Drugs Ther Perspect (2017) 33:555–565
DOI 10.1007/s40267-017-0453-3

ADIS DRUG Q&A

Intravenous minocycline in multidrug-resistant infections: a profile of its use in the USA with a focus on *Acinetobacter* infections

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Published online: 7 November 2017

Abstract Intravenous (IV) minocycline (Minocin®) is approved in the USA for use in patients with infections due to susceptible strains of many bacteria (e.g. Gram-positive and Gram-negative pathogens, including infections due to *Acinetobacter* spp.). Minocycline shows antibacterial activity against *A. baumannii* clinical isolates worldwide, and exhibits synergistic bactericidal activity against multidrug-resistant (MDR) and extensively drug-resistant (XDR) *A. baumannii* isolates when combined with other antibacterial agents. In retrospective studies, IV minocycline provided high rates of clinical success or improvement, and was generally well tolerated among patients with MDR or carbapenem-resistant *A. baumannii* infections.

Adis evaluation of IV minocycline in susceptible infections
Provides high rates of clinical success or improvement in patients with MDR or carbapenem-resistant *Acinetobacter baumannii* infections
Demonstrates antibacterial activity against *A. baumannii* clinical isolates (including MDR and XDR strains)
Exhibits synergistic bactericidal activity against *A. baumannii* isolates when combined with other antibacterials
Generally well tolerated
When used in combination with colistin, reduces the risk of colistin-associated nephrotoxicity relative to colistin alone

IV intravenous, *MDR* multidrug resistant, *XDR* extensively drug-resistant

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What is the rationale for re-introducing the IV formulation of minocycline?

Minocycline (Minocin®) is a second-generation tetracycline that has been available since the 1960s [1, 2]. An older intravenous (IV) formulation of minocycline was voluntarily withdrawn from the US market in 2005 due to declining use [2], and was reintroduced in 2009 to address the increase in MDR infections due to susceptible strains of Gram-positive and -negative pathogens, including infections due to *Acinetobacter* spp. [2, 3].

A new IV formulation of minocycline was approved by the US FDA in 2015 [4]. Trends in *Acinetobacter baumannii* resistance among clinical isolates from US patients with respiratory and blood stream infections have shown that, after the withdrawal of IV minocycline, the rate of minocycline resistance decreased from 56.5% (2003–2005) to 30.5% (2009–2012), while resistance to other antibacterial agents (such as carbapenems and colistin) increased more than twofold [5]. Among *A. baumannii* isolates collected globally from integumentary sources in 2010–2014, the rate of minocycline resistance (6.6%) was lower than that of any other antibacterial agent tested (30.9–50.3%), and showed no significant change over the course of this time period [6]. These findings suggest a potential role for IV minocycline in treating patients with infections caused by *A. baumannii* and other susceptible Gram-positive and –negative bacteria.

Why is it important to find antibacterials to treat *A. baumannii*?

Acinetobacter spp. have recently emerged as a major cause of morbidity and mortality due to healthcare-associated infections, and are often multidrug-resistant (MDR)

[2, 7, 8]. In recent years, the rates of *A. baumannii* resistance to almost all antibacterials (except minocycline) have risen in the USA [5]. Antibacterial therapy options are, therefore, becoming increasingly limited, particularly among patients with MDR or carbapenem-resistant *A. baumannii* infections.

Acinetobacter spp. are typically associated with respiratory and blood stream infections among critically ill patients, and MDR *Acinetobacter* spp. are considered a serious antibacterial resistance threat by the US Centers for Disease Control and Prevention [9]. *A. baumannii* is the most clinically relevant species within the *Acinetobacter* complex, although *Acinetobacter nosocomialis* and *Acinetobacter pitti* have also been associated with hospital-acquired infections [7]. Among *A. baumannii* clinical isolates collected from US patients in 2011–2014, the overall rate of MDR was 54.8%, and varied by state (e.g. 5% in Oregon vs 88.1% in Puerto Rico) [10]. As treatment options for MDR *A. baumannii* become increasingly limited, particularly due to the lack of new antibacterial agents, the use of older drugs to treat this pathogen has been investigated [1, 2].

For whom is IV minocycline indicated?

IV minocycline is indicated in the treatment of infections caused by isolates of designated bacteria (e.g. Gram-positive and -negative pathogens, including *Acinetobacter* spp., as well as many other bacteria) when bacteriologic testing indicates appropriate susceptibility to the drug [4]. Table 1 provides a summary of the prescribing information of IV minocycline in the USA. Consult the US prescribing information [4] for further details on the designated bacteria for which IV minocycline is indicated.

How should the susceptibility to minocycline be tested?

Consistent with principles of good antimicrobial stewardship, minocycline should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible pathogens [4]. If available, in vitro culture and susceptibility information should be considered when selecting and modifying antibacterial therapy. If culture and susceptibility information is not available, local epidemiology and susceptibility patterns should be considered when determining the empiric selection of antibacterials [4].

According to current Clinical Laboratory Standards Institute (CLSI) and FDA breakpoints, minimum inhibitory concentrations (MICs) of ≤ 4 μg/mL indicate *A. baumannii* isolates are susceptible to minocycline, MICs of 8 μg/mL indicate *A. baumannii* isolates have intermediate susceptibility to minocycline, and MICs ≥ 16 μg/mL indicate *A. baumannii* isolates are resistant to minocycline [4].

