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In Vitro Activity of Tigecycline Against *Acinetobacter baumannii*: Global Epidemiology and Resistance Mechanisms

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Abstract

Acinetobacter baumannii is a pathogen of increasing concern, **commonly** causing outbreaks in the hospital environment. **Of particular concern**, *A. baumannii* strains exhibiting resistance to carbapenems, which were **previously** considered the treatment of choice for infected patients, have dramatically increased **worldwide**, leaving a few antibacterial choices. Tigecycline, a broad-spectrum modified minocycline derivative, isconsidered as a last resort drug against multidrug-resistant *A. baumannii*. Though, resistance to tigecycline has emerged and is growing notably following increasing tigecycline usage. Comparative evaluation of the tigecycline resistance rates reported worldwide is challenging due to the absence of official interpretative criteria for in vitro susceptibility testing and the discrepancies among the different susceptibility methodologies used, with broth microdilution being considered the reference method. Tigecycline resistance is mainly associated with resistance-nodulation-cell division (RND)-type transporters, mainly **the AdeABC, AdeFGH and AdeIJK efflux pumps**, but other resistance mechanisms have also been implicated. **Tigecycline is still an attractive choice for *A. baumannii*, but further investigations are warranted so that treatment of MDR** A. ***baumannii*** **could be guided by validated *in vitro* data**.

Keywords

Tigecycline • *Acinetobacter baumannii* • Resistance • MIC • Resistance mechanisms • Susceptibility methods

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1 Introduction

Acinetobacter baumannii complex has emerged as one of the most important pathogens especially in nosocomial environments and intensive care units (ICUs) (Lin and Lan 2014). *Acinetobacter baumannii* (formerly named genomic species 2), *Acinetobacter pittii* (formerly named genomic species 3) and *Acinetobacter nosocomialis* (formerly named genomic species 13TU) (Nemec et al. 2011) represent the most pathogenic *Acinetobacter* species for humans. These three pathogenic species along with the environmental species *Acinetobacter calcoaceticus*, which has been recovered from soil and water (Towner 2009), but with minor clinical relevance have been designated as *A. calcoaceticus-baumannii complex* (Doi et al. 2015). They present similar phenotypic profile, which does not allow manual and semi-automated commercial routine identification methods to distinguish among them (Higgins et al. 2007). The precise identification of *Acinetobacter* isolates to species levels is challenging and requires genotypic methods, such as amplified 16S ribosomal DNA restriction analysis (ARDRA), tRNA spacer fingerprinting and selective amplification of restriction fragments (AFLP). Specific gene sequences can also be used, including intergenic spacer (ITS) region between the 16S and 23S rRNA genes, *rec*A, *rpo*B, and *gyr*B (Espinal et al. 2012). Lately, mass spectrometry has given the option of identifying isolates that belong to the *A. baumannii* group (consisting of the species *A. baumannii, A. pittii, A. nosocomialis*) (ECDC 2013).

A. baumannii is isolated mainly from the respiratory tract, bloodstream,, urinary tract, abdominal, skin, soft tissues and central nervous system (Spiliopoulou et al. 2014). *A. baumannii* is extremely resistant to desiccation and can survive on inanimate surfaces for a long time. It develops readily multidrug resistance by acquiring large resistance elements, called antibiotic resistance islands (Nigro and Hall 2012). The prior use of imipenem, meropenem, piperacillin/tazobactam or fourth-generation cephalosporins and >30 days of being bed-ridden are independent risk factors for extensively drug-resistant *A. baumannii* (XDRAB) infections (Chan et al. 2014; Pachon-Ibanez et al. 2004). Notably, the majority of nosocomial *Acinetobacter* isolates currently exhibit resistance rates to carbapenems as high as 80 % (ECDC 2013). It should be noted that carbapenems were widely used as last resort antibiotics for the treatment of severe infections, with carbapenem resistance to often leave few active antibiotic options. Among the available choices are most commonly included colistin and tigecycline (Sun et al. 2013), while in many cases minocycline remains also potent (Balode et al. 2013). However, tigecycline resistance in *A. baumannii* is a mounting concern. Tigecycline-resistant isolates have been recovered from patients treated with tigecycline (Hua et al. 2012; Hornsey et al. 2011), but also from patients that did received previously the drug (Deng et al. 2014; Sun et al. 2010).

