 2013 with 10 clinical trials including only the approved use of tigecycline, which showed an increased mortality with an adjusted risk difference of 0.6% (FDA, 2013; Dixit *et al.*, 2014). A boxed warning was issued for the antibiotic, cautioning administration either for approved and unapproved indications (FDA, 2013). In a critical safety review the increased mortality with tigecycline was not well understood and the authors reviewed the side-effects and drug interactions of tigecycline (Kaewpoowat *et al.*, 2014).

Therefore, a basic question concerns the future of tigecycline (Bassetti *et al.*, 2014). From this viewpoint, we propose some considerations to re-define the clinical use of tigecycline as monotherapy or combination treatment based on epidemiological, microbiological, pharmacological and clinical considerations.

MICROBIOLOGICAL ACTIVITY

The spectrum of activity of tigecycline encompasses the spectrum of community and nosocomial infections, including a broad range of Gram-positive and Gram-negative bacteria as well as anaerobes, 'atypical' bacteria (*Mycoplasma*, *Legionella* and *Chlamydia* species) and many species of multidrug-resistant bacteria such as methicillin-resistant Staphylococci, vancomycin-resistant Enterococci, MDR *Acinetobacter baumannii* and *Klebsiella pneumoniae* carbapenemase producing *K. pneumoniae* (KPC-Kp). Tigecycline is not active against *Pseudomonas aeruginosa* and *Proteus spp.*, *Morganella*

and *Providencia* species (Bradford *et al.*, 2005; Pankey, 2005; Greer, 2006; Bhattacharya *et al.*, 2009). Tigecycline has a low minimum inhibitory concentration against *C. difficile* in vitro and may be able to alter the pathogenesis of the disease in a mouse model of *C. difficile* infection (Theriot *et al.*, 2014). The microbiological activity is coupled with a novel mechanism of action that does not stimulate any induction of resistance to other classes of antibiotics (European Medicines Agency, 2014). This feature has been adapted to "carbapenem-sparing" treatment strategies where carbapenemase-producing bacteria such as KPC-Kp are an issue (Sbrana *et al.*, 2013).

The carbapenem-sparing strategy is also useful in reducing the selective pressure of carbapenems in hospitals with a high prevalence of ESBL production amongst Gram-negative bacteria (Garau, 2008). As far as tigecycline is concerned, HD was mostly given at 100 mg twice daily and interestingly, there are data showing *in vivo* bactericidal activity of HD tigecycline against ESBL-producing *K. pneumoniae* (Michail *et al.*, 2013; De Pascale *et al.*, 2014).

Pharmacokinetics and pharmacodynamics

The safety and tolerability of tigecycline administered as single or multiple doses or at various infusion rates were explored in three phase 1, randomized, double-blind, placebo-controlled studies in healthy subjects (Muralidharan *et al.*, 2005). No serious adverse events were reported in any of the three studies. The most common dose-related adverse events reported were nausea and vomiting, which are common to the tetracycline class of antibiotics. At the higher doses (200 and 300 mg), prolonging the infusion duration to 4 hours did not improve the incidence or severity of nausea, indicating that the nausea is not directly related to the C_{max} of the drug in serum. Also, the nausea and vomiting diminished when the 200 mg dose was administered to fed subjects rather than to those fasting. However, there are multiple reports of safety of HD tigecycline with appropriate dilutions and slow infusion, especially in the critical care setting (De Pascale *et al.*, 2014). Recent data show that tigecycline was associated with decreased fibrinogen levels, which was reversible after cessation of treatment and the HD

group of patients had greater decreases than those given the normal dose, without any effect of age (Zhang *et al.*, 2014).

Given at the standard approved dose of 100 mg followed by 50 mg every twelve hours, tigecycline has relatively low mean steady-state serum concentrations of 0.403 mg/L and 0.633 mg/L in subjects with complicated skin and soft tissues infection (cSSTI) included in phase 2 and 3 studies, respectively (Postier *et al.*, 2004). The half-life ($t_{1/2}$) in humans is relatively long, ranging from 37 to 67 hours in healthy volunteers, probably because of its large volume of distribution (Muralidharan *et al.*, 2005).

The pharmacokinetics of tigecycline was recently evaluated in obese versus normal weight healthy adult volunteers after a single intravenous dose of 100 mg administered in 30 minutes. The serum concentration-time profiles and exposures were similar in the obese and normal weight adults, with a mean urine recovery of 15.8% and 13.4%, respectively (Pai, 2014). The median (range) $AUC_{0-\infty}$ was 8.19 (6.12, 11.2) and 7.50 (6.78, 9.13) mg*h/L in the obese and normal weight groups, respectively. The clearance of tigecycline was not related to the total body weight (TBW). Tigecycline distributes widely into various fluids and tissues, such as lungs, skin, liver, heart, and bone (Table 1).

Tigecycline concentrations were measured in patients four hours after the administration of a single 100 mg dose (Rodvold *et al.*, 2006). The

ratio of tissue:serum was 38-fold in the gallbladder, 8.6-fold in the lungs, 2.1-fold in the colon, 0.35-fold in the bone, and 0.58-fold in the synovial fluid.

Tissue distribution in bone was recently reassessed. Serum and bone AUC for the given dose interval (AUC_{τ}) values were 2,402 ng h/mL and 11,465 ng h/g, and maximum concentration (C_{max}) values were 974 ng/mL and 2,262 ng/g, respectively. The bone to serum ratio calculated using the AUC_{τ} values was 4.77, confirming tigecycline penetration into bone (Bhattacharya *et al.*, 2014).

Tigecycline had a 74% (mean) penetration into the blister fluid (relative to serum) in a cantharidin ointment-induced blister model in healthy subjects receiving seven standard doses of tigecycline (Sun *et al.*, 2005). However, higher concentrations of tigecycline in skin and soft tissue than in the serum at the same time point after 1 to 6 days of standard treatment were recently found. The mean tissue:serum ratios at the three study time periods were 3.8 (range 0.7-5.5), 5.2 (range 0.8-7.1) and 2.8 (range 0.8-8.8) (Stein *et al.*, 2011).

Tigecycline has a moderate degree of plasma protein binding (approximately 68%). Repeated daily administration results in minimal accumulation. As the predominant component in serum, urine, and faeces is unchanged, tigecycline drug metabolism is limited. Glucuronidation and amide hydrolysis, followed by

TABLE 1 - Concentrations of tigecycline in serum, tissues and body fluids after a 100 mg dose of tigecycline.

Site and Sampling Time	Serum, mg/L*	Site, mg/L or mg/kg*	Reference
Bone (2-12 hours)	0.974	0.898 (0.26-2.26)	Bhattacharya <i>et al.</i> , 2014.
Bile			
12 hours	0.093±0.024	148.1±155.4	
24 hours	0.066±0.016	55.8±50.5	
Gallbladder			
12 hours	0.093±0.024	7.29±7.88	
24 hours	0.066±0.016	2.52±3.19	Rodvold, <i>et al.</i> , 2009.
Colon			
12 hours	0.139±0.037	1.30±2.43	
24 hours	0.078±0.029	0.575±0.485	
Lung			
12 hours	0.083±0.007	0.380±0.260	
24 hours	0.088±0.103	0.401±0.222	
Skin			
3 hours	0.56±0.25	2.128 (0.39-3.08)	Stein <i>et al.</i> , 2011
9 hours	0.26±0.12	0.728 (0.20-2.28)	

*Data are expressed as mean ± standard deviation or (range).

N-acetylation, are the main metabolic pathways in humans, and the predominant mode of excretion is via the biliary/faecal route (Zhanel *et al.*, 2006).

Tigecycline has been the subject of several pharmacokinetic-pharmacodynamic (PK/PD) analyses, using data from animal infection models as well as data from clinical trials of patients suffering from cSSSI infections or those with cIAIs (Van Ogtrop *et al.*, 2000; Meagher *et al.*, 2007; Passarell *et al.*, 2008). These analyses indicate that the ratio AUC:MIC for serum tigecycline concentration is a predictor of therapeutic response.

