A Review of Intravenous Minocycline for Treatment of Multidrug-Resistant Acinetobacter Infections

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Options for treatment of multidrug-resistant (MDR) Acinetobacter baumannii infections are extremely limited. Minocycline intravenous is active against many MDR strains of Acinetobacter, and Clinical and Laboratory Standards Institute breakpoints exist to guide interpretation of minocycline susceptibility results with Acinetobacter. In addition, minocycline intravenous holds a US Food and Drug Administration indication for treatment of infections caused by Acinetobacter. There is an accumulating amount of literature reporting successful use of minocycline intravenous for treatment of serious MDR Acinetobacter infections, particularly for nosocomial pneumonia. These results, coupled with the generally favorable tolerability of minocycline intravenous, support its use as a viable therapeutic option for treatment of MDR Acinetobacter infections.

Keywords. minocycline; intravenous; Acinetobacter; multidrug-resistant.

Increasing attention has been directed at Acinetobacter baumannii, one of the difficult-to-treat ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) as originally highlighted by the Infectious Diseases Society of America in a 2009 position paper and in a 2013 update [1, 2]. The threat posed by MDR Acinetobacter was recently rated by the US Centers for Diseases Control and Prevention as “serious” and likely to worsen without ongoing public health monitoring and prevention initiatives [3]. Options for treatment of MDR Acinetobacter infections are becoming increasingly limited.

The need for new treatments for serious infections caused by MDR strains of A. baumannii has become critical, especially given the lack of new antibacterial development within the pharmaceutical industry. As a result, reexamination of existing antibacterial agents with the potential for unique therapeutic activity against this pathogen has become essential.

One of the classes of antibiotics being explored for treatment of MDR Acinetobacter infections is the tetracyclines. Introduced shortly after the advent of penicillins and sulfonamides, tetracycline antibiotics contain a core base structure composed of 4 hexagonal rings. Minocycline, or 7-dimethylamino-6-deoxytetracycline, is a semisynthetic tetracycline derivative that was originally introduced in the 1960s [4, 5]. Historically available in both oral and intravenous dosage forms, the intravenous formulation experienced a brief hiatus followed by reappearance of this formulation in 2009 [4]. Indeed, minocycline intravenous is currently approved by the US Food and Drug Administration for treatment of minocycline-susceptible Acinetobacter species infections [6]. In addition, Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints for minocycline and Acinetobacter exist and are ≤4 µg/mL for susceptibility, 8 µg/mL for intermediate, and ≥16 µg/mL for resistance [7].

This article will briefly discuss the microbiology, pharmacokinetics, pharmacodynamics, and tolerability of minocycline, and also review the available literature.
evaluating use of minocycline intravenous specifically for treatment of MDR *Acinetobacter* infections. Relevant articles for this review were obtained via a comprehensive search of PubMed and Google Scholar and limited to the English language.

**MICROBIOLOGY**

In common with other tetracyclines, minocycline inhibits bacterial protein synthesis through binding with the 30S subunit of the bacterial ribosome, most typically resulting in a bacteriostatic effect. However, synergistic and bactericidal activity against MDR *Acinetobacter* has been noted with minocycline in combination with colistin or carbapenems [8, 9]. Resistance to tetracyclines generally occurs through increased efflux or ribosomal protection [4]; however, minocycline is able to evade most tetracycline resistance mechanisms, including some mechanisms expressed by MDR *Acinetobacter* that confer resistance to other tetracyclines [10]. Thus, due to the possibility of obtaining discordant results among tetracycline agents, in vitro susceptibility testing of *Acinetobacter* should include minocycline. *Acinetobacter* resistance to minocycline may occur, though, and appears to be associated with the tet(B) efflux gene in association with the plasmid-mediated ISCR2 mobile element [4, 11].