Tigecycline is a modified tetracycline with a 9-t-butyl- glycylamido side chain added to the central skeleton of minocycline (Petersen et al. 1999), broadening its antimicrobial spectrum and rendering it active against multidrug-resistant (MDR) gram-positive and gram- negative, anaerobic and atypical bacteria (Peleg et al. 2007). Tigecycline inhibits the 30S ribosomal subunit and is capable to escape the tetracycline resistance mechanisms *tet(A)* to *tet(E)* and *tet(K)*, which encode efflux pumps and *tet(M)* and *tet(O)* that offer ribosomal protection (Fluit et al. 2005). Tigecycline has been approved by the FDA for complicated skin and skin-structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia (Stein and Babinchak 2013). However, tigecycline has been used for off-label indications, as a last resort for the management of infections mainly due to MDR Gram-negative bacteria.

2 Global Epidemiology of Tigecycline Resistance in *A. baumannii*

Susceptibility testing of tigecycline against *A. baumannii* has been problematic, since there are no established guidelines and many studies have been controversial. Tigecycline reaches low concentrations of 0.62–0.72 mg/L in serum,

(Karageorgopoulos et al. 2008) and undergoes extensive transfer from the blood into the tissues, where levels far exceed those of serum. For instance, its concentration in alveolar cells is 77.5-fold higher than in serum (Brink et al. 2010).

CLSI and EUCAST do not suggest breakpoints for tigecycline against *A. baumannii*. EUCAST reports the epidemiological cutoff (ECOFF) MIC value of tigecycline among *A. baumannii* to be 1 mg/L and the MIC wildtype distribution to range between 0.064 and 1 mg/L. BSAC, on the other hand redirects the researchers to EUCAST PK/PD non-species-specific breakpoints of S = 0.25 mg/L and R = 0.5 mg/L in order to interpret the results (BSAC 2015). However, so far, most of the researchers use the less strict breakpoints suggested by the FDA for *Enterobacteriaceae* (susceptible MIC $\leq$ 2 mg/L; resistant MIC $\geq$8 mg/L) or the EUCAST criteria for *Enterobacteriaceae* (susceptible MIC $\leq$ 1 mg/L; resistant MIC $\geq$ 2 mg/L).

Moreover, the *in vitro* activity of tigecycline against *A. baumannii* varies depending on the method used. E-test is reported to give increased MICs and therefore higher resistance rates than the broth microdilution method with FDA (Pillar et al. 2008; Thamlikitkul and Tiengrim 2008; Kulah et al. 2009), EUCAST (Grandesso et al. 2014) and BSAC criteria (Casal et al. 2009) used. It has been suggested that increased concentration of manganese in Mueller-Hinton agar results in increased MICs (Fernandez-Mazarrasa et al. 2009; Casal et al. 2009; Thamlikitkul et al. 2007) and smaller zone diameters (Thamlikitkul and Tiengrim 2008; Canigia and Bantar 2008), which could result in discrepancies when MHA from different manufacturers are used, or even among lots of the same manufacturer (Pillar et al. 2008). Fernandez-Mazarassa et al. consider that media with low manganese are more clinically relevant, since the concentration in human sera is low (0.8–1.2 μg/L) (Fernandez-Mazarrasa et al. 2009). However, other studies have shown excellent agreement between E-test and broth microdilution (Zarkotou et al. 2012). Agar dilution has shown acceptable minor errors compared to broth microdilution method (Zarate et al. 2010). Jones et al. proposed some modification of the tigecycline FDA disk diffusion breakpoints for *Enterobacteriacae* ($\geq$19 mm sensitive/$\leq$14 mm resistant) when applied to *Acinetobacter spp* ($\geq$16 sensitive/$\leq$12 mm resistant) (Jones et al. 2007). Application of these modified breakpoints, though, is controversial (Liao et al. 2008). Aged media have been accounted for increased MICs (Hope et al. 2005) because the activity of tigecycline is affected by the amount of dissolved oxygen leading to acceleration of oxidative degradation (Bradford et al. 2005).