Particularly in patients with cSSTI, the classification-and-regression-tree (CART) analysis-identified AUC₂₄/MIC breakpoint of 17.9 was a statistically significant predictor of clinical outcome ($p=0.0376$) (Meagher *et al.*, 2007). When exposure-response analyses were performed in cIAIs, CART analyses identified a significant AUC:MIC breakpoint of 6.96 for microbiological and clinical responses (p values of 0.0004 and 0.399, respectively) (Passarell *et al.*, 2008). More recently, the influence of a number of factors, including adequate antibacterial therapy, on the clinical response of patients with IAIs treated with tigecycline at standard dose was demonstrated. Of the six significant factors identified, an AUC:MIC ratio of >3.1 was found to be the most important factor in determining outcome. Most importantly to consider, this was the only factor that is amenable to intervention by the clinician.

So far, pharmacological parameters may explain why in one phase III cSSTIs study there were lower rates of clinical cure and microbiological eradication in the microbiologically evaluable population at the test-of-cure (Beedt *et al.*, 2005).

An *in vitro* pharmacodynamic model simulating exposures likely to occur in the epithelial lining fluid of patients with pneumonia showed that tigecycline had little activity against KPC-Kp isolates when simulated alone or in combination with rifampin. In contrast, a statistically significant synergistic antimicrobial effect was noted when tigecycline and meropenem were simulated together for KPC-Kp isolates with MICs of ≤ 2 and ≤ 16 $\mu\text{g/ml}$, respectively (Wiskirchen *et al.*, 2011).

TIGECYCLINE IN CLINICAL PRACTICE

Tigecycline is approved in Europe for the treatment of cSSTIs and cIAIs with supporting studies of non-inferiority (Table 2). After its introduction in clinical practice, the novel mechanism of action and the activity against MDR bacteria were mostly intended as a new weapon, as empiric and targeted treatment, against difficult-to-treat infections.

Numerous papers were published on the microbiology and treatment of critically ill patients as well as patients with cancer or multiple organ failures, generating confusion with the official indications (Table 3). A clinical puzzle was built, with pieces made from epidemiological settings, monotherapy or combination therapies, primary or salvage treatment with standard dosage or in a variety of HD syndromes and critical illnesses. In a recent paper by Montravers *et al.* on real-life experience with tigecycline in 254 patients with cSSTI in four countries, there were 112 (44.4%) first-line treatments and monotherapy was used in 181 patients (71.8%) (Montravers *et al.*, 2013). When used as monotherapy, treatment success was reported in 86.7% of cases, and a less favorable clinical outcome amongst patients who received combination therapy could be explained by a potential bias within the groups (Montravers *et al.*, 2013).

The first experience outside of the official indications in surgical critically ill patients with severe sepsis and septic shock was reported in a surgical ICU by Swoboda *et al.* (2008). The authors retrospectively analysed 70 patients (cancer: 51%; renal replacement therapy: 57%; mean APACHE II score at admission: 27; intra-abdominal infection: 50%). As many as 76% of patients received tigecycline in combination, mainly with a carbapenem, and 64% were treated as a second line. Overall, tigecycline resulted in markedly reduced mortality (Swoboda *et al.*, 2008).

In a prospective observational study in 26 French ICUs, a total of 156 patients with several syndromes were treated with tigecycline and 53% had a SOFA score ≥ 7 and 93% had received other anti-infective agents (Montravers *et al.*, 2014). Tigecycline was given at standard dosage in 97% of patients and in combination in 65%

of them; the global success rate was 60% at the end of treatment and the survival rate at day 28 was 85% in the whole cohort and significantly higher in the less severely ill patients.

There also are numerous papers reporting tigecycline administration and success or failure in a variety of diseases, including VAP and complicated nosocomial intra-abdominal infections (IAIs) caused by MDR Gram-negative bacteria including Enterobacteriaceae, *P. aeruginosa*, *Acinetobacter* spp. and *S. maltophilia* (Table 3).

The main result was that confusion was generated by mixing different syndromes, empiric and targeted treatment, different severity of diseases, monotherapy and combination treat-

ment. Eventually, this substantial heterogeneity was taken as a substrate for meta-analysis.

META-ANALYSES OF EFFICACY AND SAFETY

Meta-analyses are powerful tools to solve a clinical problem, but there is no universal agreement on their theoretical validity, practical application or interpretation (Piantadosi, 2000). Critical points are represented by the baseline heterogeneity of included studies, with conclusions that may be weak or strong depending on these studies, by the definition of "treatment", and the methods used to synthesize the

TABLE 2 - Pivotal clinical studies with tigecycline in complicated skin and skin structure infection (cSSSI) and complicated intra-abdominal infections (cIAIs).

Author	Type of infection	No. patients	Drug regimen		Outcome
			Tigecycline	Comparator	
Ellis-Grosse <i>et al.</i> , 2005	cSSSI (polymicrobial etiology, need for surgical intervention, suspected or confirmed deep soft tissue involvement and/or comorbidities)	1116	100 mg, followed by 50 mg IV twice daily. (N = 556)	Vancomycin (1 g IV twice daily) plus aztreonam (2 g IV twice daily). (N = 550)	Clinical responses to tigecycline and comparators at test-of-cure were similar (86.5% versus 88.6% in clinically evaluable population) as well as overall eradication rate of MRSA (78.1% and 75.8% respectively) and adverse events
Babinchak <i>et al.</i> , 2005	cIAI (requiring a surgical procedure for an intra-abdominal abscess or peritonitis associated with an abscess or perforation)	1642	100 mg, followed by 50 mg IV every 12 h. (N = 817)	Imipenem-cilastatin 500/500 mg IV every 6 h. (N = 821)	Small proportion of patients with APACHE II >15 (22 [3.5%] tigecycline vs. 13 [2.1%] imipenem/cilastatin). Clinical cure and eradication rates in the evaluable population were similar in the two groups. 9/117 <i>E. coli</i> were found to produce ESBL, with tigecycline MIC range equivalent to non-ESBL producer strains. 7 (78%) of 9 patients with ESBL-producing <i>E. coli</i> achieved clinical cure or eradication after tigecycline.

TABLE 3 - Clinical heterogeneity of real-life treatment with tigecycline.

Study, (no. patients)	Type of infections, (no. patients)	Pathogens	Treatments [M=monotherapy; C=combination; (no. pts)]	Dosage (S=standard H=high)	Outcomes
Scahfer <i>et al.</i> , 2007. Retrospective, (25).	VAP (22, 3 with BSI), BSI (3) 60% surgical	MDRAB 30% TG-IR, 5% TG-R	M (5) C (20)	S	Resolution 84%; microbial eradication 80%
Swoboda <i>et al.</i> , 2008 Retrospective, (70).	cIAI (40, 10 + HAP), HAP (12) BSI (2), UTI (2), cSSTI (6), bone and joint (1), unknown (2)	Gram-positive (58) <i>S. maltophilia</i> (13), <i>A. baumannii</i> (1), <i>E. cloacae</i> (1), <i>B. cepacia</i> (1)	M (1) C(44)	S	30% ICU mortality (Outcomes of Gram-negative infections cannot be separated)
Vasilev <i>et al.</i> , 2008 Prospective, open non comparative phase III, (34).	cSSTI (24) cIAI (5), HAP (5), CAP (1), BSI (1)	<i>A. baumannii</i> (17), <i>K. pneumoniae</i> (6), <i>E. coli</i> (9), Enterobacter spp., (4)	M(34)	S	Clinical cure 72.2%; microbiological cure 66.7%. <i>A. baumannii</i> infections clinical cure 82.4%; microbiological cure 64.7%
Anthony <i>et al.</i> , 2008 Retrospective, (18; 19 infections).	VAP (6, 3 with empyema), HAP (2), BSI (1), UTI (2), tracheobronchitis (2), mediastinitis with secondary BSI (1), other (4)	10 MDRAB; 44% TG-S, 56% TG-IR <i>6 K. pneumoniae</i> (4 ESBL+, 1 ESBL + KPC-Kp), 2 <i>E. cloacae</i> , 1 <i>E. coli</i> (KPC-Kp)	M (9) C (9)	S	Positive clinical response 50%, uncertain 10%, survival 60%; all deaths related to infection with TG-IR pathogens; microbiological response in 75%; emergence of resistance in 1 patient
Gallagher <i>et al.</i> , 2008. Retrospective, (28; 29 infections).	HAP (17, 2 with BSI), BSI (4), UTI (3), IAI (1), wound infection (3), tracheobronchitis (1)	29 <i>A. baumannii</i>	M (12) C (17)	NA	28% positive clinical outcome; 44 % microbiological eradication; 62% negative outcome, 68% mortality (19 patients, attributable in 15/19 patients); Clinical and microbiological outcomes associated significantly
Curcio <i>et al.</i> , 2009. Prospective noncomparative, (75).	VAP (6 with BSI)	<i>A. baumannii</i> . 44/73 IMP-S, 29/73 only COL-S/TG-S	22 patients no other antibiotics or 48 h (37% concomitant anti-pseudomonal treatment)	NA	69.9% clinical success. Success in 2/6 bacteraemic infections. 33% crude mortality
Gordon <i>et al.</i> , 2009. Retrospective, (34).	IAI (6, 1 + HAP, 3 + VAP), HAP (8), BSI (9, 7 + other), bone and joint and cSSTI (10), intracranial (1)	<i>A. baumannii</i> (19), mixed with <i>A. baumannii</i> (15)	M (12) C (22)	S	68% positive clinical outcome; 29.4% microbiological eradication; 56% positive results in bacteraemia. Mortality: overall 41%, attributable 26.4%; 3 breakthrough BSI (1 with resistance)
Poulakou <i>et al.</i> , 2009 Retrospective, (45).	VAP/HCAP (21, 2 with BSI), BSI (10), SI (14)	<i>A. baumannii</i> (26 MDR, 2 PDR, all CRB-R) TG MIC 1–8 mg/L, <i>K. pneumoniae</i> (20 MDR, 3 PDR), TG MIC 1–3 mg/L, Enterobacteriaceae (3)	M (22) C (23)	S	Clinical success: VAP 90%, BSI 80%, SI 64.3%, monotherapy group 81.8%, combined therapy group 78.3 %, 4 breakthrough Gram- negative BSI (1 with emergence of resistance), 10 superinfections from microorganisms inherently resistant to TG