**PHARMACOKINETICS AND PHARMACODYNAMICS**

Pharmacokinetic and pharmacodynamic characteristics of minocycline intravenous, along with dosing recommendations, are contained in Table 1. Peak serum concentrations following a 200-mg intravenous dose of minocycline range from 2.52 to 6.63 µg/mL and average 4.18 µg/mL. Twelve-hour trough concentrations achieved at steady state with dosing of 100-mg intravenous every 12 hours, as per the US prescribing label, range from 1.4 to 1.8 µg/mL. [6]. These achievable peak and trough serum concentrations with standard human doses of minocycline intravenous exceed the mutant prevention concentration of 1 µg/mL, which has been reported with *Acinetobacter* [12]. The drug is 76% protein bound and has a volume of distribution of 1.3 L/kg [13]. Minocycline has enhanced lipophilicity over earlier tetracyclines, which enhances tissue penetration [14]. The 15- to 23-hour half-life of minocycline is longer than that of the earliest tetracyclines, making it a long-acting agent within the class [6, 15]. Renal impairment appears to have little effect on the half-life or area under the concentration–time curve; MIC, minimum inhibitory concentration; MPC, mutant prevention concentration.

**CLINICAL EXPERIENCE**

The favorable pharmacokinetic profile of minocycline intravenous, along with its stability to many tetracycline resistance mechanisms, suggests a potential role for minocycline intravenous for treatment of some serious MDR *Acinetobacter* infections. Data concerning antibiotic treatment of infections caused by MDR bacteria in general are limited and typically descriptive. Published data evaluating minocycline intravenous for treatment of MDR *Acinetobacter* infections generally consist of observational data in the form of case reports and series.

**Minocycline Intravenous for *Acinetobacter* Pneumonia**

In a retrospective case series conducted at Presley Regional Medical Center in Memphis, Tennessee, Wood et al described their experience in treating 7 critically ill trauma patients with late-onset ventilator-associated pneumonia (VAP) caused by *A. baumannii*, 4 of whom were treated with minocycline 100 mg intravenous every 12 hours for 10–20 days [18]. The
A. baumannii strains in these 4 patients were all resistant to amikacin and sulbactam. Three of the 4 strains were also resistant to imipenem, with the fourth strain showing intermediate susceptibility to imipenem. All 4 MDR strains were susceptible to tetracycline, with appropriately inferred susceptibility to minocycline [7]. To qualify as having VAP, all patients were required to have A. baumannii growth of ≥10^5 colony-forming units (CFU)/mL from bronchoalveolar lavage (BAL), in addition to fever, leukocytosis or leukopenia, macroscopically purulent sputum, and new or changing infiltrate on chest radiography.

All 4 patients with A. baumannii VAP treated with minocycline intravenous were deemed successes, defined as clinical improvement and absence of A. baumannii from follow-up BAL culture. One of these 4 patients did not undergo a follow-up BAL, but was judged a success based on predefined criteria of clinical improvement and survival to hospital discharge. Two of the 4 patients deemed successes received minocycline intravenous monotherapy, whereas the other 2 patients received combination therapy with minocycline intravenous and imipenem in 1 case and trovafloxacin and amikacin in the other. The A. baumannii strains in these combination therapy cases were not susceptible to the agents accompanying the minocycline intravenous. The patient receiving the combination of minocycline intravenous, trovafloxacin, and trimethoprim-sulfamethoxazole was coinfected with Pseudomonas aeruginosa and Stenotrophomonas maltophilia. This patient ultimately died later in their hospital course due to septic shock from P. aeruginosa VAP, but was not deemed a minocycline failure as A. baumannii was not found in the follow-up BAL performed after a 14-day course of intravenous minocycline. This first report of successful use of minocycline intravenous for treatment of clinically and microbiologically confirmed VAP caused by MDR A. baumannii provided the basis for continued study of minocycline intravenous for serious Acinetobacter infections.