The use of VITEK 2 in determining susceptibility of tigecycline against *A. baumannii* is also controversial. Leal Castro et al., reported that VITEK 2 was reliable with agreement up to 94 % (Leal Castro et al. 2010), while unacceptable errors have been reported elsewhere when VITEK 2 was used (Zarkotou et al. 2012; Grandesso et al. 2014). Piewngam et al., suggests that disk diffusion, E-test and VITEK-2 could be useful when breakpoints are adjusted, i.e. for disk diffusion $\geq$17 sensitive/$\leq$12 resistant and MIC breakpoints S $\leq$ 1/R $>$ 2 mg/L (Piewngam and Kiratisin 2014).

As previously reported, routine identification methods commonly used by laboratories in most regions cannot distinguish among the *Acinetobacter* complex, with non-*baumannii* species tending to present better sensitivity profiles (Chuang et al. 2011).

Worldwide studies of in vitro activity of tigecycline against *Acinetobacter spp*. report a wide range of non-susceptibility rates (Table 1). This could be due to a number of reasons, such as the small sample size examined, the possible clonal relationship between the isolates tested or the inclusion of only MDR *A. baumannii* isolates in some reports, which tend to exhibit higher resistance rates. Moreover, the identification and the susceptibility testing method used, the breakpoints adopted and the year of sample collection may also play a role.

Table 1 Worldwide reports of tigecycline resistance in Acinetobacter species

Reference	Pathogen	No of isolates	Region	Methodology	Susceptibility breakpoints	Non-susceptible rates %	Collection date
Navon-Venezia et al. (2007)	*Acinetobacter baumannii*	82	Israel	E-test	≤2, FDA	78	2003
Tan et al. (2007)	*Acinetobacter spp*	55	Singapore	Agar Dilution method	≤2, FDA	29	2004–2006
Kulah et al. (2009)	*Acinetobacter baumannii*	91	Turkey	BMD	≤2, FDA	14.3	2005–2007
Liao et al. (2008)	*Acinetobacter baumannii*	393	Taiwan	BMD	≤2, FDA	19.1	2006
Liu et al. (2008)	*Acinetobacter baumannii*	393	Taiwan	BMD	≤2, FDA	19.1	2006
Dizbay et al. (2008)	*Acinetobacter baumannii (MDR)*	66	Turkey	E-test		47	1/9/2006
Araj et al. (2008)	*Acinetobacter spp*	64	Lebanon	Disk diffusion	S ≥16 mm R ≤ 12	2	3/2006–12/2007
Teng et al. (2014)	*Acinetobacter calcoaceticus complex*	141	Taiwan	Disk diffusion	S ≥19 mm R ≤ 14	29	7/2006–6/2012
Behera et al. (2009)	*Acinetobacter baumannii (MDR)*	26	India	E-test	≤2, FDA	57.6	7–9/2007
Chang et al. (2012)	*Acinetobacter baumannii (MDR)*	141	Taiwan	BMD	≤2, FDA	45.5	2007
Kim et al. (2010)	*Acinetobacter spp (imipenem non-susceptible)*	190	Korea	Agar Dilution method	≤1 > 2, BSAC	23.4	2007
Al-Sweih et al. (2011)	*Acinetobacter spp (88.4 % MDR)*	250	Kuwait	E-test	≤2, FDA	13.6	5–12/2008
Taneja et al. (2011)	*Acinetobacter calcoaceticus- baumannii*	224	India	Disk diffusion	NS	14.2	2/07–6/08
Guven et al. (2014)	*Acinetobacter baumannii (MDR)*	145	Turkey	NS	≤2, FDA	RR 81	2008–2011
Van et al. (2014)	*Acinetobacter calcoaceticus- baumannii*	63	Northern Vietnam	VITEK-2	≤2, FDA	41.3	2009
Baadani et al. (2013)	*Acinetobacter spp*	1307	Riyadh, Saudi Arabia	VITEK-2	≤2, FDA	RR 9.7	2011
Jiang et al. (2014)	*Acinetobacter baumannii (MDR)*	42	China	WalkAway 96 PLUS NC50	N/A	40.5	12/2012–1/2013
Farrell et al. (2010)	*Acinetobacter spp*	397	Asia, W. Pacific	BMD	≤2, FDA	0.2	2008