In the international surveillance SENTRY study [11], the susceptibility to minocycline was higher than that to doxycycline and tetracycline (Table 2). This indicates that a surrogate class representative (i.e. tetracycline) should not be used to test for minocycline in vitro susceptibility. Testing should be performed directly using CLSI methods or validated commercial antimicrobial susceptibility test systems [11], such as broth or agar dilution or disk diffusion techniques. The accuracy of five standard minocycline susceptibility methods was compared using 107 carbapenem-resistant *A. baumannii* isolates [12]. All testing methods were associated with low rates of major susceptibility errors (0.9% of isolates for all methods) and very major errors (0–5.6%) for minocycline. However, rates of minor errors were high (14.0–37.4%), usually due to overcalling strains that were susceptible to minocycline by reference testing methods as having intermediate susceptibility or resistance to minocycline using the other methods [12]. The highest major and minor error rates were both shown using the Etest with Mueller-Hinton agar (MHA) method, and the lowest major and minor error rates were both shown using the disk diffusion with MHA method [12].

The US prescribing information provides detailed information on the methods, interpretive criteria, and acceptable quality control ranges for susceptibility testing [4].

What is the pharmacokinetic profile of minocycline?

In healthy volunteers receiving a single IV dose of minocycline 200 mg, mean serum concentrations of minocycline were 4.18 and 1.38 μg/mL at the end of infusion and after 12 h, respectively [4]. Following 3 days' administration of IV minocycline 100 mg every 12 h or 200 mg once daily, minocycline trough plasma concentrations were 1.4–1.8 and $\approx$ 1 μg/mL, respectively [4]. Due to its enhanced lipophilicity, the tissue penetration of minocycline is greater than that of tetracycline and doxycycline, with tissue:serum concentration ratios of > 1.0 in the lung, liver, gallbladder and bile fluids, prostate, and other genitourinary organs [3].

Minocycline has at least six metabolites (some of which are active), is eliminated predominantly via the liver and hepatobiliary circulation, with $\approx$ 5–12% of a dose recovered in the urine and 20–35% in the feces, and a serum elimination half-life of 15–23 h following IV administration [1, 3, 4].

Table 1 Prescribing summary of intravenous minocycline (Minocin®) in the treatment or prevention of infections that are proven or strongly suspected to be caused by susceptible bacteria in the USA [4]

How is IV minocycline available, and how should it be reconstituted and stored?	
Availability	Single-use vials containing 100 mg of sterile lyophilized minocycline powder
Storage before reconstitution/dilution	Controlled room temperature (20–25 °C; 68–77 °F)
	Immediately further dilute in 100–1000 mL with sodium chloride, dextrose, or dextrose + sodium chloride injection USP, or in 250–1000 mL lactated Ringer's injection USP (do not dilute with calcium-containing solutions, as a precipitate may form)
Reconstitution and dilution	Reconstitute with 5 mL sterile water for injection USP
Storage after dilution in IV bag	Room temperature for up to 4 h or refrigerated (2–8 °C; 36–46 °F) for up to 24 h
What is the administration regimen of IV minocycline?	
Usual adult dose	Initial dose of 200 mg, then 100 mg administered over 60 min every 12 h and should not exceed 400 mg in 24 h (e.g. initial doses of 200 mg, then 100 or 200 mg every 12 h have been used)
Usual pediatric dose (children aged > 8 years)	Initial dose of 4 mg/kg, then 2 mg/kg administered over 60 min every 12 h, not to exceed the usual adult dose
In whom is the use of IV minocycline contraindicated?	
Patients who have shown hypersensitivity to any of the tetracyclines or to any of the components of the formulation	
How should IV minocycline be used in special populations?	
Patients with impaired renal function (exposure to tetracyclines may ↑)	Azotemia, hyperphosphatemia, acidosis, and possible liver toxicity may occur
	Monitor levels of creatinine and BUN
	Total daily dosage should not exceed 200 mg in 24 h
Patients with impaired hepatic function or taking other hepatotoxic drugs	Use with caution (hepatotoxicity has been reported with minocycline)
Women who are, or become, pregnant during treatment	Advise of the risk of fetal harm; tetracyclines cross the placenta and are found in fetal tissues, and can have toxic effects on the developing fetus (based on animal studies)
Women who are breastfeeding	Discontinue breastfeeding or minocycline based on the importance of the drug to the woman
Children aged < 8 years	Use is not recommended unless the expected benefits outweigh the risks
What other special warnings and precautions pertain to the use of IV minocycline and other tetracyclines?	
Permanent discoloration of teeth	Do not use during tooth development periods (i.e. last half of pregnancy and from infancy up to 8 years of age) unless other drugs are not likely to be effective or are contraindicated
Skeletal development (all tetracyclines form a stable calcium complex in any bone-forming tissue)	↓ In fibula growth rate seen in premature infants receiving oral tetracycline 25 mg/kg every 6 h; reaction was reversible on drug discontinuation
	Retardation of skeletal development may occur if tetracyclines are taken during early pregnancy (based on animal studies)
DRESS and hypersensitivity syndromes	Discontinue use immediately if syndrome is recognized (may be fatal)
Photosensitivity (exaggerated sunburn)	Has been reported in some individuals taking tetracyclines, including minocycline
CNS-related adverse effects (e.g. light-headedness, dizziness, and vertigo)	Generally transient; usually rapidly disappear after discontinuation
	If adverse events occur, caution patients about driving vehicles or using hazardous machinery
Clostridium difficile-associated diarrhea	Consider as cause of diarrhea in all cases that occur after antibacterial use
IH (↑ risk in women of childbearing age who are overweight or with IH history)	If visual disturbance occurs, evaluate promptly (risk of permanent vision loss)
	Monitor patients until they are stable (may take weeks after drug discontinuation)
What potential clinically relevant interactions may occur between IV minocycline and other drugs used in the hospital setting?	
Anticoagulant therapy	Some patients may require a ↓ in anticoagulant dosage (tetracycline class can ↓ prothrombin activity)
Methoxyflurane	Concurrent use may result in fatal renal toxicity

