J Antimicrob Chemother 2014; **69**: 2606–2610
doi:10.1093/jac/dku189 Advance Access publication 30 May 2014

Journal of Antimicrobial Chemotherapy

Tigecycline in treatment of multidrug-resistant Gram-negative bacillus urinary tract infections: a systematic review

K. Brust[1]*, A. Evans[2] and R. Plemmons[1]

[1]*Division of Infectious Disease, Scott & White Healthcare, Texas A&M Health Science Center College of Medicine, Temple, TX, USA;* [2]*Department of Pharmacy, Scott & White Healthcare, Temple, TX, USA*

*Corresponding author. Tel: +1-254-724-2600; Fax: +1-254-724-2061; E-mail: kbrust@sw.org

Received 3 October 2013; returned 11 December 2013; revised 4 April 2014; accepted 5 May 2014

Objectives: To review cases of multidrug-resistant (MDR) Gram-negative bacillus urinary tract infections (UTIs) treated with tigecycline and the literature related to this subject.

Methods: We performed a systematic review of the literature identifying patients with MDR Gram-negative bacillus UTIs treated with tigecycline.

Results: Fourteen cases describing treatment of UTIs caused by MDR Gram-negative bacilli with tigecycline are reviewed. Favourable clinical outcomes were noted in 11 of 14 cases. An initial favourable microbiological outcome was noted in 12 cases. Post-treatment cultures in two cases were positive for tigecycline-resistant organisms.

Conclusions: The clinical efficacy of tigecycline for treatment of UTIs has not been extensively evaluated. Based on the available literature, tigecycline appears to have efficacy in some patients with MDR Gram-negative bacillus UTIs. Further research in this area is needed to fully elucidate the role of tigecycline in treating such patients.

Keywords: GAR-936, carbapenem-resistant Enterobacteriaceae, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, KPC

Introduction

Multidrug-resistant (MDR) Gram-negative bacilli are becoming an increasingly problematic cause of hospital-acquired infections and antibiotic options for treatment of infections caused by these organisms are often limited. Tigecycline is a relatively new antibiotic in the armamentarium against these problem microbes. Use of tigecycline for the treatment of urinary tract infections (UTIs) has been questioned because of low peak serum concentrations and limited excretion into urine.[1,2] In our accompanying letter in this issue,[3] we report a case of UTI caused by carbapenem-resistant *Klebsiella pneumoniae* that was successfully treated with tigecycline and here we review published cases of UTIs caused by MDR Gram-negative bacilli that were treated with tigecycline.

Methods

We performed a systematic review of the literature examining use of tigecycline in the treatment of UTIs. The databases searched included PubMed, MD Consult, Micromedex and Academic Search Premiere. We looked for pertinent randomized controlled trials, systematic reviews, case series, poster presentations and human case reports. In our search, we included studies related to the pharmacokinetics and pharmacodynamics of tigecycline. Search terms included 'tigecycline', 'urinary tract infections', 'multidrug-resistant pathogens' and 'Gram-negative bacilli'. Eligible patients for inclusion were adults (≥18 years of age) who had UTIs caused by MDR Gram-negative bacilli and who had received tigecycline treatment.

A positive clinical response was defined as partial or complete improvement in signs/symptoms of UTI while a negative clinical response was defined as lack of improvement or worsening of signs/symptoms of UTI. A positive microbiological response was defined as sterilization of urine during or after treatment with tigecycline, while a negative microbiological response was defined as failure to eradicate the organism during or at the end of therapy.

Results

Forty-five studies were reviewed for potential inclusion in this study (Figure 1). Twenty-two studies referenced some aspect of treatment of UTI caused by MDR Gram-negative bacilli with tigecycline. Nine studies yielded a total of 13 cases of UTI treated with tigecycline. All 13 cases had details regarding antibiotic treatment choices, source of infection, pathogens and clinical/microbiological outcomes. No other case reports were available for inclusion. A summary of these cases (along with our own case) is included in Table 1.[3–12]

The median age of patients was 63 years (range 25–76 years). Five of the patients were immune-compromised (three patients