Scheetz et al. (2007)	*Acinetobacter baumannii (carbapenemase non-susceptible)*	93	USA	BMD	≤2, FDA	5	2001–2005
Garza-Gonzalez et al. (2010)	*Acinetobacter baumannii*	550	Mexico	BMD	≤1 > 2, BSAC	3	07/2006–06/2007
Denys et al. (2013)	*Acinetobacter baumannii*	2900	USA	BMD	≤2, FDA	MIC50/90 = 0.5/<2 mg/L	2005–2011
Sader et al. (2014)	*Acinetobacter spp*	1257	USA	BMD	≤2, FDA	MIC50/90 = 0.5/2 mg/L	2006–2012
Garcia et al. (2009)	*Acinetobacter baumannii*	208	Chile	Agar Dilution method	≤2, FDA	20	10/2005–12/2006
Rizek et al. (2015)	*Acinetobacter baumannii (MDR)*	47	Brazil	BMD	≤2, FDA	0	NS
Ahmed et al. (2012)	*Acinetobacter baumannii complex (CR)*	232	Pretoria, South Africa	VITEK-2	≤0.25 ≥ 8	24	2/7/2010
Seifert et al. (2006)	*Acinetobacter baumannii*	215	Europe and USA	BMD	≤2, FDA	14.9	1990–2003
Insa et al. (2007)	*Acinetobacter baumannii*	142	Spain	E-test	≤2, FDA	12	1/2003–7/2006
Capone et al. (2008)	*Acinetobacter baumannii (MDR)*	80	Italy	BMD		27.5	1/2004–6/2005
Cattoir et al. (2014)	*Acinetobacter baumannii (MDR)*	1161	France	BMD		MIC 90 = 1 mg/L	2004–2012
Papaparaskevas et al. (2009)	*Acinetobacter spp (imipenem -resistant)*	187	Greece	BMD		MIC50/90 = 1/1	12/2006–6/2007
Spiliopoulou et al. (2014)	*Acinetobacter baumannii 92.1 % MDR)*	441	Greece	E-test	≤2, FDA	NS	1/2006–12/13
Ricciardi et al. (2009)	*Acinetobacter baumannii (MDR)*	50	Italy	E-test	≤2, FDA	50	1/2008–1/2009
Zarkotou et al. (2012)	*Acinetobacter baumannii (CR)*	56	Greece	BMD	≤2, FDA	14	2008–2011
Buccoliero et al. (2011)	*Acinetobacter baumannii*	81	Italy	VITEK-2	≤2, FDA	0	2011
Sader et al. (2005)	*Acinetobacter spp*	326	worldwide	BMD	≤2, FDA	5.5	2000–2004
Mendes et al. (2010)	*Acinetobacter spp*	5127	worldwide	BMD	≤2, FDA	3	2005–2009

NS not specified, *FDA* Food and Drug Administration, *EUCAST* European Committee on Antimicrobial Susceptibility Testing, *BSAC* British Society for Antimicrobial Chemotherapy, *MDR* multidrug resistant, *RR* resistance rate, *BMD* broth microdilution