Study, (no. patients)	Type of infections, (no. patients)	Pathogens	Treatments [M=monotherapy; C=combination; (no. pts)]	Dosage (S=standard H=high)	Outcomes
Jamal <i>et al.</i> , 2009 Retrospective, (24).	HAP/VAP (5), BSI (9), CR-BSI (1), UTI (2), cSSSI (1)	MDRAB [1st outbreak isolates meropenem- susceptible (MIC 2–3 mg/L)]. TG MIC 0.75–2 mg/L	First outbreak: start with combination, switch to MER Second and third outbreaks: TG monotherapy	S	First outbreak 6 patients, 50% mortality, time to pathogen clearance 8.3 days; Second outbreak: 12 patients, 8.6% mortality, time to clearance 2.8 days; Third outbreak: 6 patients 0% mortality; time to clearance 3.1 days
Freire <i>et al.</i> , 2010 Phase 3, multicentre, randomized, double-blind study, (945).	Non-VAP (27), VAP (40)	67 <i>A. baumannii</i> (MIC range 0.12–8 mg/L)	TG plus optional adjunctive therapy with CAZ or IMP and optional adjunctive therapy with VAN An AMG was permitted for double coverage against <i>P.</i> <i>aeruginosa</i>	S	Cure rates 67.9% for TG and 78.2% for IMP (CE patients) and 62.7% and 67.6% (c-mITT patients), respectively; Overall mortality: TG 14.1%, IMP 12.2% (more deaths occurred in VAP treated with TG (NS). Overall TG was noninferior to IMP for the c-mITT but not the CE population; this difference appears to have been driven by results in VAP patients. <i>A. baumannii</i> infections, clinical response: non- VAP TG 90% IMP 70.6%; VAP TG 57.1% IMP 94.7%. Eradication of <i>A.</i> <i>baumannii</i> at test of cure: 71%
Metan <i>et al.</i> , 2010. Retrospective, (21).	SI, VAP	18 <i>A. baumannii</i> infections, 3 mixed	M (7) C (14)	NA	Clinical success 80.95%; 14-day attributable mortality 9.5%; Crude 30-day mortality 19.1%: SI better outcomes
Kuo <i>et al.</i> , 2011 Retrospective, (66).	Group 1, FDA-approved indications (12); Group 2, HAP (38); Group 3, UTI (4), osteomyelitis (4), CRBSI (3), BSI (3), 57.6% ICU patients	25 MDRAB. <i>K.</i> <i>pneumoniae</i> , <i>Citrobacter</i> spp., <i>Serratia</i> spp., <i>S. maltophilia</i> , <i>P. aeruginosa</i> , <i>Providencia stuartii</i>	Combinations (65,1%) MDRAB: 10 TG monotherapy, 15 combination therapy	S	Positive clinical outcome 30.3%; higher clinical success rate for group 1 than 2 (higher disease severity and risk factors in group 2); MDRAB infections: positive clinical outcome 12%; microbiological eradication in only 1 patient; 18 persistent infections and four superinfections. Hospital mortality 68%. VAP by MDRAB: success rate 5.6%
Ye <i>et al.</i> , 2011 Retrospective, (112).	116 pneumonia involving <i>A. baumannii</i> ; 10 with bacteraemia	Monomicrobial <i>A. baumannii</i> pneumonia in 26.7%; polymicrobial 73.3% (30.2% with gram(+) and 56.7% with gram(-)	Combinations (62.1%) Monomicrobial (31): 9 TG monotherapy and 22 combination therapy Polymicrobial (85): 35 TG monotherapy and 50 combination therapy	S	Monomicrobial MDRAB pneumonia: significantly lower clinical resolution rate than polymicrobial (45.2 vs. 65.9%; no difference with monotherapy). Among 6 episodes with MDR bacteraemia only those with tigecycline MIC B 1 mg/L survived. 30-day mortality 36.2%
Guner <i>et al.</i> , 2011 Retrospective, (33).	VAP (19), BSI (11), SSI (2)	MDRAB or polymicrobial infection involving MDRAB	M (2) C (31)	S	Positive clinical outcome 63.63%; 30-day overall mortality 57.6%; Attributable mortality 24.2%; Superinfections 39.3%

→

Study, (no. patients)	Type of infections, (no. patients)	Pathogens	Treatments [M=monotherapy; C=combination; (no. pts)]	Dosage (S=standard H=high)	Outcomes
Ku <i>et al.</i> , 2012 Retrospective, (106).	CR-BSI (9), HAP/VAP (50), UTI (14), SSTI (22)	82 <i>A. baumannii</i> , 12 CRE, 12 mixed (82% isolates non susceptible to TG)	M (16) Colistine monotherapy 71 C (19)	S	Patients colistin COL alone o + TG: more likely to die than only TG (37% vs 0%); Colistine: higher severity of acute illness and delays in initiation of effective antimicrobial therapy
Moon <i>et al.</i> , 2012 Retrospective, (108).	HAP (44), SSI (22), cIAI (18), BSI (5), non-ICU population	<i>A. baumannii</i> 50.3%, <i>S. aureus</i> 10.3%, <i>K. pneumoniae</i> 7.9%, Enterococcus spp. 6.7%, <i>E. coli</i> 5.5%, <i>P. Aeruginosa</i> 4.9%	M (71) C (27)	NA	Overall 30-day mortality 52.9%;30- day mortality of HAP 60.5%; 30- day mortality of Acinetobacter spp. infection 59.4 %; Superinfection: 29.6% (mostly <i>P. aeruginosa</i>)
Kim <i>et al.</i> , 2013 Retrospective, (9).	BSI 9	<i>A. baumannii</i> CRB-R and COL-S, TG-S	M (1) C (8)	S	Attributable mortality 55.5%; All- cause hospital mortality 66.7%
Lee <i>et al.</i> , 2013 Retrospective, (386).	HAIs	MDRAB	TG 266 patients (108 monotherapy, 158 combinations) non-TG 120 patients	S	TG vs non-TG groups; not significantly different number of infection-related deaths, length of hospital stay, or length of ICU stay and survival rates. Unfavourable outcomes significantly lower in the TG group than in the non-TG group (30.8% vs 50%). The most significant predictors of favourable outcomes: TG treatment and microbial eradication
Ramirez <i>et al.</i> , 2013 Phase II study high doses TG in combination (105).	HAP/VAP	8 <i>A. baumannii</i> , 15 Enterobacteriaceae, 3 <i>Haemophilus</i> spp., 23 <i>S. aureus</i>	C (105)	H	Clinical cure with TG 200 mg/day (85.0%) was numerically higher than with tigecycline 150 mg/day (69.6%) and imipenem (75.0%)
Bassetti <i>et al.</i> , 2013. Observational multicentre registry (1,782).	cSSTI (254), cIAI (785), pneumonia, BSI, sepsis, ICU admission heterogeneous	At least 1 resistant pathogen: cSSTI 30.5% cIAI 17.5%	M (50) Combinations: 175 TG-based	S	Clinical response rates with TG alone or in combination: cSSTIs 79.6% and cIAIs 77.4%; All-cause mortality: cSSTI 9.4%, cIAI 18.7%
Chuang <i>et al.</i> , 2014 Retrospective, (294).	HAP/VAP	MDRAB	Combinations: 17.41 TG-based, 119 colistin-based	S	Significantly higher mortality rate in the TG-based group (60.7%) vs. the COL group (44%); Post hoc analysis: mortality difference in cases with higher tigecycline MIC (2 lg/mL)
Montravers <i>et al.</i> , 2014. Prospective observational multicentre, (156).	IAI (56%), cSSSI (19%), other (25%), bacteraemia in 12% Hospital-acquired (89%), ICU population;	Gram(+) 41.2%; Gram (-) 47.2%; Mixed 18.6%	C (65%)	S	Global success rate 60% (end of treatment; significantly higher with treatment duration more than 9 days (76% vs. 47%) and in patients with BMI B 35 kg/m ² (56 % vs 13 %); Survival rate at day 28, 85% (significantly higher in the less severely ill patients)