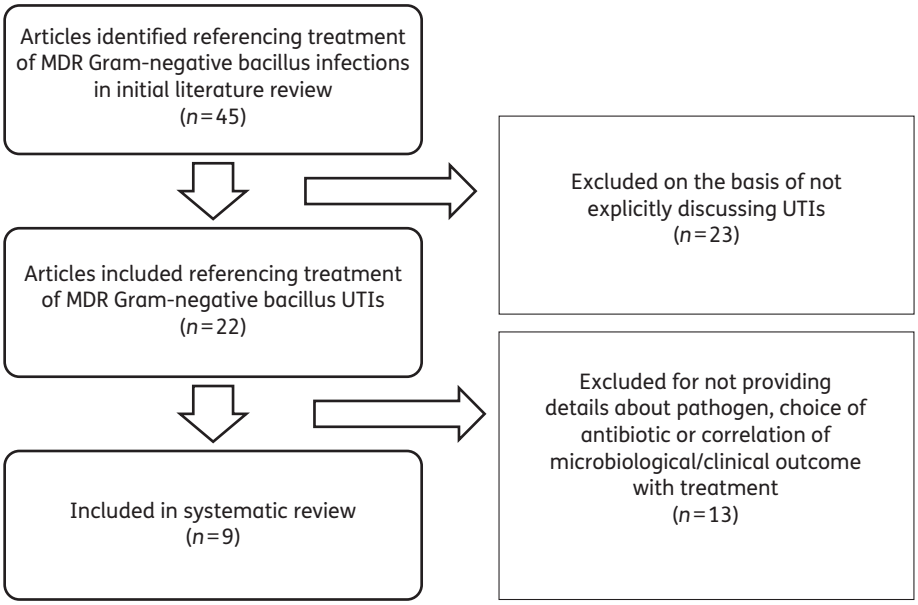

Figure 1. Study flow diagram.

with diabetes and two renal transplant patients). Six patients had renal insufficiency ranging from stage 3 (glomerular filtration rate 30–59 mL/min/1.73 m^2) to stage 5 (glomerular filtration rate <15 mL/min/1.73 m^2 or dialysis).[13] Five patients had abnormal urinary tract anatomy or factors complicating standard treatment, including prostatitis, polycystic kidney disease with infected renal cysts, neurogenic bladder with chronic urinary reflux and staghorn calculi. Standard dosing of tigecycline was used except in our case and the case reported by Cunha *et al.*,[5] in which doses higher than those approved by the FDA were used. Median duration of therapy, including all cases described here, was 13.5 days (range 4–42 days). Urinary pathogens in order of frequency included *Acinetobacter baumannii* (five cases), *Escherichia coli* (four cases) and *K. pneumoniae* (three cases). Two of the 14 patients had more than one organism isolated from their urine prior to treatment with tigecycline (*K. pneumoniae* and *Enterobacter aerogenes* in one patient and *A. baumannii* with vancomycin-resistant *Enterococcus* spp. in another).

Twelve of the 14 cases had an initial favourable microbiological response. In our case, the patient had a negative urine culture after tigecycline therapy and urological intervention to remove the infected stone and ureteral stent.[3] Two perioperative doses of amikacin may have contributed to our patient's clinical response, but the impact of this is difficult to assess since amikacin was given at the time of staghorn calculus removal, which also eliminated a potential nidus of persistent infection. At the very least, tigecycline appears to have suppressed our patient's bacteraemia and prevented further complications as she awaited removal of the infected kidney stone. In the report by Kuo *et al.*,[10] no details are given with regard to the microbiological failure described. In the case report by Elemam *et al.*,[6] the elderly female's urinalysis showed persistent pyuria despite treatment with tigecycline and her urine culture continued to grow >100 000 cfu/mL of *K. pneumoniae*. Her *K. pneumoniae* isolate had a tigecycline MIC of 4 mg/L (intermediate resistance) prior to treatment, but full resistance developed with an MIC of >8 mg/L during a 10 day course of treatment. The patient continued to grow the same MDR pathogen after a year despite clinical resolution of symptoms. In Reid's[11] case, involving a renal/liver transplant patient, subsequent development of a tigecycline-resistant strain also occurred. In the patient described in that report, *A. baumannii* UTI recurred following treatment with tigecycline and new sites of involvement became apparent, including pneumonia, paraspinal abscess and lumbar osteomyelitis. The patient ultimately required treatment with colistin and ceftazidime. Use of colistin potentially contributed to the loss of her renal graft.