As for specific regions worldwide, tigecycline non-susceptibility in the Middle-East countries ranges from 2 to 81 % (Guven et al. 2014; Navon-Venezia et al. 2007; Kulah et al. 2009; Dizbay et al. 2008; Baadani et al. 2013; Araj and Ibrahim 2008; Al-Sweih et al. 2011). The highest rates reported come from Israel (Navon-Venezia et al. 2007) and Turkey (Guven et al. 2014) with tigecycline resistance percentages of 66 % and 81 %, respectively. Navon-Venezia et al. have used the E-test methodology, which has been reported to give higher tigecycline MICs. Guven et al., reported increase in tigecycline resistance among MDR *A. baumannii* from 12.5 % in 2008 to 81.3 % in 2011 respectively (Guven et al. 2014).

In Asia, non-susceptibility rates ranged from 14.2 to 57.6 % (Behera et al. 2009; Taneja et al. 2011; Liao et al. 2008; Chang et al. 2012; Teng et al. 2014; Kim et al. 2010; Jiang et al. 2014; Van et al. 2014; Tan and Ng 2007; Liu et al. 2008). In India, two studies reported 14.2 % and 57.6 % non-susceptibility rates (Behera et al. 2009; Taneja et al. 2011). The higher rate was reported among MDR *A. baumannii* in a limited sample. In Taiwan, two studies report a rate of 19 % (Liu et al. 2008) and 29 % for tigecycline non-susceptible *A. baumannii* (Teng et al. 2014), while another Taiwanese study testing MDR *A. baumannii* isolates showed a rate of 45.5 % (Chang et al. 2012). In Asia and Western Pacific region, non-susceptibility rate was reported to be 0.2 % (Farrell et al. 2010)

In the Americas, tigecycline non-susceptibility was $\leq$5 % in North America (Scheetz et al. 2007; Garza-Gonzalez et al. 2010). Also, Denys et al., as part of the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) and Sader et al. in the USA reported $MIC_{50/90}$ values of 0.5/$\leq$2 mg/L (Denys et al. 2013; Sader et al. 2014). In South America, non-susceptibility varied between 0 and 20 % (Garcia et al. 2009; Rizek et al. 2015).

In South Africa, non-susceptibility was reported to be 24 % (Ahmed et al. 2012). In Europe, non-susceptibility ranged from 0 to 50 % (Zarkotou et al. 2012; Buccoliero et al. 2012; Capone et al. 2008; Ricciardi et al. 2009; Seifert et al. 2006; Insa et al. 2007). Spiliopoulou et al. reported an increase in tigecycline resistance from 25.5 % in 2010 to 66.5 % in 2013. MIC_{90} in two T.E.S.T. surveys conducted in Greece and France was estimated to be 1 mg/L (Papaparaskevas et al. 2010; Cattoir and Dowzicky 2014). Two worldwide studies estimate non-susceptibility rate of *A. baumannii* to tigecycline to be 5.5 % and 3 % respectively (Sader et al. 2005; Mendes et al. 2010).

3 Mechanisms of Tigecycline Resistance in *A. baumannii*

Resistance mechanisms to tigecycline among *A. baumannii* are still not fully elucidated. Nevertheless, efflux pumps seem to play a vital role. Three efflux pumps, AdeABC, AdeFGH and AdeIJK that are part of the resistance-nodulation division family (RND), up to now, have been associated with resistance to tigecycline in this species. MexXY and AcrAB that have been reported to be implicated in tigecycline resistance among *Enterobacteriaceae* and *P. aeruginosa*, also belong to the RND family. AdeABC, AdeFGH and AdeIJK pumps are thee-component systems consisting of a membrane fusion protein (MFP), an inner membrane transporter, and an outer membrane factor (OMF) (Peleg et al. 2007). This three component system allows crossing of both the inner and the outer membrane (Coyne et al. 2011), making them very effective. All three proteins in each pump are co-transcribed (Marchand et al. 2004; Coyne et al. 2010b; Damier-Piolle et al. 2008). Members of the RND family are proton antiporters, using the proton gradient to power efflux, exchanging one H+ ion for one drug molecule (Paulsen 2003).