MDRAB multidrug-resistant *Acinetobacter baumannii*, VAP ventilator-associated pneumonia, CAP community-acquired pneumonia, HCAP healthcare-associated pneumonia, HAP hospital-acquired pneumonia, UTI urinary tract infection, BSI bloodstream infection, CR-BSI catheter-related BSI, cIAI complicated intra-abdominal infection, cSSTI complicated skin and soft tissue infection, SI surgical infection, MDR multidrug resistant, PDR pandrug resistant, MIC minimal inhibitory concentration, XDRAB extensively drug resistant *A. baumannii*, TG tigecycline, CRE carbapenem-resistant, ESBL extended spectrum beta-lactamase, KPC-Kp carbapenemase-producing *Klebsiella pneumoniae*, NS non-statistically significant.

results, suggesting caution and experience for the applied methods and reporting (Piantadosi, 2000). The meta-analyses published on tigecycline included patients with infectious diseases other than cSSIs and cIAIs, treated with monotherapy or combination therapy, inside and outside the ICU, with empiric and targeted

treatment, including bloodstream infections, HAP and VAP.

All the meta-analyses, summarized in Table 4, concluded that tigecycline should be used with caution or that it should be reserved as a last resort in combination with other antimicrobial drugs. These simple recommendations did not

TABLE 4 - Summary of meta-analyses of tigecycline treatment.

Study	Aim of the study	N. trials/patients	Type of infections	Conclusions
Cai <i>et al.</i> , 2011.	Efficacy and safety of tigecycline and empirical antibiotic regimens in cSSSIs, cIAIs and other infections caused by MRSA or VRE	8 randomized clinical trials, 4,651 patients	cSSIs, cIAIs, Community acquired pneumonia (CAP), MRSA or VRE infections	Tigecycline monotherapy: similar clinical and microbiological success rates, but incidence of adverse events significantly higher than comparator. No significant difference for all-cause mortality and drug-related mortality. Author conclusions: tigecycline monotherapy is as effective as comparison; however, due to high risk for mortality, adverse effects and emergence of resistant isolates, prudence is required
Tasina <i>et al.</i> , 2011	Efficacy of tigecycline for the treatment of adult patients with serious bacterial infection	14 published (N = 10) and unpublished (N = 4) multicentre randomised trials, ≈ 7,400 patients,	cSSIs, cIAIs, CAP, MRSA or VRE infections	Tigecycline efficacy lower than that of comparators (small heterogeneity between studies) but the difference was not significant. Treatment efficacy was not significant for microbiological mITT and microbiologically assessable populations. Adverse events more frequent in the tigecycline group. All-cause mortality was higher for group than comparators (difference not significant).
Yahav <i>et al.</i> , 2011	Comparison of tigecycline with any other antibiotic regimen for the treatment of any infection	15 clinical trials, 7654 patients	cSSIs, cIAIs, CAP, Hospital acquired pneumonia (HAP), MRSA or VRE infections, diabetic foot infections ± osteomyelitis	Overall mortality: higher with tigecycline; clinical failure: significantly higher with tigecycline; microbiological failure non-statistically significant higher. Authors statement: due to the increased mortality, probably explained by decreased clinical and microbiological efficacy, tigecycline monotherapy should be avoided for severe infections and reserved as a last-resort drug.
Prasad <i>et al.</i> , 2012	Comparison of tigecycline with any other antibiotic regimen for the treatment of any infection	13 RCT, 7434 patients	cSSSIs, cIAIs, CAP, HAP, MRSA, VRE, diabetic foot infections	Mortality: Tigecycline versus comparator antibiotics was associated with a 0.7% absolute or 30% relative increase in mortality rates (RR, 1.30; 95% CI, 1.02–1.65; p = .04); Non-cure rates: a significant 2.9% absolute or 12% relative increase (RR, 1.12; 95% CI, 1.02-1.23; p = .02). Subgroup analysis for type of infection: in each type but CAP the non-cure rate was numerically increased with tigecycline.

*McGovern *et al.* pointed out that tigecycline has not been systematically studied and is not indicated in the treatment of septic shock, primary bacteraemia, and urinary tract infection; a clinical trial of tigecycline use in hospital-acquired pneumonia (HAP) failed to meet its primary endpoint and a phase II trial studying two higher doses of tigecycline in this indication was recently terminated due to enrollment difficulties; several trials were not identified and were not included in the analysis.⁶⁹

take into account the complex system of interactions of drug(s)-patient(s)-bacteria. Clearly, one antimicrobial could be less effective than another if a poor clinical outcome may be predicted or if it was not properly dosed; it may be less effective also because it does not reach adequate levels at the site of action, as occurs in critically ill patients when altered pathophysiological conditions increase the volume of distribution or clearance. Adequate dosing is necessary in such different pathophysiological situations.

In almost all studies included in the meta-analyses, tigecycline was used at the fixed standard dose while the doses of the comparators were correctly adjusted on the basis of weight and creatinine clearance or on the basis of other clinical evaluations (Babinchak *et al.*, 2005; Tanaseanu *et al.*, 2008; Chen *et al.*, 2010; Freire *et al.*, 2010).

In particular, the clinical assessment and PK/PD analysis was evaluated in the study of Freire *et al.* (2010) where the efficacy and safety of tigecycline at the usual fixed dosing regimen were compared to imipenem/cilastatin at 500 mg to 1 g intravenously every 8 hours on the basis of clinical judgment, in patients with HA pneumonia. A total of 123 patients died during the study; 66/467 (14.1%) in the tigecycline group and 57/467 (12.2%) in the imipenem/cilastatin group. However, a subanalysis revealed that in non-VAP patients, the mortality was the same in both regimens [41/336 (12.2%) in the tigecycline group and 43/345 (12.5%) in the imipenem/cilastatin group], whereas the mortality in VAP patients was 25/131 (19.1%) and 15/122 (12.3%) in the tigecycline and imipenem/cilastatin groups, respectively. The analysis demonstrated an increased mortality with tigecycline versus comparators in VAP patients. But why were the results different when excluding patients with VAP?