Table 1 continued

What are special warnings and precautions pertain to the inclusion of magnesium in the IV minocycline formulation?	
Heart block or myocardial damage	Closely monitor patients with these cardiac conditions
Impaired renal function	Monitor levels of magnesium (excreted by the kidney) in patients with impaired function
Potentially serious drug interactions	May occur with CNS depressants, neuromuscular blocking agents and cardiac glycosides

DRESS drug rash with eosinophilia and systemic symptoms, *IH* intracranial hypertension, *IV* intravenous, ↑ increase(s/d); ↓ decrease(s/d)

Plasma concentrations of minocycline increased in a dose proportional manner as the minocycline dose increased (6–96 mg/kg/day) in an in vivo study in rabbits, with results that can be bridged to the human dose [13]. Increases in exposure of tissues to minocycline were also dose proportional. The results further suggested that minocycline could be active against susceptible target organisms in plasma, tissues, and other bodily fluids, as the antibacterial was highly distributed throughout the body [13]. In body tissues, concentrations of minocycline were highest in the liver, followed by the lungs, heart, spleen, kidney, brain and adipose tissue; in bodily fluids, concentrations were highest in the choroid, then epithelial lining fluid, pulmonary alveolar macrophages, vitreous humor, aqueous humor and cerebrospinal fluid [13].

Pharmacodynamic/pharmacokinetic considerations

The efficacy of minocycline correlated with the area under the plasma concentration-time curve (AUC):MIC ratio in animal models of *A. baumannii* pneumonia [14, 15]. For example, the 24-h free AUC:MIC (*f*AUC:MIC) ratios for minocycline were 10.6–16.1 and 13.1–24.2 for bacteriostatic and bactericidal effects, respectively [14]. The exposure to minocycline was equivalent to dosages of 200–400 mg/day in humans [14], thereby supporting the importance of ensuring that adequate dosages of IV minocycline are administered to maximize efficacy.

Single compartment dilutional pharmacokinetic models of *A. baumannii* infection have been used to determine the in vitro relationship between exposure to minocycline and antibacterial effect [16, 17]. In one model, minocycline exhibited bactericidal activity (i.e. -1 $\log_{10}$ drop) against *A. baumannii* at *f*AUC:MIC ratios of 23.2 at 24 h, and 30.4 at 48 h [16]. Based on this model, an *f*AUC:MIC ratio target of 15–20 was considered reasonable for minocycline against *A. baumannii* [16]. In another model [17], *f*AUC:MIC ratios at 24 h were 16.4 and 23.3 for bacteriostatic and bactericidal effects against *A. baumannii*, respectively, suggesting a reasonable *f*AUC:MIC ratio target of 20–25. As resistance emerged at *f*AUC:MIC ratios of 5–15, suggesting that combination treatment with minocycline + another antibacterial, or an increase of minocycline dosage to > 400 mg/day, should be considered when treating *A. baumannii* strains, in order to reduce the emergence of resistance [17].

What is the pharmacodynamic profile of minocycline?

Minocycline is a semisynthetic derivative of tetracycline that is thought to exert its primarily bacteriostatic effects through inhibition of protein synthesis [4]. Like other tetracyclines, minocycline reversibly binds to the bacterial ribosomal 30S subunit, which results in conformation changes in the 16S ribosomal RNA that inhibit the association of aminoacyl transfer RNA with the ribosome, and ultimately disrupt bacterial protein synthesis [1, 3]. Of note, minocycline may also have immunomodulatory effects in the treatment of *A. baumannii* infection [18]. According to a recent in vitro study [18], minocycline reduced the production of inflammatory cytokines in macrophages, in addition to enhancing their antibacterial activity.

Antibacterial activity in vitro

The in vitro antibacterial activity of minocycline against clinical isolates of *A. baumannii* (including MDR *A. baumannii* isolates) based on the MIC required to inhibit growth in 90% of isolates (MIC_{90}) has been shown in ongoing global and US surveillance studies (Table 2) [11, 19–23].

In TEST (2004–2013) [19], minocycline MIC_{90} values were 8 and 16 μg/mL against *A. baumannii* and MDR *A. baumannii* isolates, respectively. These values are consistent with those in other surveillance studies including:

- A regional update of TEST (2011–2014) [24] Minocycline MIC_{90} values against MDR *A. baumannii* were 8 μg/mL in Africa, Asia-Pacific, Latin America, and North America, and 16 μg/mL in Europe and the Middle East.
- Isolates collected from global integumentary sources (2010–2014) [6] Minocycline MIC_{90} value of 8 μg/mL against *A. baumannii* ($n = 1235$; 43.2% of which were MDR).