The *ade*ABC operon is found in 80 % of *Acinetobacter* isolates (Coyne et al. 2010a), *ade*FGH in 90 % (Coyne et al. 2010b) and *ade*IJK is considered intrinsic to the species and is found in all *Acinetobacter* isolates (Damier-Piolle et al. 2008). AdeABC pump is controlled by a two-component system (AdeRS), namely a response regulator (AdeR) and a sensor kinase

(AdeS) (Marchand et al. 2004). AdeFGH is controlled by the LysR-type transcriptional regulator AdeL (Coyne et al. 2010b) and AdeIJK by the TetR transcriptional regulator AdeN (Rosenfeld et al. 2012).

Several compounds have been reported to be substrates for the AdeABC system, including aminoglycosides, tetracyclines, fluoroquinolones, trimethoprim, chloramphenicol (Bratu et al. 2008) as well as cefotaxime (Magnet et al. 2001). Overexpression of the AdeABC has been observed in tigecycline-resistant *A. baumannii* and was associated with increased MICs of tigecycline (Bratu et al. 2008; Peleg et al. 2007; Ruzin et al. 2010). On the other hand, two other studies (Yoon et al. 2013; Deng et al. 2014) found no correlation between tigecycline MICs and the levels of AdeABC expression, suggesting the presence of other mechanisms of tigecycline resistance. It should be noted that increased expression of the *adeB* gene was also found in tigecycline-susceptible strains, which could indicate the role of the AdeABC efflux pumps on other functions necessary for the pathogenesis of clinical strains of *A. baumannii*, such as colonization, infection and the persistence of organisms in the host (Rumbo et al. 2013).

Amino acid changes in the AdeRS system have also been implicated in AdeABC overexpression, but their actual contribution remains uncertain. In AdeS, point mutations Asp30Gly (Coyne et al. 2010b) in the sensor domain, Met62Ile (Hornsey et al. 2010), in clinical isolates Thr153Met in the histidine box in spontaneous mutants (Marchand et al. 2004) and Arg152Lys in clinical isolates (Yoon et al. 2013) downstream from the putative His-149 site with presumable loss of phosphorylation, have been described. In AdeR, Asp20Asn near the site of phosphorylation (Higgins et al. 2010), Pro116Leu in the helix of the receiver domain (Marchand et al. 2004) and Glu219Ala in the DNA binding domain (Yoon et al. 2013) have been reported. Lastly, polymorphisms Ala94Val (Hornsey et al. 2010; Rumbo et al. 2013), Gly186V, Phe214Leu in the AdeS and Ala136Val in the AdeR (Rumbo et al. 2013) have also been observed.

The mutation Ala94Val might have been erroneously considered as a functional mutation (Hornsey et al. 2010). Further studies in two *A. baumannii* isolates recovered by the same patient detected multiple mutations, raising the possibility of a mixed infection or re-infection, as it could not be determined whether they were evolved from one another during tigecycline treatment (Hornsey et al. 2011).

Concurrent point mutations Gly103Asp in AdeS and Ala91Val in AdeR located immediately upstream of the putative −10 promoter sequence of the *adeABC* operon, in a lab mutant obtained after tigecycline exposure have been reported (Hornsey et al. 2011). IS*Aba*-1 insertion in the AdeS has been proposed as a mechanism of resistance (Ruzin et al. 2007; Sun et al. 2012). Sun et al. demonstrated that the truncated AdeS was able to interact with AdeR and then enhance the adeABC expression (Sun et al. 2012).

Nevertheless, in some cases overexpression of the AdeABC system could not be associated with changes in the AdeRS system (Bratu et al. 2008; Peleg et al. 2007; Sun et al. 2010; Hornsey et al. 2010), implying alternative ways of control. BaeSR two component system has been shown to positive regulate the expression of *adeA* and *adeB* in both clinical isolates and laboratory induced tigecycline-resistant strains (Lin et al. 2014).