We should answer with data from the PK/PD analysis of tigecycline: the mean AUC_{0-12} were 2.726 and 3.198 mg*h/L ($P < 0.041$) in VAP and non-VAP patients, respectively. The clearance was also faster in VAP patients (23.3 L/h) compared with non-VAP patients (20.7 L/h). Consequently the median $AUC_{0-24/MIC}$ observed in VAP patients was 60% lower ($P < 0.002$) than the value observed in non-VAP patients (1.730

vs 4.389). Moreover, the weight of the patients enrolled in this study was significantly higher in the group treated with tigecycline compared to the group treated with imipenem-cilastatin (Freire *et al.*, 2010). The conclusion is that in the study by Freire *et al.* the lower efficacy and the consequent higher mortality can potentially be explained by the lower drug exposure due to physiological changes that occur in patients with VAP (Freire *et al.*, 2010). The lesson we have learned in the past twenty years is that in critically ill patients, the dose should be adjusted on the basis of pathophysiological changes.

Bhavnani *et al.* evaluated the impact of different factors on the probability of clinical response in tigecycline-treated patients with IAIs, using phase 2 and 3 clinical data (Bhavnani *et al.*, 2010). A final multivariable logistic regression model based on 123 patients demonstrated six factors to be predictive of clinical success: a weight < 94 kg, the absence of *P. aeruginosa* in baseline cultures, an APACHE II score of < 13 , non-Hispanic race, complicated appendicitis or cholecystitis and an AUC:MIC ratio of > 3.1 . These findings demonstrated the impact of individual and multiple factors on clinical response in the context of drug exposure (Bhavnani *et al.*, 2010).

As far as pharmacokinetics and pharmacodynamics is concerned, in his comment on the meta-analysis Scaglione (2011) stated that pathophysiological changes, such as an increased volume of distribution and/or increased clearance, may occur in critically ill patients, and may impact on antibiotic distribution and concentration, resulting in slow and possible incomplete penetration into infected tissues (Scaglione, 2011). For this reason, the dosage of tigecycline may not be adequate in some patients and there is a high probability that the dosing affects mortality, at least in critically ill patients (Scaglione, 2011).

RE-DEFINING TIGECYCLINE THERAPY TREATMENT

Re-defining tigecycline therapy is needed to correctly understand the effects of tigecycline alone or in combination treatment, based on

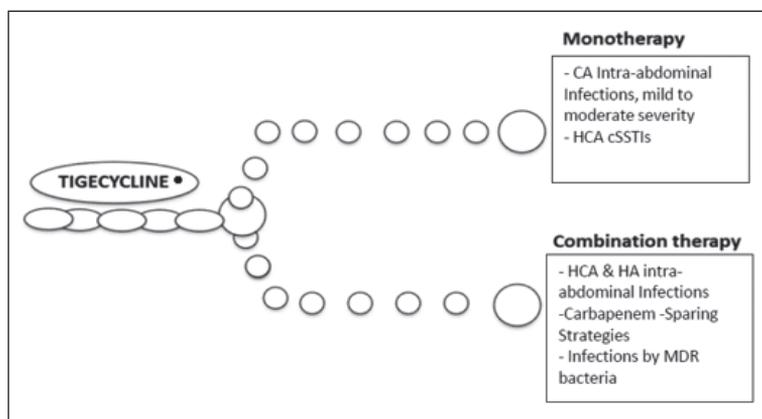


FIGURE 1 - Re-defining tigecycline dividing into monotherapy and combination treatment. Abbreviations: CA = community-acquired; HCA = health-care associated; cSSSI = complicated skin and skin structure Infections; MDR = multi-drug resistant. *The dosage of tigecycline requires careful microbiological, clinical and pharmacological considerations.

epidemiological, pharmacological and clinical characteristics. Monotherapy may be used in official indications in patients with CA infections and selected patients with HCA infections, whilst HD combination therapy is given in a variety of patients with nosocomial and health-care associated infections, as primary or salvage treatment, also as a carbapenem-sparing strategy (Figure 1). Accordingly, data from patients treated with monotherapy or combination therapy should be analysed separately.

The examples for this suggestion come from the official studies in patients with SSTIs and IAIs, clinical experience, as well as from a consensus paper, mostly in patients with IAIs (Sartelli *et al.*, 2011). The use of tigecycline in IAIs is particularly attractive in view of its PK/PD properties and its favourable *in vitro* activity against several ESBL-producing Enterobacteriaceae and carbapenemase-producing Enterobacteriaceae, *Acinetobacter* spp., *Stenotrophomonas maltophilia*, anaerobic bacteria and Enterococci. The IDSA guidelines for IAIs, published in 2010, suggested the use of tigecycline for adult patients with mild-to-moderate community acquired infections as single-agent therapy (evidence level A-I) (Solomkin *et al.*, 2010). Even if tigecycline has *in vitro* activity against MRSA there are few published data regarding microbiological and clinical efficacy in the treatment of patients with IAIs, and vancomycin should remain the first-line agent (Solomkin *et al.*, 2010).

A very good assessment of tigecycline use was recently published by the World Society of

Emergency Surgery (WSES) in the setting of cIAIs (Sartelli *et al.*, 2011). According to the Consensus, the decision tree for the antimicrobial management of IAIs mainly depends on three factors: presumed pathogens involved and risk factors for major resistance patterns; severity of disease; presumed/identified source of infection. Since the major pathogens involved in community-acquired IAIs are Enterobacteriaceae, *Streptococcus* spp and anaerobes (especially *B. fragilis*), while Enterococci are frequently responsible for hospital-acquired cIAIs, tigecycline monotherapy was recommended for community-acquired biliary and extrabiliary cIAIs in patients not critically ill with risk factors for ESBL, whereas tigecycline combination therapy was recommended in the following situations:

- Antimicrobial therapy for community-acquired biliary cIAIs in critically ill patients (severe sepsis), in the presence of risk factors for ESBL (plus piperacillin ± fluconazole);
- Antimicrobial therapy for hospital-acquired cIAIs in non-critically ill patients (no severe sepsis) and risk factors for MDR pathogens (plus piperacillin and fluconazole);
- Antimicrobial therapy for hospital-acquired cIAIs in critically ill patients (± severe sepsis) and risk factors for MDR pathogens (plus piperacillin and an echinocandin).

In patients with cSSTIs, a recent consensus of the Italian Society of Infectious diseases suggested tigecycline for the treatment of infections due to MRSA (evidence level AI), especially cellulitis due to HA-MRSA, and for surgical site infections (Esposito *et al.*, 2011).

In contrast with these recommendations, the 2014 IDSA guidelines did not mention tigecycline for cSSTIs, (Esposito *et al.*, 2009; Stevens *et al.*, 2014) probably because of the warnings published.

THE ECOLOGICAL POINT OF VIEW

Tigecycline has a very wide spectrum of activity, a new mechanism of action and does not stimulate cross-resistance to other classes of antibiotics. From an ecologic point of view, carbapenemase-producing bacteria are increasing at alarming rates and proactive strategies have not successfully been implemented (Canton *et al.*, 2012; Rocchetti *et al.*, 2014). There are very few therapeutic options against KPC-Kp and other MDR Enterobacteriaceae. Carbapenemase production is normally associated with resistance to all β -lactams and these strains usually also harbor mechanisms of resistance to other classes of antimicrobials. No less disturbing is that extended-spectrum β -lactamase (ESBL) production combined with alterations in porin expression in *K. pneumoniae* and VIM-1-producing *Enterobacter cloacae* may be the cause of treatment failure or breakthrough bacteraemia during therapy with carbapenems, despite apparent *in vitro* susceptibility.

Therefore, implementation of infection control measures has become of major importance for controlling the spread of carbapenem-resistant Enterobacteriaceae (CRE) (Tacconelli *et al.*, 2014). In this scenario, due to its unique mechanism of action and to the lack of induction of resistance to other antibiotic classes, tigecycline, alone or in combination with anti-pseudomonal agents, can be an alternative to carbapenems because it may reduce the selection pressure for nosocomial pathogens (Livermore, 2005).

Hirsch *et al.* reviewed a total of 15 papers involving 55 unique patient cases. Agents with consistent *in vitro* activity against isolates harboring KPC-Kp included tigecycline and the tetracyclines, the polymyxins and the aminoglycosides. From a clinical point of view, tigecycline and the aminoglycosides were associated with positive outcomes in the majority of cases (Hirsch *et al.*, 2010).