Table 2 In vitro activity of minocycline against *Acinetobacter baumannii* isolates collected internationally in 2004–2013 (TEST [19, 20, 22, 23], SENTRY [11] and a global surveillance programme [21])

Isolate (no. of isolates)	MIC_{90} (μg/mL)	Isolates (%)[a]		Other results/comments regarding the susceptibility *of A. baumannii* isolates
		Susceptible	Resistant	
Global (2004–2013) [11, 19–21]				
A. baumannii (1312–16,778) [11, 19–21]	≥ 8 [11, 19–21]	72.3–84.5 [11, 19–21]	5.1–12.6 [19–21]	Susceptibility to minocycline was higher than that of doxycycline and tetracycline (79.1 vs 59.6 and 30.2% of isolates); 98.8% of isolates were susceptible to colistin (MIC_{90} 1 μg/mL) and 80.7% of isolates were inhibited by tigecycline ≤ 1 μg/mL [11]
				MIC range: ≤ 0.5 to ≥ 32 μg/mL [19]
				MIC_{50}: 2 μg/mL [21]
MDR *A. baumannii* (1070–6743) [19–21]	>8–16 [19–21]	66.2–75.4 [19–21]	8.3–15.4 [19–21]	Susceptibility rates with other antibacterials were generally more than twofold lower in MDR isolates than in non-MDR isolates [19]
				MIC range: ≤ 0.5 to ≥ 32 μg/mL [19]
				MIC_{50}: 4 μg/mL [21]
XDR *A. baumannii* (943) [21]	> 8 [21]	62.9 [21]	16.9 [21]	MIC_{50}: 4 μg/mL [21]
USA (2005–2011) [Pacific, Mountain, West North Central, East North Central, Middle Atlantic, New England, South Atlantic, East South Central, and West South Central regions] [22]				
A. baumannii (2900 across USA; 72–721 in each region)	Across USA:8	Across USA: 84.1	NR	MIC_{50} across USA: ≤ 0.5 μg/mL
	By region: 4–8	By region: 68.5–97.4		MIC_{50} by region: ≤ 0.5–2 μg/mL
MDR *A. baumannii* (883)	Across USA: 8	Across USA: 72.1	NR	MIC_{50} across USA: 2 μg/mL
	By region: 4–16	By region: 54.0–92.3		MIC_{50} by region: 1–4 μg/mL
Pediatric patients (2004–2012) [23]				
A. baumannii (1302)	4	90.8	NR	Isolates from patients aged 1–5 years had significantly higher minocycline susceptibility rates than those from patients aged ≥ 18 years (92.0 vs 84.6%; $p = 0.0001$)
				Minocycline MIC_{90} values were lower in pediatric isolates than in the overall population (4 vs ≥ 8)
				Global rate of MDR *A. baumannii* isolates: 19.5% (5.6, 51.1 and 52.5% in North America, Latin America and the Middle East, respectively)

CLSI Clinical and Laboratory Standards Institute, *MDR* multidrug-resistant (i.e. nonsusceptible to ≥ 1 agent in ≥ 3 antibacterial classes), *MIC* minimum inhibitory concentration (determined using the CLSI broth microdilution method), *MIC_{50}* MIC required to inhibit growth in 50% of isolates, *MIC_{90}* MIC required to inhibit growth in 90% of isolates, *NR* not reported, *XDR* extensively drug-resistant (i.e. nonsusceptible to ≥ 1 agent in all but ≤ 2 antibacterial classes)

[a]Using CLSI breakpoints indicating susceptibility, intermediate susceptibility, and resistance to minocycline (i.e. ≤ 4, 8, and ≥ 16 μg/mL, respectively)

- Isolates collected from patients in intensive care units (2004–2010) [20] Minocycline MIC_{90} value of 8 μg/mL for both *A. baumannii* ($n = 4241$; 58.7% of which were MDR) and MDR *A. baumannii* isolates ($n = 2491$).

Susceptibility to minocycline remained consistent among *A. baumannii* clinical isolates collected in 2004–2013 in the global and US surveillance studies (Table 2) [11, 19–23].

Bactericidal activity in vitro and in vivo

Minocycline + other antibacterials demonstrated synergistic bactericidal activity against clinical *A. baumannii* [25], MDR *A. baumannii* [26, 27], and extensively drug-resistant (XDR) *A. baumannii* [28] isolates in vitro. When used alone, minocycline was bacteriostatic against MDR *A. baumannii* isolates at concentrations achieved with therapeutic dosages, and bactericidal when combined with colistin [27], rifampicin [26, 27], imipenem [27], erythromycin [26], amikacin

[26], or polymyxin B [26]. In isolates not harbouring the *tetB* gene, bactericidal effects were observed with minocycline 2–8 μg/mL + colistin, and minocycline 0.5–8 μg/mL + rifampicin or imipenem [27]. Minocycline also inhibited the growth of XDR *A. baumannii* isolates when used alone at a concentration 4 μg/mL, with synergistic bactericidal activity being shown with minocycline 4 μg/mL + meropenem at 12 h, and minocycline 2 μg/mL + colistin within 2–6 h [28].