All of the cases reviewed except three had an initial positive clinical response. Our patient was followed for over a year and had no subsequent hospitalizations for UTI or sepsis.[3] No details are known regarding long-term clinical outcome in the single case of treatment failure reported by Anthony *et al.*[4] and for the case of treatment failure reported by Kuo *et al.*[10] the subject was only noted to be alive at final disposition. In the case reported by Elemam *et al.*,[6] 10 days of tigecycline did not resolve the patient's dysuria, which was her only presenting symptom. That patient was otherwise asymptomatic after 1 year without antibiotic therapy in the interim. Importantly, no significant adverse effects were reported in this series of cases other than the anticipated nausea. No patient in this series discontinued treatment secondary to significant adverse events.

Discussion

Tigecycline is a relatively new antibiotic in the glycylcycline class (a derivative of minocycline). It has been approved by the FDA for complicated intra-abdominal infections, complicated skin and skin structure infections and community-acquired pneumonia.[14] Tigecycline has shown excellent *in vitro* activity against most

Table 1. Case review of MDR Gram-negative bacillus UTIs treated with tigecycline[3–12]

Reference	Age (years)/sex	Comorbid conditions	Secondary sites of infection	Urinary pathogen	Tigecycline dosing	Length of tigecycline therapy (days)	Potentially active concomitant antibiotics	Development of tigecycline resistance	Clinical outcome	Microbiological outcome
Anthony *et al.*[4]	54/female	DM	none	*A. baumannii* (MDR)	standard	17	none	NA	positive	positive
Anthony *et al.*[4]	64/male	DM	none	*K. pneumoniae* (ESBL)	standard	11	none	NA	negative	positive
Cunha *et al.*[5]	elderly male	NA	none	*K. pneumoniae* (KPC) and *E. aerogenes* (MDR)	200 mg intravenously daily	14	none	NA	positive	positive
Drekonja *et al.*[12]	63/male	NA	prostatitis	*E. coli* (ESBL)	standard	14	ertapenem	NA	positive	positive
Elemam *et al.*[6]	70/female	NA	none	*K. pneumoniae* (KPC)	NA	10	rifampicin	yes	negative	negative
Gallagher *et al.*[7]	63/sex NA	NA	none	*A. baumannii* (MDR)	standard	4	none	NA	positive	positive
Gallagher *et al.*[7]	49/sex NA	NA	none	*A. baumannii* (MDR)	standard	13	none	NA	positive	positive
Gallagher *et al.*[7]	63/sex NA	NA	Yes, but not specified	*A. baumannii* (MDR)	standard	12	colistin	NA	positive	positive
Geerlings *et al.*[8]	44/male	renal transplant	prostatitis	*E. coli* (ESBL)	NA	42	none	no	positive	positive
Geerlings *et al.*[8]	66/female	PCKD with ESRD on HD	infected renal cysts	*E. coli* (ESBL)	NA	42	none	no	positive	positive
Krueger *et al.*[9]	25/female	neurogenic bladder with chronic urinary reflux	septic shock with respiratory failure and need for bilateral ureteral dilatation	*E. coli* (ESBL)	NA	13	meropenem	NA	positive	positive
Kuo *et al.*[10]	76/male	CKD	lumbar osteomyelitis with epidural abscess	*A. baumannii* (MDR)	standard	12	piperacillin/tazobactam, imipenem	NA	negative, but patient alive	negative
Reid *et al.*[11]	53/female	renal and liver transplant	pneumonia with negative sputum culture; bloodstream infection with CoNS	*A. baumannii* (MDR) and VRE	standard	14	levofloxacin, piperacillin/tazobactam	yes	initially positive then relapse with pneumonia, paraspinal abscess and lumbar osteomyelitis	positive[a]
Brust *et al.*[3]	53/female	DM, stage 3 CKD, nephrolithiasis	none	*K. pneumoniae* (KPC)	varying high doses	17	piperacillin/tazobactam, amikacin	no	positive	positive

ESBL, extended-spectrum β-lactamase; NA, not available; VRE, vancomycin-resistant *Enterococcus* spp; CKD, chronic kidney disease; PCKD, polycystic kidney disease; HD, haemodialysis; DM, diabetes mellitus; CoNS, coagulase-negative staphylococci.