A very good example of carbapenem-sparing strategy, using tigecycline plus gentamicin or colistin, was recently published in Italy by Sbrana *et al.* (2013) who reported the effectiveness (92% favorable response; 14% 30-day crude mortality rate) in 22 polytrauma ICU patients with different KPC-Kp infectious episodes (Sbrana *et al.*, 2013).

CONCLUSION

Tigecycline is characterized by a unique mechanism of action and a broad spectrum of activity, including MDR pathogens, and is not associated with cross-resistance. For these reasons, tigecycline has been used in a variety of CA, HCA and HA infections with variable severity and different dosages. We propose a re-definition to separately analyse tigecycline monotherapy and HD combination treatment because of different epidemiological, microbiological and clinical characteristics.

Whilst available clinical data suggest strong caution with monotherapy in severe infections, monotherapy may be safe in the official indications, although individual pharmacological characteristics need to be considered as far as the dosage is concerned. A combination treatment with HD tigecycline may be appropriate in patients with a variety of HCA and HA infections, especially cIAIs, possibly due to MDR Gram-negative or carbapenemase-producing bacteria, but also as part of a carbapenem-sparing strategy, as a primary empiric or targeted treatment and even as a de-escalation.

ACKNOWLEDGEMENTS

We thank Ray Hill, an independent medical writer, who provided English-language, copy editing and journal style assistance prior to submission. This assistance was funded by Pfizer, Italy.

Funding: none.

Transparency declarations: FDR and GDP were speakers for or participated in Advisory Boards for Pfizer. FS has received speaker's honoraria from Astra-Zeneca, GlaxoSmithKline, Sanofi-Aventis and Pfizer.

REFERENCES

- ANTHONY K.B., FISHMAN N.O., LINKIN D.R., GASINK L.B., EDELSTEIN P.H., LAUTENBACH E. (2008). Clinical and microbiological outcomes of serious infections with multidrug-resistant gram-negative organisms treated with tigecycline. *Clin. Infect. Dis.* **46**, 567-570.
- BABINCHAK T., ELLIS-GROSSE E., DARTOIS N., ROSE G.M., LOH E. TIGECYCLINE 301 STUDY GROUP; TIGECYCLINE 306 STUDY GROUP. (2005). The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. *Clin. Infect. Dis.* **41**, S354-367.
- BASSETTI M., ECKMANN C., BODMANN K.F., DUPONT H., HEIZMANN W.R., MONTRAVERS P., GUIRAO X., CAPARELLA M.R., SIMONEAU D., SÁNCHEZ GARCÍA M. (2013). Prescription behaviours for tigecycline in real-life clinical practice from five European observational studies. *J. Antimicrob. Chemother.* **68**, 5-14.
- BASSETTI M., POULAKOU G., GIAMARELLOU H. (2014). Is there a future for tigecycline? *Intensive Care Med.* **40**, 1039-1045.
- BREEDT J., TERAS J., GARDOVSKIS J., MARITZ F.J., VAASNA T., ROSS D.P., GIOUD-PAQUET M., DARTOIS N., ELLIS-GROSSE E.J., LOH E. TIGECYCLINE 305 cSSSI STUDY GROUP. (2005). Safety and efficacy of tigecycline in treatment of skin and skin structure infections: results of a double-blind phase 3 comparison study with vancomycin-aztreonam. *Antimicrob Agents Chemother.* **49**, 4658-4666.
- BHATTACHARYA M., PARAKH A., NARANG M. (2009). Tigecycline. *J. Postgrad Med.* **55**, 65-68.
- BHATTACHARYA I., GOTFRIED M.H., JI A.J., SAUNDERS J.P., GOURLEY I., DIEHL A., KORTH-BRADLEY J.M. (2014). Reassessment of tigecycline bone concentrations in volunteers undergoing elective orthopedic procedures. *J. Clin. Pharmacol.* **54**, 70-74.
- BHAVNANI S.M., RUBINO C.M., AMBROSE P.G., BABINCHAK T.J., KORTH-BRADLEY J.M., DRUSANO G.L. (2010). Impact of different factors on the probability of clinical response in tigecycline-treated patients with intra-abdominal infections. *Antimicrob. Agents Chemother.* **54**, 1207-1212.
- BRADFORD P.A., WEAVER-SANDS D.T., PETERSEN P.J. (2005). 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. *Clin. Infect. Dis.* **41**, S315-332.
- CAI Y., WANG R., LIANG B., BAI N., LIU Y. (2011). Systematic review and meta-analysis of the effectiveness and safety of tigecycline for treatment of infectious disease. *Antimicrob. Agents Chemother.* **55**, 1162-1172.
- CANTON R., AKOVA M., CARMELI Y., GISKE C.G., GLUPCZYNSKI Y., GNIADKOWSKI M., LIVERMORE D.M., MIRIAGOU V., NAAS T., ROSSOLINI G.M., SAMUELSEN Ø., SEIFERT H., WOODFORD N., NORDMANN P.; EUROPEAN NETWORK ON CARBAPENEMASES. (2012). Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. *Clin. Microbiol. Infect.* **18**, 413-431.
- CHEN Z., WU J., ZHANG Y., WEI J., LENG X., BI J., LI R., YAN L., QUAN Z., CHEN X., YU Y., WU Z., LIU D., MA X., MAROKO R., COOPER A. (2010). Efficacy and safety of tigecycline monotherapy vs. imipenem/cilastatin in Chinese patients with complicated intra-abdominal infections: a randomized controlled trial. *BMC Infect. Dis.* **10**, 217.
- CHUANG Y.C., CHENG C.Y., SHENG W.H., SUN H.Y., WANG J.T., CHEN Y.C., CHANG S.C. (2014). Effectiveness of tigecycline-based versus colistin-based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting: a matched cohort analysis. *BMC Infect. Dis.* **14**, 102.
- CURCIO D., FERNANDEZ F., VERGARA J., VAZQUEZ W., LUNA C.M. (2009). Late onset ventilator-associated pneumonia due to multidrug-resistant *Acinetobacter* spp.: experience with tigecycline. *J. Chemother.* **21**, 58-62.
- DE PASCALE G., MONTINI L., PENNISI M., BERNINI V., MAVIGLIA R., BELLO G., SPANU T., TUMBARELLO M., ANTONELLI M. (2014). High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria. *Crit. Care.* **18**, R90.
- DIXIT D, MADDURI R.P., SHARMA R. (2014). The role of tigecycline in the treatment of infections in light of the new black box warning. *Expert Rev. Anti Infect. Ther.* **12**, 397-400.
- DRYDEN M. (2013). Tigecycline: an antibiotic for the twenty-first century. *J. Antimicrob. Chemother.* **68**, 3-4.
- ELLIS-GROSSE E.J., BABINCHAK T., DARTOIS N., ROSE G., LOH E. (2005). Tigecycline 300 cSSSI Study Group; Tigecycline 305 cSSSI Study Group. 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. *Clin. Infect. Dis.* **41**, S341-353.
- ESPOSITO S., BASSETTI M., BORRE S., BOUZA E., DRYDEN M., FANTONI M., GOULD I.M., LEONCINI F., LEONE S., MILKOVICH G., NATHWANI D., SEGRETI J., SGANGA G., UNAL S., VENDITTI M.; ITALIAN SOCIETY OF INFECTIOUS TROPICAL DISEASES; INTERNATIONAL SOCIETY OF CHEMOTHERAPY. (2011). Diagnosis and management of skin and soft-tissue infections (SSTI): a literature review and consensus statement on behalf of the Italian Society of Infectious Diseases and International Society of Chemotherapy. *J. Chemother.* **23**, 251-262.
- EUROPEAN MEDICINES AGENCY (EMA). (2011). Ques-