Against minocycline-resistant isolates of *A. baumannii*, minocycline + colistin also displayed synergistic activity against all isolates of minocycline-resistant *A. baumannii*, with the combination being more effective than other minocycline-based combinations, and as effective as meropenem + colistin [29]. The combination of polymyxin B and minocycline also shown bactericidal efficacy against *Klebsiella pneumoniae* carbapenemase–producing *K. pneumonia* in a preliminary in vitro study [30].

Consistent with the vitro activity of minocycline, it displayed bactericidal activity in vivo [14, 15, 25, 26, 31]. In neutropenic animal models of *A. baumannii* pneumonia, minocycline displayed bactericidal activity [14, 31], and reduced 24-h bacterial tissue burden when used as monotherapy [15, 25, 31]. Reductions in 24-h bacterial tissue burden were greater when minocycline was used in combination with polymyxin B [25], and lung tissue inflammatory infiltration reduced to a greater extent with minocycline + rifampicin or amikacin than with polymyxin B alone [26].

Resistance issues

Resistance to tetracycline is commonly due to the acquisition of genes that encode efflux pumps [11]. Of the six major facilitator superfamily efflux pumps detected in *Acinetobacter* spp., TetB is the only one capable of transporting minocycline from bacteria [11]. The *tetB* gene was detected in all XDR *A. baumannii* isolates with minocycline resistance collected in Argentina (1983–2011); all *tetB*-positive isolates had a plasmid-borne IS*CR2* element, which may help explain the spread of minocycline resistance in *Acinetobacter* spp. [32]. The widespread prevalence of the *tetB*::IS*CR2* resistance element in XDR *A. baumannii* isolates was confirmed in isolates collected in Argentina in 2009–2013 [33].

Most *tetB*-negative *A. baumannii* isolates are susceptible to minocycline, whereas *tetB*-positive isolates have lower susceptibility rates [34, 35]. In a study using 258 clinical isolates of *A. baumannii* collected world-wide in 1998–2015, resistance to minocycline, doxycycline, levofloxacin, and meropenem were shown in 44.6, 68.8, 93.0, and 80.6% of isolates, respectively [34]. MIC values for minocycline had a high degree of separation between the 93 *tetB*-negative isolates and the 165 *tetB*-positive isolates (≤ 0.0625–4 vs 4–32 μg/mL); the MIC of almost all (93%) *tetB*-positive isolates were > 4 μg/mL (i.e. higher than the susceptibility breakpoint for minocycline), whereas all *tetB*-negative isolates had MIC values lower than this breakpoint [34]. In another study using 107 carbapenem-resistant *A. baumannii* isolates, all *tetB*-negative and 71.1% of *tetB*-positive isolates were susceptible to minocycline, with median minocycline MICs of 4 (range 0.125–16) μg/mL and 1 (range ≤ 0.06–2) μg/mL, respectively [35]. These findings suggest that testing for the presence of *tetB* may be a rapid surrogate method for determining susceptibility to minocycline (i.e. the absence of *tetB* predicts susceptibility to minocycline), with further studies being warranted [34].

The addition of polymyxin B 0.25 or 0.5 μg/mL enhances the activity of minocycline against *tetB*-positive *A. baumannii* isolates, including those resistant to polymyxin B, by a factor of 2–154 [36]. In a study using 167 clinical isolates of *tetB*-positive *A. baumannii* isolates, including 4 resistant to polymyxin B, only 12.0% of isolates were susceptible (i.e. MIC ≤ 4 μg/mL) to minocycline alone (MIC 0.5–32 μg/mL) [36]. The addition of polymyxin B 0.125, 0.25, or 0.5 μg/mL increased susceptibility rates to 18.0, 58.1, and 100%, respectively, with corresponding MIC values of 0.5–16, 0.5–16, and ≤ 0.06–4 μg/mL. In the isolates resistant to polymyxin B, MIC values were 8–32 μg/mL with minocycline alone and 2–4 μg/mL with minocycline + polymyxin B 0.5 μg/mL [36]. Clinical studies of the use of minocycline + polymyxin B in the treatment of *A. baumannii* infections, especially those resistant to one or both of these antibacterials, would be of interest.

Several efflux pump systems from the resistance-nodulation-cell division family are also associated with MDR *A. baumannii* [11, 37]. In clinical isolates of MDR *A. baumannii* collected in Spain (2010), overexpression of the AdeABC efflux pump system was associated with increased MIC values for minocycline (> 2 μg/mL), tigecycline (> 0.5 μg/mL), and gentamycin (> 8 μg/mL), while overexpression of the AdeIJK efflux pump (alone or together with TetB) was associated with increased minocycline MIC values (≥ 2 μg/mL) [37].

In vitro, a few intrinsic mechanisms may modestly elevate minocycline MIC values, with these values remaining within the *A. baumannii* susceptible range [38, 39]. Mutations in minocycline-resistant strains have been located in *adeN* (a negative regulator of the AdeIJK

efflux pump), *trm* (*S*-adenosyl methionine-dependent methyltransferase), and/or the ≈ 720 bp region between the *rluC* and *rne* genes [38]. The maximum minocycline MIC (4 μg/mL) in these mutants was lower or at the current CLSI susceptibility breakpoint [38]. The minocycline mutant prevention concentration (1 μg/mL) was below the minocycline peak and trough plasma concentrations obtained with the usual dosage [39]. Of note, unlike tigecycline, minocycline is not a substrate for the adeABC efflux system [39].

What is the effectiveness of IV minocycline in *Acinetobacter* infections?