Chan et al subsequently conducted a retrospective analysis of 55 patients with carbapenem-resistant A. baumannii VAP at Harborview Medical Center in Seattle, Washington [19]. Ventilator-associated pneumonia was defined by a quantitative BAL culture of ≥10^5 CFU/mL or brush specimen ≥10^5 CFU/mL of carbapenem-resistant Acinetobacter performed by bronchoscopy during hospitalization. Clinical response was defined as resolution or improvement in signs and symptoms of VAP or microbiologic eradication of carbapenem-resistant Acinetobacter from subsequent BALs or sputum cultures at completion of therapy. All patients with polymicrobial VAP received combination therapy with appropriate agents directed at other causative pathogens in addition to Acinetobacter. Of the total population of patients, 19 received minocycline intravenous therapy at a dose of 200 mg once, followed by 100 mg intravenous every 12 hours. A clinical response was noted in 15 of 19 (78.9%) patients receiving minocycline intravenous. Patients receiving minocycline 200 mg oral or per tube every 12 hours had an 82.4% (14/17) successful response rate. Although approximately two-thirds of patients treated with minocycline received combination therapy with at least 1 other agent, clinical response rates did not differ between the minocycline monotherapy group (81.8%) vs the minocycline combination therapy group (80%). The overall minocycline clinical success rate of 80.6% also compared favorably to the 60%, 66.7%, 77.8%, and 90% response rates noted for sulbactam-, polymyxin-, aminoglycoside-, and tigecycline-based comparative therapies, respectively. Although this retrospective analysis provided only limited details of the specific clinical responses of minocycline intravenous-treated patients, it did evaluate a large number of Acinetobacter VAP infections that were confirmed based on a predefined strict definition. The effectiveness of step-down therapy from minocycline intravenous to oral was also suggested by this report.

In another retrospective analysis, Jankowski et al reported the results of minocycline intravenous treatment of 3 intensive care unit patients with MDR A. baumannii pneumonia at Ohio State University Medical Center [20]. These cases of pneumonia were included as a component of this broader report of that institution’s use of minocycline intravenous for various MDR Acinetobacter infections. Specific definitions for infections assessed were not provided. The 3 patients received minocycline 100 mg intravenous every 12 hours for 10–13 days in combination with another active agent. Of note, minocycline susceptibility was not reliably predicted by susceptibilities to tigecycline, with some isolates exhibiting lower minimum inhibitory concentrations with minocycline than tigecycline. All 3 patients had documented or presumed eradication of Acinetobacter. Two of the 3 patients had a clinical response to therapy with minocycline and survived to discharge. The single patient who died experienced eradication of Acinetobacter from BAL and urine, but ultimately had withdrawal of care. Surviving patients were longitudinally followed and were not readmitted to the authors’ hospital within 90 days after discharge.

Bishburg et al recently published their experience using minocycline intravenous in treating resistant gram-negative and methicillin-resistant Staphylococcus aureus (MRSA) infections at Newark Beth Israel Medical Center [21]. This report included 2 patients with pneumonia caused solely by A. baumannii. A specific definition for pneumonia was not provided. Both cases of Acinetobacter pneumonia clinically improved and were deemed successfully treated with minocycline 100 mg intravenous every 12 hours for durations between 7 and 14 days. Whether additional antibiotics were added to minocycline intravenous in these cases of Acinetobacter pneumonia was not specifically addressed. No adverse effects were noted with minocycline in either of the cases, and both patients were discharged from the hospital.
Minocycline for Other Acinetobacter Infections

In addition to their aforementioned pneumonia cases, Jankowski et al also described their use of minocycline intravenous for a case of bacteremia and a case of skin and soft tissue infection caused by MDR Acinetobacter [20]. The patient with bacteremia received a minocycline loading dose of 200 mg intravenous, followed by 100 mg intravenous every 12 hours for 20 days, in addition to colistin for 19 of the 20 days. Bacterial eradication and clinical cure were achieved. The patient was discharged, was not continued on any antibiotics following discharge, and was not readmitted to the authors’ hospital within 90 days following discharge. However, at a 90-day postdischarge evaluation, the patient was noted to have died. The other case was a wound infection caused by MDR Acinetobacter. This patient was treated with minocycline 100 mg intravenous every 12 hours for 10 days and colistin for 17 days. Presumed bacterial eradication was achieved, and the patient was discharged from the hospital alive. At 90-day postdischarge follow-up, the patient was still alive.