- tions and answers on the review of Tygacil (tigecycline): Outcome of a renewal procedure. Available at <http://www.ema.europa.eu/ema/>. Accessed 14 July 2014.
- EUROPEAN MEDICINES AGENCY (EMA). (2014). Tygacil (tigecycline): EPAR - Summary of product characteristics. Available at <http://www.ema.europa.eu/ema/>. Accessed 14 July 2014.
- FDA. (2010). FDA Drug Safety Communication: Increased risk of death with Tygacil (tigecycline) compared to other antibiotics used to treat similar infections. Available at <http://www.fda.gov/drugs/drugsafety/ucm224370.htm>. Accessed 14 July 2014.
- FDA. (2013). FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning. Available at <http://www.fda.gov/Drugs/DrugSafety/ucm369580.htm>. Accessed 14 July 2014.
- FREIRE A.T., MELNYK V., KIM M.J., DATSENKO O., DZ-YUBLIK O., GLUMCHER F., CHUANG Y.C., MAROKO R.T., DUKART G., COOPER C.A., KORTH-BRADLEY J.M., DARTOIS N., GANDJINI H. 311 STUDY GROUP. (2010). Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. *Diagn Microbiol Infect Dis.* **68**, 140-151.
- GALLAGHER J.C., ROUSE H.M. (2008). Tigecycline for the treatment of Acinetobacter infections: a case series. *Ann. Pharmacother.* **42**, 1188-1194.
- GARAU J. (2008). Other antimicrobials of interest in the era of extended-spectrum beta-lactamases: fosfomycin, nitrofurantoin and tigecycline. *Clin. Microbiol. Infect.* **14**, 198-202.
- GORDON N.C., WAREHAM D.W. (2009). A review of clinical and microbiological outcomes following treatment of infections involving multidrug-resistant Acinetobacter baumannii with tigecycline. *J. Antimicrob. Chemother.* **63**, 775-770.
- GREER N.D. (2006). Tigecycline (Tygacil): the first in the glycylicycline class of antibiotics. *Proc (Bayl Univ Med Cent)* **19**, 155-161.
- GUNER R., HASANOGLU I., KESKE S., KALEM A.K., TASYARAN M.A. (2011). Outcomes in patients infected with carbapenem-resistant Acinetobacter baumannii and treated with tigecycline alone or in combination therapy. *Infection.* **39**, 515-518.
- HIRSCH E.B., TAM V.H. (2010). Detection and treatment options for Klebsiella pneumoniae carbapenemases (KPCs): an emerging cause of multidrug-resistant infection. *J. Antimicrob. Chemother.* **65**, 1119-1125.
- JAMAL W., SALAMA M., DEHRAB N., AL HASHEM G., SHAHIN M., ROTIMI V.O. (2009). Role of tigecycline in the control of a carbapenem-resistant Acinetobacter baumannii outbreak in an intensive care unit. *J. Hosp. Infect.* **72**, 234-242.
- KAEWPOOWAT Q., OSTROSKY-ZEICHNER L. (2015). Tigecycline: a critical safety review. *Expert Opin. Drug Saf.* **14**, 335-342.
- KIM N.H., HWANG J.H., SONG K.H., CHOE P.G., KIM E.S., PARK S.W., KIM H.B., KIM N.J., PARK W.B., OH M.D. (2013). Tigecycline in carbapenem-resistant Acinetobacter baumannii bacteraemia: susceptibility and clinical outcome. *Scand. J. Infect. Dis.* **45**, 315-319.
- KU K., POGUE J.M., MOSHOS J., BHEEMREDDY S., WANG Y., BHARGAVA A., CAMPBELL M., KHANDKER N., LEPHART P.R., CHOPRA T., HAYAKAWA K., MARTIN E.T., ABREU-LANFRANCO O., DHAR S., KAYE K.S., MARCHAIM D. (2012). Retrospective evaluation of colistin versus tigecycline for the treatment of Acinetobacter baumannii and/or carbapenem-resistant Enterobacteriaceae infections. *Am. J. Infect. Control.* **40**, 983-987.
- KUO S.C., WANG F.D., FUNG C.P., CHEN L.Y., CHEN S.J., CHIANG M.C., HSU S.F., LIU C.Y. (2011). Clinical experience with tigecycline as treatment for serious infections in elderly and critically ill patients. *J. Microbiol. Immunol. Infect.* **44**, 45-51.
- LEE Y.T., TSAO S.M., HSUEH P.R. (2013). Clinical outcomes of tigecycline alone or in combination with other antimicrobial agents for the treatment of patients with healthcare-associated multidrug-resistant Acinetobacter baumannii infections. *Eur. J. Clin. Microbiol. Infect. Dis.* **32**, 1211-1220.
- LIVERMORE D.M. (2005). Tigecycline: what is it, and where should it be used? *J. Antimicrob. Chemother.* **56**, 611-614.
- MCGOVERN P., BABINCHAK T., QUINTANA A. (2011). Clarification to the systematic review and meta-analysis involving tigecycline. *Antimicrob. Agents Chemother.* **55**, 4941.
- MEAGHER A.K., PASSARELLI J.A., CIRINCIONE B.B., VAN WART S.A., LIOLIOS K., BABINCHAK T., ELLIS-GROSSE E.J., AMBROSE P.G. (2007). Exposure-response analyses of tigecycline efficacy in patients with complicated skin and skin-structure infections. *Antimicrob Agents Chemother.* **51**, 1939-1945.
- METAN G., ALP E., YILDIZ O., PERCIN D., AYGEN B., SUMERKAN B. (2010). Clinical experience with tigecycline in the treatment of carbapenem-resistant Acinetobacter infections. *J. Chemother.* **22**, 110-114.
- MICHAIL G., LABROU M., PITIRIGA V., MANOUSAKA S., SAKELLARIDIS N., TSAKRIS A., POURNARAS S. (2013). Activity of Tigecycline in combination with Colistin, Meropenem, Rifampin, or Gentamicin against KPC-producing Enterobacteriaceae in a murine thigh infection model. *Antimicrob. Agents Chemother.* **57**, 6028-6033.
- MONTRAVERS P., BASSETTI M., DUPONT H., ECKMANN C., HEIZMANN W.R., GUIRAO X., GARCÍA M.S., CAPPARELLA M.R., SIMONEAU D., BODMANN K.F. (2013). Efficacy of tigecycline for the treatment of complicated skin and soft-tissue infections in real-life clinical