Given the difficulty of performing large prospective trials in less common pathogens such as *Acinetobacter spp*., prospective randomized clinical trials of IV minocycline have not been conducted. Moreover, such trials were not required by the FDA when IV minocycline was first approved several decades ago. Nevertheless, several retrospective single-centre studies have documented the effectiveness of IV minocycline in the treatment of infections caused by *A. baumannii* and other pathogens, MDR *A. baumannii* [40–42], and carbapenem-resistant *A. baumannii* [43, 44] in the clinical practice setting in the USA.

Treatment with IV minocycline was associated with clinical improvement or treatment success in small studies in hospitalized patients with MDR [40–42] or carbapenem-resistant *A. baumannii* [43, 44] (Table 3). In the largest of these studies, treatment with IV minocycline achieved clinical success in 73% of patients with MDR *A. baumannii* infections (Table 3) [40], most commonly respiratory, blood, and respiratory + blood infections (58, 18, and 7% of patients, respectively). [40]. During the 30-day follow-up period, one patient (who had achieved presumed microbiologic eradication with minocycline + colistin for 14 days) was readmitted at 16 days post-discharge with worsening respiratory status due to an MDR *A. baumannii* infection. Upon readmission, the minocycline MIC had increased from 4 to 6 mg/L (i.e. intermediate susceptibility) on MDR *A. baumannii* respiratory culture. The patient achieved clinical success following treatment with colistin + doripenem for 14 days [40].

Limited data suggest that minocycline is also an effective option for treating carbapenem-resistant *K. pneumonia* infection [45]. In a case series of four patients with carbapenem-resistant *K. pneumonia* infection in one US hospital, all patients achieved a good clinical response with twice-daily oral minocycline 200 mg, with one patient developing further carbapenem-resistant bacteremia 18 days after completion of the initially successful therapy [45].

What is the tolerability profile of IV minocycline?

IV minocycline is generally well tolerated when used to treat infections. No adverse events were considered to be related to treatment with IV minocycline in retrospective studies in patients with MDR or carbapenem-resistant *A. baumannii* infections [40, 41, 43]. In one of these studies, a patient with carbapenem-resistant *A. baumannii* pneumonia developed acute kidney injury, which was presumed to be related to the use of concomitant colistin [43]. According to a review of adverse event data in 84 patients with MDR *A. baumannii*, neutropenia + eosinophilia was reported in one minocycline recipient [46].

The tetracycline class of antibacterials are commonly associated with gastrointestinal effects (e.g. nausea, anorexia, and diarrhea), CNS effects (e.g. dizziness, lightheadedness, and vertigo), fever, permanent tooth discolouration, photosensitivity and other dermatologic conditions, liver and renal toxicity, hypersensitivity, and respiratory, genitourinary, musculoskeletal and blood disorders [4]. When administered via IV, local reactions (e.g. injection-site erythema or pain) may occur; tinnitus and decreased hearing have also been reported in recipients of IV minocycline [4]. Appropriate precautions should be following to minimize the risk and severity of adverse events (Table 1) [4].

How is IV minocycline being used in the hospital setting?

Based on data extracted from the Premier Research database (a large database of > 500 US hospitals), a retrospective study analysed the patterns of use of IV minocycline in the hospital setting [47]. The study included 521 inpatients in 44 US hospitals who received at least one dose of IV minocycline during an 18-month study period (1 Jan 2014 to 30 Jun 2015). Patients had a mean age of 61.8 years, and frequently had comorbid conditions (29.2–36.8% of patients had chronic pulmonary disease, renal disease, congestive heart failure, and/or diabetes). The mean Charlson Comorbidity Index score of minocycline recipients was 3.17 [47], which is considered relatively high (a score of ≥ 5 essentially indicates a 100% risk of dying at 1 year) [48].

The most common primary International Classification of Diseases, 9th edition (ICD-9) diagnoses for which patients received IV minocycline were 'infectious and parasitic diseases' and 'respiratory system diseases' (28.1 and 19.4% of patients, respectively) [47]. The primary infections most frequently treated with IV minocycline were septicemia (26.7% of patients), complications of

Table 3 Efficacy of intravenous minocycline in adult patients with *Acinetobacter baumannii* infections in retrospective single-center studies