AdeIJK has also been implicated in tigecycline resistance (Damier-Piolle et al. 2008; Rosenfeld et al. 2012; Rumbo et al. 2013; Amin et al. 2013). Alterations detected in AdeN in mutants overexpressing the AdeIJK were deletion of cytosine 582 and a 394-bp deletion of the 3′ part of the AdeN (Rosenfeld et al. 2012). Polymorphisms of the AdeN reported are His111Pro, Ile112Phe, Pro16Lys (Rumbo et al. 2013).

Studies have shown that overexpression of AdeFGH is associated with tigecycline resistance (Coyne et al. 2010a). AdeL point mutations, Val139Gly, Thr319Lys, insertion at position 981 of a thymidine leading to 300- and 200- increase in *adeG* have been described (Coyne et al. 2010b). In contrast to this

observation, Amin et al. reported that AdeL transcriptional factor and the AdeFGH pump does not contribute to antimicrobial resistance since deletion of *adeL- adeFGH* operon had no impact on antimicrobial susceptibility in the clinical isolates studied, raising the question about the reliability of the method of selecting mutants via exposure to antibiotics and inserting resistance cassettes rather than generating marker less gene deletions (Amin et al. 2013).

Sun et al., noted that 11 tigecycline-resistant isolates showed no increase in adeA, 7/11 showed response to 1-(1-naphthyl)-piperazine (NMP), which is an efflux pump inhibitor and 4/11 showed no response to NMP, indicating that additional pumps or completely different mechanisms might contribute to tigecycline resistance (Sun et al. 2014). The involvement of a new RND pump together with *tetA* (39) has been suggested as a mechanism of tigecycline resistance (Rumbo et al. 2013). Other mechanisms have also been proposed for tigecycline resistance. *TetX1* gene, a new resistance mechanism to tigecycline reported previously in *Bacteroides fragilis* strains, was detected in 12/64 (18.8 %) tigecycline non-susceptible *A. baumannii* isolates (Deng et al. 2014). The TetX protein modifies first and second generation tetracyclines and requires NADPH, Mg^{+2} and O_2 for its activity (Moore et al. 2005). Decreased susceptibility to tigecycline has been mediated by a mutation in *trm* encoding SAM-dependent methyltransferase that play a role in epigenetic regulation and antibiotic resistance (Chen et al. 2014). A frameshift mutation in *plsC*, encoding 1-acyl-sn-glycerol-3-phosphate acyltransferase observed in a mutant after gradient exposure to tigecycline was proposed as a mechanism of tigecycline resistance, by influencing the membrane's permeability to tigecycline (Li et al. 2015).

Research focused on outer membrane proteins (OMPs) in *A. baumannii* has demonstrated that inactivation of AbuO, an outer membrane, homolog of TolC from Escherichia coli, that is regulated by the transcriptional regulator SoxR, conferred increased susceptibility to tigecycline in a lab mutant (Srinivasan et al. 2015).

4 Discussion

A. baumannii is considered as one of the most significant pathogens, particularly in the hospital setting (Boucher et al. 2009). Multidrug-resistant (MDR) *A. baumannii*, defined as resistant to three or more classes of antibiotics is of great concern, since often the only antimicrobial treatment choices remain colistin and tigecycline. Tigecycline resistance has been observed during therapy, but resistant isolates have also been recovered from patients without any previous tigecycline administration, probably partly due to AdeABC overexpression induced by other antibiotics that are also substrates for the pump. In addition, resistance to tigecycline against MDR *A. baumannii*, even before the drug was commercially available, has been reported (Navon-Venezia et al. 2007; Kulah et al. 2009; Dizbay et al. 2008). The development of resistance to any particular agent has often been shown to correlate with its overall use in the population (Stein and Babinchak 2013). It seems that tigecycline-resistant *A. baumannii* rates are increasing ever since it was approved by the FDA (2005) and the European Medicines Agency (2006) (Stein and Babinchak 2013) but also maybe partly due to indiscriminate or off-label use, i.e. suboptimal concentration of tigecycline in serum could promote tigecycline resistance, making this superbug even more promiscuous. Notably, neither the branding company nor the official institutions CLSI and EUCAST recommend the use of tigecycline against *A. baumanni* due to insufficient data. The wild type MIC distribution of tigecycline in *A. baumannii* ranges between 0.064 and 1 mg/L. It is evident that tigecycline most probably cannot offer a bacteriostatic effect in bacteraemia, where the achievable serum concentration of tigecycline at normal dosing is 0.62–0.72 mg/L, a value below the FDA breakpoint (Karageorgopoulos et al. 2008). The use of tigecycline in tissue infections, where tigecycline reaches higher concentrations might be more promising. Taken together, these observations suggest that caution should be given to unreasonable use of