[a]At least 20 days after tigecycline discontinued, subsequent isolation of *K. pneumoniae* revealed resistance.

Gram-negative pathogens with the notable exceptions of *Pseudomonas aeruginosa* and *Proteus mirabilis*. It has found an additional application in the treatment of infections caused by MDR organisms, most notably *A. baumannii* and carbapenemase-producing Enterobacteriaceae.[15] Tigecycline generally evades efflux pumps and ribosomal protection, the two major mechanisms of resistance to tetracycline. The CLSI does not currently have MIC interpretive criteria for tigecycline against enteric Gram-negative organisms. The FDA has assigned breakpoints for tigecycline of ≤2 mg/L as susceptible, 4 mg/L as intermediate and ≥8 mg/L as resistant.[14]

Pharmacokinetic and pharmacodynamic parameters of tigecycline have been studied, although some gaps in knowledge still exist. Tigecycline follows linear kinetics and has a large volume of distribution, ranging from ∼5 to >10 L/kg.[16] In a study by Nicasio *et al.*,[17] clinical efficacy was most closely associated with the AUC/MIC ratio. They further determined that the free AUC/MIC ratio was the best parameter for evaluating tigecycline efficacy against strains of *E. coli* and *K. pneumoniae*, including 'one carbapenemase-producing organism'. This study concluded that the free AUC_{24}/MIC ratio needed to achieve adequate kill was between 1.3 and 1.8. Ratios in this range can be achieved at standard dosing when the tigecycline MIC is ≤1 mg/L.[17] The free AUC_{24}/MIC ratio of 2.84 calculated for our patient exceeded those target levels and supports the apparent efficacy of tigecycline in treating our patient's bacteraemia.[3]

Tigecycline is primarily eliminated by the hepatobiliary/faecal route and only minimally via the renal system. Unchanged parent drug is the primary compound found in the urine.[16] The tigecycline package insert states that 33% of a dose is excreted in the urine, with 22% of the dose excreted as unchanged drug and the remainder appearing as inactive metabolites (tigecycline epimer and *N*-acetyl-9-aminominocycline).[14,16] Other published literature, however, shows a range of excretion percentages for unchanged drug in the urine ranging from 5% to 35%.[1,15,16,18–20] One of the most recent studies reported that 16% of an administered dose was found unchanged in urine.[18] Acknowledging the variable urinary excretion percentages in the above studies, the most critical pharmacological parameter would appear to be tigecycline concentration in the urine. Nix and Matthias[21] postulate achievable urinary drug levels in the 7.5–11 mg/L range. Using standard dosing in healthy patients, tigecycline serum levels are relatively low and sharply decline after the end of the infusion.[1] Although clinical cures have been achieved with tigecycline in cases of bacteraemia where the organism has had an MIC indicating susceptibility, monotherapy with tigecycline is generally not recommended in the setting of bacteraemia.[22] One study showed that tigecycline monotherapy for treatment of carbapenem-resistant *K. pneumoniae* bacteraemia had an associated mortality of 80%.[23] Combination therapy (tigecycline with an aminoglycoside or carbapenem) has been recommended for treatment of bacteraemia caused by MDR Gram-negative bacilli.[23]

The impact of impaired renal function on tigecycline pharmacokinetics is not entirely clear. Korth-Bradley *et al.*[18] conducted an age-, sex- and weight-matched patient study looking at tigecycline pharmacokinetics in patients with severe chronic kidney disease (defined as creatinine clearance <30 mL/min but not receiving dialysis) and end-stage renal disease requiring dialysis (ESRD) versus patients with normal renal function. Their group found a 20% reduction in tigecycline clearance in subjects with severe chronic kidney disease and ESRD and a 30% higher AUC in the same groups.[18] In addition, the ESRD group had a significantly longer half-life and higher peak concentration. In contrast, Meagher *et al.*[15] found no significant difference in the pharmacokinetics of tigecycline in healthy patients versus patients with severe renal impairment.