Type of infection (study dates)	Relevant patient population and treatment regimens	Main clinical outcomes
MDR *A. baumannii*		
MDR *A. baumannii* [40] (Sep 2010–Mar 2013)	All 55 pts had MDR *A. baumannii* infections (nonsusceptible to ≥ 1 agent from ≥ 3 antibacterial classes) with cultures susceptible to minocycline (i.e. MIC ≤ 4 μg/mL)	73% of patients achieved clinical success (defined as complete or partial resolution of MDR *A. baumannii* infection signs and symptoms without the need for escalated antibacterial treatment; primary outcome) with minocycline
	Pts received IV minocycline 100 mg twice daily within 72 h of the onset of infection for ≥ 48 h (median treatment duration 9 days); most (76%) pts also received a 200 mg loading dose	27% pts had clinical failure (i.e. persistent signs and symptoms of infection with the need for additional antibacterial agents); a total of 78% of pts achieved documented or presumed microbiologic eradication with minocycline
	All but 3 pts received ≥ 1 other concomitant antibacterial agent, most commonly colistin ($n = 45$), doripenem ($n = 20$), and ampicillin/sulbactam ($n = 17$)	Overall rate of *A. baumannii* infection-related mortality was 25% (14 deaths; 12 from pneumonia and 2 from pneumonia + bacteremia); median hospital length of stay was 31 days; median infection-related hospital length of stay was 16 days
MRSA or MDR Gram-negative bacteria [41] (Nov 2009–Apr 2012)	5/21 pts had MDR *A. baumannii* infections and received minocycline 100 mg every 12 h	All pts with MDR *A. baumannii* infections showed clinical improvement with minocycline
MDR *A. baumannii* VAP [42] (Jan–Dec 1998)	4/7 pts received minocycline 100 mg every 12 h (+ imipenem/cilastatin in 1 pt; + trovafloxacin + trimethoprim/sulfamethoxazole in 1 pt); 3/7 received doxycline100 mg every 12 h	All (4/4) minocycline and 2/3 doxycycline recipients achieved treatment success (defined as the absence of *A. baumannii* from follow-up bronchoalveolar lavage culture and/or improvement in clinical symptoms)
Carbapenem-resistant *A. baumannii*		
Carbapenem-resistant Gram-negative bacteria [43] (not reported)	7/9 pts had carbapenem-resistant *A. baumannii* infections and received twice-daily IV minocycline 100 or 200 mg ($n = 2$ and 5) × 4−13 days; 6 pts also received colistin, meropenen, and/or ampicillin/sulbactam ($n = 5$, 1, and 1)	5 (71%) patients with carbapenem-resistant *A. baumannii* infections achieved clinical cure (defined as resolution of signs and symptoms of infection) with minocycline
		3/5 pts in whom repeat cultures were reported achieved microbiologic cure
		2 pts without clinical or microbiologic cure subsequently died
Carbapenem-resistant *A. baumannii* VAP [44] (Jul 2004 to Dec 2007)	19/55 pts received IV minocycline (200 mg loading dose, then 100 mg twice daily) or IV doxycycline	In the combined minocycline/doxycycline groups, 79% (15/19) achieved a clinical response (defined as improvement and resolution of VAP or microbiologic eradication of *A. baumannii*)

IV intravenous, *MDR* multidrug-resistant, *MRSA* methicillin-resistant *Staphylococcus aureus*, *pt(s)* patient(s), *VAP* ventilator-associated pneumonia

device, implant, procedure, or medical care (7.7%), skin and subcutaneous tissue infection (6.9%), pneumonia (6.3%), and respiratory failure (5.8%) [47].

Overall, the patient population receiving IV minocycline was severely ill, with 65.5% of patients being treated in ICU, and 54.1% requiring the use of mechanical ventilation [47]. Almost all patients (≈ 91%) required immediate admission to hospital, including 74.9% who required emergency admission and 15.4% who required urgent admission [47].

The use of IV minocycline in US hospitals appears to be increasing substantially over time [47]. In the 44 US hospitals included in the retrospective study of the Premier Research database, < 50 patients received IV minocycline in 2009; however, ≈ 400 patients were projected to receive it in 2015 [47]. The mean overall length of IV minocycline treatment was 5.4 days, with most (68.3%) patients receiving treatment for ≥ 3 days. On the first day of administration, 21.3% of patients received 100 mg of IV minocycline, 44.5% received 200 mg, 25.1% received 300 mg, and 7.9% received 400 mg; a total of 69.6% received a first-day loading dose of 200 or 300 mg. For the remainder of treatment, the majority of patients received 200 mg of IV minocycline per day (e.g. 75.3 and 74.4% of patients on days 2 and 3 of treatment) [47].

In a breakdown of mean hospital costs per IV minocycline recipient in the survey, the cost of IV minocycline ($US1108) accounted for 5.7% of the total pharmacy costs, which in turn accounted for 20% ($US19,453) of the total per patient cost of $US96,450 [47]. Room + board was the leading single cost component ($US35,347; 37% of the total costs); operating room costs ($US15,258) accounted for 16% of total costs, with all other cost categories each accounting for < 1–7% of the total costs [47].

Does adding minocycline reduce the risk of polymyxin-associated toxicity?

Minocycline and polymyxins (e.g. colistin) display synergistic antibacterial activity [27, 28, 36], and may be used in combination to treat MDR *A. baumannii* infections. However, polymyxins are well known to have nephrotoxic and neurotoxic effects, even at the plasma concentrations needed for bactericidal activity [49, 50]. The addition of minocycline to polymyxin treatment may potentially ameliorate polymyxin-associated nephrotoxicity and neurotoxicity, in addition to its synergistic antibacterial activity. According to a recent systematic review of the potential mechanism of minocycline in kidney diseases [49], minocycline provides protection against the development and progression of kidney disease by suppressing apoptosis, scavenging free radicals, scavenging, preventing inflammation and mitochondrial dysfunction, and inhibiting matrix metalloproteinase. Moreover, in an in vitro study, minocycline provided protective effects against colistin-associated neurotoxicity by scavenging reactive oxygen species and suppressing apoptosis [50].

Two retrospective cohort studies (based on data extracted from the Premier Research database) analysed the occurrence of acute renal failure (ARF) in adult patients admitted to an ICU with an ICD-9 diagnosis of pneumonia or sepsis who had received IV colistin for ≥ 3 days during the study period (1 Jan 2010 to 31 Dec 2015) [51, 52].