tigecycline in poorly penetrated anatomic sites, in order to restrain the development of further resistance.

A major role in tigecycline resistance in *A. baumannii* is exerted by the RND-efflux pumps, though the mechanisms of resistance are more complicated and diverse than what has so far been described and need to be further elucidated.

Tigecycline was shown to exhibit good *in vitro* bacteriostatic activity against *A. baumannii*, including strains resistant to imipenem (Pachon-Ibanez et al. 2004). Additionally, tigecycline has shown considerable, though not consistent, antimicrobial activity against MDR, including carbapenem-resistant, *Acinetobacter* spp. (Karageorgopoulos et al. 2008). Uncertain clinical efficacy regardless of excellent *in vitro* activity of tigecycline (MIC < 2 mg/L) against MDR *A. baumannii* has been reported, suggesting poor correlation between clinical and microbiological outcome (Gordon and Wareham 2009). It has been reported that *A. baumannii* isolates with tigecycline MICs of >2 mg/L were associated with higher mortality rate and that pre-therapy MIC determination of tigecycline against *A. baumannii*, may predict clinical success (Anthony et al. 2008). Another study from Taiwan that compared the effectiveness of tigecycline- versus colistin-based therapy for the treatment of pneumonia caused by MDR *A. baumannii* revealed that the excess mortality rate in the tigecycline-based group observed compared to the colistin-based group was significant only among those patients with MIC >2 μg/mL but not for those with MIC ≤ 2 μg/mL (Chuang et al. 2014). In a systematic review and meta-analysis of the efficacy and safety of tigecycline, increased mortality, clinical failure and rate of septic shock development was observed with the use of tigecycline (Yahav et al. 2011). It has also been reported that when tigecycline therapy and non-tigecycline therapy was compared in terms of survival rate for the treatment of infections due to MDR *A. baumannii*, no significant difference was found between the two groups, although the rate of unfavourable outcome was significant lower in the tigecycline group (Lee et al. 2013). The FDA, in a drug safety communication recommended that health care professionals should reserve tigecycline for use in situations when alternative treatments are not suitable, based on an analysis showing increased risk of death when tigecycline was used compared to other antibacterial drugs (FDA 2013).

In the absence of established interpretative criteria for in vitro susceptibility testing, the non-susceptibility of tigecycline in *A. baumannii* cannot be accurately validated. Nevertheless, when tigecycline is intended to be used, it is important to confirm the *in vitro* susceptibility test using the recognized standard of broth microdilution (Bradford et al. 2005) in order to avoid any discrepancies. It seems that more light should be shed to the activity of the drug against *A. baumannii* so that official institutions could establish interpretative criteria for in vitro susceptibility testing.

In conclusion, it is evident that the status of tigecycline against *A. baumannii* remains obscure. On one hand, patients with life-threatening infections due to MDR *A. baumanni* isolates demand an effective confrontation, on the other hand approved indications of tigecycline are limited and its clinical effect against A. *baumanni* is uncertain. Tigecycline is still an attractive choice for *A. baumannii*, but further investigations are warranted so that treatment of MDR *A. baumannii* could be guided by validated data.

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