The decision to escalate the tigecycline dose in our patient to achieve higher than usual blood levels was based on tigecycline's linear kinetics and the experience of Cunha *et al.*[5,24] Unfortunately, such dose escalation may lead to an increase in nausea and vomiting. This adverse effect may be ameliorated by using prophylactic antiemetics and increasing the fluid carrier volume.[24] We were able to dose our patient with twice the usual amount of drug without any intolerable side effects by using a reduced concentration of drug (0.5 rather than 1 mg/mL), changing the 200 mg intravenous daily dosing to 100 mg every 12 h, and extending the infusion time to 2 h (double the recommended infusion time, according to the package insert).[3,14] None of the above dosage modifications was likely to alter the drug's antibacterial activity since it correlates with the AUC/MIC pharmacodynamic index.[16]

Although tigecycline has been shown to be efficacious in treatment of a variety of serious infections, concerns remain about the drug's safety profile. A pooled analysis of Phase 3 and 4 clinical trials showed an adjusted risk difference of 0.6% (95% CI 0.1, 0.2) for all-cause mortality, thus favouring the comparator drug.[25,26] This prompted issuance of a black-box warning by the FDA to use tigecycline in the severely ill only if other options are limited.[26] Despite these concerns, tigecycline has several attributes that favour its use for treating MDR infections when other options are limited. These include ease of dosing and administration, a broad spectrum of antimicrobial activity, lack of dose adjustment with renal impairment and few significant adverse effects.[27] Compared with aminoglycosides and colistin, tigecycline represents a less toxic option for treating infections caused by MDR organisms. Use of tigecycline for treatment of UTIs is complicated by relatively low-level urinary elimination of active drug with potential for treatment failure due to exposure to low AUC/MIC conditions and subsequent development of resistance. If higher tigecycline urinary concentrations can be achieved by maximizing the dose, tigecycline may be an acceptable option for treatment of MDR urinary pathogens.

Conclusions

Based on a review of published cases and our own experience, tigecycline appears to have produced some favourable clinical and microbiological outcomes in patients with MDR Gram-negative bacillus UTIs even when used as monotherapy. Most of the supportive data for the use of tigecycline in UTIs come from treatment of multidrug-resistant organisms when few other options were available. Using higher doses (>100 mg/day) of tigecycline may improve efficacy in treatment of UTIs, but side effects may then be more pronounced. We have demonstrated tolerability of the drug at twice the usual dose through doubling both the amount of diluent as well as the infusion time and maintaining dosing every 12 h. We advocate aggressive treatment of underlying urinary stone disease as this will allow the best chance of cure. With the use of a more aggressive dosing regimen, tigecycline may be a valuable option for the treatment of MDR Gram-negative bacillus UTIs, but concerns regarding efficacy

with UTI-associated bacteraemia remain and combination therapy is most likely the safest approach when possible.

Funding

This study was supported by internal funding.

Transparency declarations

None to declare.

References

1 Muralidharan G, Micalizzi M, Speth J *et al*. Pharmacokinetics of tigecycline after single and multiple doses in healthy subjects. *Antimicrob Agents Chemother* 2005; **49**: 220–9.

2 Rodvold KA, Gotfried MH, Cwik M *et al*. Serum, tissue and body fluid concentrations of tigecycline after a single 100 mg dose. *J Antimicrob Chemother* 2006; **58**: 1221–29.

3 Brust K, Evans A, Plemmons R. Favourable outcome in the treatment of carbapenem-resistant Enterobacteriaceae urinary tract infection with high-dose tigecycline. *J Antimicrob Chemother* 2014; **69**: 2875–6.

4 Anthony KB, Fishman NO, Linkin DR *et al*. Clinical and microbiological outcomes of serious infections with multidrug-resistant Gram-negative organisms treated with tigecycline. *Clin Infect Dis* 2008; **46**: 567–70.

5 Cunha BA. Single daily high-dose tigecycline therapy of a multidrug-resistant (MDR) *Klebsiella pneumoniae* and *Enterobacter aerogenes* nosocomial urinary tract infection. *J Chemother* 2007; **19**: 753–4.

6 Elemam A, Rahimian J, Mandell W. Infection with panresistant *Klebsiella pneumoniae*: a report of 2 cases and a brief review of the literature. *Clin Infect Dis* 2009; **49**: 271–4.