One analysis included a total of 4602 IV colistin recipients, with 3512 receiving colistin alone, 95 colistin + minocycline (including those who received both minocycline and tigecycline), and 995 colistin + tigecycline (an overlap period of ≥ 3 days was required for combination therapy) [51]. The unadjusted rate of colistin-associated ARF when colistin was used alone (21.2% of patients) significantly decreased when colistin minocycline was administered [11.6%; $p = 0.003$; OR 0.49 (95% CI 0.26–0.92)], but significantly increased when colistin was used with tigecycline [25.6%; $p = 0.024$; OR 1.28 (95% CI 1.09–1.51)]. In addition, the unadjusted mortality rate did not differ significantly between colistin alone and colistin + minocycline (27.0 vs 31.6% of patients), but was significantly higher with colistin + tigecycline (35.4%) than that with colistin alone [$p < 0.001$; OR 1.48 (95% CI 1.28–1.72)] [51]. There were no significant between-group differences with regard to unadjusted rates of 30-day hospital readmission (26.6 vs 30.8 and 26.4% of colistin alone, colistin + minocycline, and colistin + tigecycline recipients, respectively) [51].

Similar results with colistin + minocycline versus colistin alone were shown in the other analysis, which included a total of 5120 patients with 5025 receiving colistin alone and 95 colistin + minocycline (median duration of overlap therapy 7.36 days). Colistin was initiated before, concomitantly, and after minocycline in 45.3, 35.8, and 18.9% of patients, respectively) [52]. The rate of colistin-associated ARF was significantly lower with colistin + minocycline than with colistin alone based on unadjusted data [11.6 vs 23.0%; $p = 0.009$; OR 0.48 (95% CI 0.23–0.83)] and adjusted (propensity score matching) data [11.6 vs 24.7%; $p = 0.007$; OR 0.40 (95% CI 0.20–0.79)]. There were no significant between-group differences with regard to either unadjusted or adjusted rates of in-hospital mortality or 30-day readmission. Based on conventional regression analysis, the development of ARF significantly ($p < 0.001$) increased per-patient hospital costs (additional $US10,308) and hospital length of stay (additional 3.4 days) in this study [52].

What conclusions can be made regarding the clinical use of IV minocycline?

IV minocycline is an option in the treatment of patients with susceptible MDR *A. baumannii* infections, particularly when used with a second antibacterial agent, such as colistin or polymyxin B. It may also be used to treat other difficult-to-treat infections caused by susceptible bacteria. Retrospective studies in the clinical-practice setting have shown IV minocycline to be generally effective and well tolerated in patients with MDR [40–42] or carbapenem-resistant *A. baumannii* [43, 44] infections. IV minocycline is also a re-emerging option in the treatment of susceptible carbapenem-resistant infections caused by the Enterobacteriaceae family of Gram-negative bacteria (e.g. *Escherichia coli*, *K. pneumoniae*, and *Enterobacter* spp.), which is a common and increasingly resistant source of infection [30, 53].

Analyses of data from the Premier Research database are helpful in showing how IV minocycline is being used as mono- and combination therapy in the clinical-practice setting in the USA [47, 51, 52]. However, as the data in these analyses were derived from administrative records, only very limited information regarding causative pathogens and treatment outcomes are available. Despite these

limitations, the analyses have indicated that there is an increasing need for clinically effective antibacterials, such as minocycline, to treat MDR *A. baumannii* and other serious infections, and that the addition of IV minocycline, but not IV tigecycline, to colistin treatment may reduce the risk of colistin-associated acute renal failure.

The use of IV minocycline may also be cost effective in the treatment of MDR *A. baumannii* infections from a US hospital perspective, according to the results of a decision-tree model [54]. IV minocycline monotherapy was predicted to be cost saving relative to meropenem monotherapy for the treatment of MDR *A. baumannii* after a positive culture (incremental gain of 3.38 life-years (LYs), and a decrease in hospital-related costs of $US2099 (2014 values)]. After the failure of carbapenem therapy, a switch to IV minocycline was estimated to be a cost saving relative to a switch to colistin (incremental gain of 3.12 LYs, and decrease in cost of $US1599), and cost effective relative to tigecycline (incremental cost per LY gained of $415) [54]. However, the results of this analysis are limited by the incorporation of assumed clinical outcomes, which was necessary due to the lack of robust comparative clinical data, and the simplistic model design, which considered only the use of antibacterial monotherapy instead of both mono- and combination therapy [54].

Head-to-head comparative clinical and pharmacoeconomic studies would help clarify the position of IV minocycline relative to other antibacterials in the treatment of susceptible MDR and XDR *A. baumannii* infections.

Acknowledgements The manuscript was updated from *Drugs* 2016;76(15):1467-76 [55], and was reviewed by: *D.R. Abernethy*, Office of Clinical Pharmacology, US Food and Drug Administration, Silver Spring, MD, USA; *M. Morgado*, CICS-UBI Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal. During the peer review process, the marketing authorization holder of IV minocycline was offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with ethical standards

Funding The preparation of this review was not supported by any external funding.

Conflict of interest K.A. Lyseng-Williamson, S.L. Greig SL, and L.J. Scott are employees of Adis/Springer, are responsible for the article content and declare no conflicts of interest.
Additional information about this Adis Drug Q&A can be found here http://www.medengine.com/Redeem/F1CCF060601D5A39

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