- practice from five European observational studies. *J. Antimicrob. Chemother.* **68**, 15-24.
- MONTRAVERS P., DUPONT H., BEDOS J.P., BRET P. TIGECYCLINE GROUP. (2014). Tigecycline use in critically ill patients: a multicentre prospective observational study in the intensive care setting. *Intensive Care Med.* **40**, 988-997.
- MOON S.Y., PECK K.R., CHANG H.H., KIM S.W., HEO S.T., SON J.S., RYU S.Y., MOON C., JUNG S.I., SHIN S.Y., LEE J.A., JOUNG M.K., CHUNG D.R., KANG C.I., SONG J.H. (2012). Clinical experience of tigecycline treatment in infections caused by extensively drug-resistant *Acinetobacter* spp. *Microb. Drug Resist.* **18**, 562-566.
- MURALIDHARAN G., MICALIZZI M., SPETH J., RAIBLE D., TROY S. (2005). Pharmacokinetics of tigecycline after single and multiple doses in healthy subjects. *Antimicrob. Agents Chemother.* **49**, 220-229.
- PAI M.P. (2014). Serum and urine pharmacokinetics of tigecycline in obese class III and normal weight adults. *J. Antimicrob. Chemother.* **69**, 190-199.
- PANKEY G.A. (2005). Tigecycline. *J. Antimicrob. Chemother.* **56**, 470-480.
- PASSARELL J.A., MEAGHER A.K., LIOLIOS K., CIRINCIONE B.B., VAN WART S.A., BABINCHAK T., ELLIS-GROSSE E.J., AMBROSE P.G. (2008). Exposure-response analyses of tigecycline efficacy in patients with complicated intra-abdominal infections. *Antimicrob. Agents Chemother.* **52**, 204-210.
- PIANTADOSI S. (2000). *Clinical Trials: A Methodologic Perspective (First Edition)*. Wiley Online Library.
- POSTIER R.G., GREEN S.L., KLEIN S.R., ELLIS-GROSSE E.J., LOH E. TIGECYCLINE 200 STUDY GROUP. (2004). 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. *Clin. Ther.* **26**, 704-714.
- POULAKOU G., KONTOPIDOU F.V., PARAMYTHIOTOU E., KOMPOTI M., KATSIARI M., MAINAS E., NICOLAOU C., YPHANTIS D., ANTONIADOU A., TRIKKA-GRAPHAKOS E., ROUSSOU Z., CLOUVA P., MAGUINA N., KANELLAKOPOULOU K., ARMAGANIDIS A., GIAMARELLOU H. (2009). Tigecycline in the treatment of infections from multi-drug resistant gram-negative pathogens. *J. Infect.* **58**, 273-284.
- PRASAD P., SUN J., DANNER R.L., NATANSON C. (2012). Excess deaths associated with tigecycline after approval based on noninferiority trials. *Clin. Infect. Dis.* **54**, 1699-1709.
- RAMIREZ J., DARTOIS N., GANDJINI H., YAN J.L., KORTH-BRADLEY J., MCGOVERN P.C. (2013). Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. *Antimicrob. Agents Chemother.* **57**, 1756-1762.
- ROCCHETTI A., ZOTTI C.M., ARGENTERO P.A., RASO R., BIGLINO A., LIVIGNI S., ROMAGNOLI S., CORCIONE S., DE ROSA F.G., GHISETTI V. (2014). Epidemiology of carbapenemase-producing *Klebsiella pneumoniae* in a north-west Italian region: report from the regional surveillance system. 24th European Society of Clinical Microbiology and Infectious Diseases (ECCMID) Meeting. Barcelona, Spain.
- RODVOLD K.A., GOTTFRIED M.H., CWIK M., KORTH-BRADLEY J.M., DUKART G., ELLIS-GROSSE E.J. (2006). Serum, tissue and body fluid concentrations of tigecycline after a single 100 mg dose. *J. Antimicrob. Chemother.* **58**, 1221-1229.
- SARTELLI M., VIALE P., KOIKE K., PEA F., TUMIETTO F., VAN GOOR H., GUERCIONI G., NESPOLI A., TRANÀ C., CATENA F., ANSALONI L., LEPPANIEMI A., BIFFL W., MOORE F.A., POGGETTI R., PINNA A.D., MOORE E.E. (2011). WSES consensus conference: Guidelines for first-line management of intra-abdominal infections. *World J. Emerg. Surg.* **6**, 2.
- SBRANA F., MALACARNE P., VIAGGI B., COSTANZO S., LEONETTI P., LEONILDI A., CASINI B., TASCINI C., MENCHETTI F. (2013). Carbapenem-sparing antibiotic regimens for infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* in intensive care unit. *Clin. Infect. Dis.* **56**, 697-700.
- SCAGLIONE F. (2011). Comment on: Efficacy and safety of tigecycline: a systematic review and meta-analysis. *J. Antimicrob. Chemother.* **66**, 2892-3; author reply 2895-2896.
- SCHAFFER J.J., GOFF D.A., STEVENSON K.B., MANGINO J.E. (2007). Early experience with tigecycline for ventilator-associated pneumonia and bacteremia caused by multidrug-resistant *Acinetobacter baumannii*. *Pharmacotherapy.* **27**, 980-987.
- SOLOMKIN J.S., MAZUSKI J.E., BRADLEY J.S., RODVOLD K.A., GOLDSTEIN E.J., BARON E.J., O'NEILL P.J., CHOW A.W., DELLINGER E.P., EACHEMPATI S.R., GORBACH S., HILFIKER M., MAY A.K., NATHENS A.B., SAWYER R.G., BARTLETT J.G. (2010). Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin. Infect. Dis.* **50**, 133-164.
- STEIN G.E., SMITH C.L., MISSAVAGE A., SAUNDERS J.P., NICOLAOU D.P., BATTJES S.M., KEPROS J.P. (2011). Tigecycline penetration into skin and soft tissue. *Surg. Infect. (Larchmt)*. **12**, 465-467.
- STEVENS D.L., BISNO A.L., CHAMBERS H.F., DELLINGER E.P., GOLDSTEIN E.J., GORBACH S.L., HIRSCHMANN J.V., KAPLAN S.L., MONTROYA J.G., WADE J.C. (2014). Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin. Infect. Dis.* **59**, e10-52.
- SWOBODA S., OBER M., HAINER C., LICHTENSTERN C., SEILER C., WENDT C., HOPPE-TICHY T., BÜCHLER M.,

- WEIGAND M.A. (2008). Tigecycline for the treatment of patients with severe sepsis or septic shock: a drug use evaluation in a surgical intensive care unit. *J. Antimicrob. Chemother.* **61**, 729-33.
- SUN H.K., ONG C.T., UMER A., HARPER D., TROY S., NIGHTINGALE C.H., NICOLAU D.P. (2005). Pharmacokinetic profile of tigecycline in serum and skin blister fluid of healthy subjects after multiple intravenous administrations. *Antimicrob. Agents Chemother.* **49**, 1629-1632.
- TACCONELLI E., CATALDO M.A., DANCER S.J., DE ANGELIS G., FALCONE M., FRANK U., KAHLMEYER G., PAN A., PETROSILLO N., RODRÍGUEZ-BAÑO J., SINGH N., VENDITTI M., YOKOE D.S., COOKSON B. EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY. (2014). ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. *Clin. Microbiol. Infect.* **20**, 1-55.
- TANASEANU C., BERGALLO C., TEGLIA O., JASOVICH A., OLIVA M.E., DUKART G., DARTOIS N., COOPER C.A., GANDJINI H., MALLICK R. 308 STUDY GROUP; 313 STUDY GROUP. (2008). Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia. *Diagn. Microbiol. Infect. Dis.* **61**, 329-338.
- TASINA E., HAIDICH A.B., KOKKALI S., ARVANITIDOU M. (2011). Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis. *Lancet Infect. Dis.* **11**, 834-844.
- THERIOT C.M., SCHUMACHER C.A., BASSIS C.M., SEEKATZ A.M., YOUNG V.B. (2014). The Effects of Tigecycline and Vancomycin Administration on Established *C. difficile* Infection. *Antimicrob. Agents Chemother.* [Epub ahead of print].
- VASILEV K., RESHEDKO G., ORASAN R., SANCHEZ M., TERAS J., BABINCHAK T., DUKART G., COOPER A., DAR-TOIS N., GANDJINI H., ORRICO R., ELLIS-GROSSE E. 309 STUDY GROUP. (2008). A Phase 3, open-label, non-comparative study of tigecycline in the treatment of patients with selected serious infections due to resistant Gram-negative organisms including *Enterobacter* species, *Acinetobacter baumannii* and *Klebsiella pneumoniae*. *J. Antimicrob. Chemother.* **62**, i29-40.
- VAN OGTROP M.L., ANDES D., STAMSTAD T.J., CONKLIN B., WEISS W.J., CRAIG W.A., VESGA O. (2000). In vivo pharmacodynamic activities of two glycylicyclines (GAR-936 and WAY 152,288) against various gram-positive and gram-negative bacteria. *Antimicrob. Agents Chemother.* **44**, 943-949.
- WISKIRCHEN D.E., KOOMANACHAI P., NICASIO A.M., NICOLAU D.P., KUTI J.L. (2011). In vitro pharmacodynamics of simulated pulmonary exposures of tigecycline alone and in combination against *Klebsiella pneumoniae* isolates producing a KPC carbapenemase. *Antimicrob. Agents Chemother.* **55**, 1420-1427.
- YAHAV D., LADOR A., PAUL M., LEIBOVICI L. (2011). Efficacy and safety of tigecycline: a systematic review and meta-analysis. *J. Antimicrob. Chemother.* **66**, 1963-1967.
- YE J.J., LIN H.S., KUO A.J., LEU H.S., CHIANG P.C., HUANG C.T., LEE M.H. (2011). The clinical implication and prognostic predictors of tigecycline treatment for pneumonia involving multidrug-resistant *Acinetobacter baumannii*. *J. Infect.* **63**, 351-361.
- ZHANEL G.G., KARLOWSKY J.A., RUBINSTEIN E., HOBAN D.J. (2006). Tigecycline: a novel glycylicycline antibiotic. *Expert Rev. Anti Infect. Ther.* **4**, 9-25.
- ZHANG Q., ZHOU S., ZHOU J. (2014). Tigecycline treatment causes a decrease in fibrinogen levels. *J. Antimicrob. Agents Chemother.* [Epub ahead of print].