7 Gallagher JC, Rouse HM. Tigecycline for the treatment of *Acinetobacter* infections: a case series. *Ann Pharmacother* 2008; **42**: 1188–94.

8 Geerlings SE. Successful treatment with tigecycline of two patients with complicated urinary tract infections caused by extended-spectrum β-lactamase-producing *Escherichia coli*. *J Antimicrob Chemother* 2010; **65**: 1145–54.

9 Krueger WA, Kempf VA, Peiffer M *et al*. Treatment with tigecycline of recurrent urosepsis caused by extended-spectrum-β-lactamase-producing *Escherichia coli*. *J Clin Microbiol* 2008; **46**: 817–20.

10 Kuo SC, Wang FD, Fung CP *et al*. Clinical experience with tigecycline as treatment for serious infections in elderly and critically ill patients. *J Microbiol Immunol Infect* 2011; **44**: 45–51.

11 Reid GE. Rapid development of *Acinetobacter baumannii* resistance to tigecycline. *Pharmacotherapy* 2007; **27**: 1198–201.

12 Drekonja DM, Johnson JR. Tigecycline treatment for urinary tract infections: case report and literature review. *J Chemother* 2011; **23**: 168–70.

13 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39** Suppl 1: S1–266.

14 Tygacil® (Tigecycline For Injection) Package Insert. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021821s021lbl.pdf (20 May 2014, date last accessed).

15 Meagher AK, Ambrose PG, Grasela TH *et al*. The pharmacokinetic and pharmacodynamic profile of tigecycline. *Clin Infect Dis* 2005; **41** Suppl 5: S333–40.

16 Hoffmann M, DeMaio W, Jordan RA *et al*. Metabolism, excretion, and pharmacokinetics of [^{14}C]tigecycline, a first-in-class glycylcycline antibiotic, after intravenous infusion to healthy male subjects. *Drug Metab Dispos* 2007; **35**: 1543–53.

17 Nicasio AM, Crandon JL, Nicolau DP. In vivo pharmacodynamic profile of tigecycline against phenotypically diverse *Escherichia coli* and *Klebsiella pneumoniae* isolates. *Antimicrob Agents Chemother* 2009; **53**: 2756–61.

18 Korth-Bradley JM, Troy SM, Matschke K *et al*. Tigecycline pharmacokinetics in subjects with various degrees of renal function. *J Clin Pharmacol* 2012; **52**: 1379–87.

19 Noskin GA. Tigecycline: a new glycylcycline for treatment of serious infections. *Clin Infect Dis* 2005; **41** Suppl 5: S303–314.

20 Sesoko S, Umemura K, Nakashima M. Pharmacokinetics (PK), safety, and tolerability of tigecycline (GAR-936) in healthy Japanese males. In: *Abstracts of the Forty-second Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, 2002*. Abstract A-1403, p. 22. American Society for Microbiology, Washington, DC, USA.

21 Nix DE, Matthias KR. Should tigecycline be considered for urinary tract infections? A pharmacokinetic re-evaluation. *J Antimicrob Chemother* 2010; **65**: 1311–2.

22 Gardiner D, Dukart G, Cooper A *et al*. Safety and efficacy of intravenous tigecycline in subjects with secondary bacteremia: pooled results from 8 phase III clinical trials. *Clin Infect Dis* 2010; **50**: 229–38.

23 Quereshi ZA, Paterson DL, Kilayko MC *et al*. Treatment outcomes of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. *Antimicrob Agents Chemother* 2012; **56**: 2108–13.

24 Cunha BA. Pharmacokinetic considerations regarding tigecycline for multidrug-resistant (MDR) *Klebsiella pneumoniae* or MDR *Acinetobacter baumannii* urosepsis. *J Clin Microbiol* 2009; **47**: 1613.

25 Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. *Clin Infect Dis* 2012; **54**: 1699–709.

26 *FDA Drug Safety Communication: FDA Warns of Increased Risk of Death with IVAntibacterial Tygacil (Tigecycline) and Approves new Boxed Warning.* http://www.fda.gov/Drugs/DrugSafety/ucm369580.htm# (2 January 2014, date last accessed).

27 Nicolau DP. Management of complicated infections in the era of antimicrobial resistance: the role of tigecycline. *Expert Opin Pharmacother* 2009; **10**: 1213–22.