Bishburg et al recently published their experience using minocycline intravenous in treating resistant gram-negative and MRSA infections at Newark Beth Israel Medical Center [21]. This report included 3 patients with polymicrobial infections involving A. baumannii: 2 with skin and soft tissue infection (including a postoperative wound infection) and 1 with osteomyelitis. Specific definitions for infections assessed and details of any adjunctive therapies were not provided. Each patient with polymicrobial infection involving MDR Acinetobacter clinically improved and was deemed successfully treated with minocycline 100 mg intravenous every 12 hours for durations of therapy up to 7 days, followed by oral minocycline for continued therapy. No adverse effects were noted with minocycline in any of the cases, and all 3 patients were discharged from the hospital.

The availability of minocycline in both intravenous and oral dosage forms is convenient and can help promote continuity of treatment. Griffith et al reported a case series of 8 patients with specifically defined traumatic wound infections with presumptive osteomyelitis caused by MDR Acinetobacter baumannii from Brooke Army Medical Center in Fort Sam Houston, Texas [22]. Initial therapy with minocycline intravenous was not provided in any case. However, this study occurred during the period of time that minocycline intravenous was not available on the US market. All patients were treated with minocycline 100 mg orally twice daily for 4–7 weeks, and all isolates of A. baumannii were susceptible to minocycline. Three patients received prior therapy with colistin (2 cases) and imipenem (1 case). Seven of the 8 patients’ infections involved pathogens, all of which were treated with other concomitant antibiotics in addition to minocycline. However, in the majority of cases, the additional antibiotic was inactive against the Acinetobacter strain identified. Patients were followed for an average of 6 weeks. All patients also underwent serial surgical debridement of nonviable or overtly infected tissue, and 4 patients had retained, surgically placed hardware. Treatment was deemed successful in 7 of the 8 patients treated with minocycline. The other patient was clinically responding to minocycline, but developed eosinophilia and neutropenia, which resolved upon discontinuation of minocycline. No other adverse effects of minocycline were noted in any other patient.

ADVERSE EVENTS

Minocycline is, in general, well tolerated. In an early clinical evaluation of minocycline intravenous for treatment of 24 severe infections (non-Acinetobacter), no toxicities or adverse effects of the agent were noted [23]. Very limited details regarding the tolerability of minocycline intravenous for treatment of MDR Acinetobacter infections in the previously discussed clinical reports are available. One patient receiving minocycline intravenous for treatment of a traumatic wound infection caused by MDR Acinetobacter experienced reversible eosinophilia and neutropenia while clinically improving on minocycline [22]. No adverse effects of minocycline intravenous were noted in any of the 8 patients receiving the drug for treatment of infections caused by MDR organisms, including 5 with MDR Acinetobacter infections [21]. Of interest, additional safety data are available for nonantimicrobial use of minocycline intravenous. Minocycline intravenous at doses of up to 10 mg/kg/day for 72 hours was reported to be safe and well tolerated in 60 patients receiving the drug in the setting of acute ischemic stroke, with only a single patient experiencing dose-limiting hepatic enzyme elevation [24].

As with other tetracyclines, minocycline should be avoided in pregnancy and in children aged <8 years due to its ability to cause permanent tooth discoloration [6]. Minocycline may cause photosensitivity, lightheadedness, dizziness, vertigo, gastrointestinal disturbances, and local injection site reactions [6, 25, 26]. Drug rash with eosinophilia and systemic symptoms, hepatotoxicity, Clostridium difficile–associated diarrhea, pseudotumor cerebri, serum sickness–like reaction, hematologic abnormalities, drug-induced lupus, and antianabolic effects may rarely occur [6, 27]. A thorough study of the possible effects of minocycline intravenous on the QTc interval has not been conducted. Overall, minocycline intravenous appears to have a favorable risk–benefit profile when considered for treatment of serious MDR Acinetobacter infections.

DISCUSSION

A total of 23 cases of MDR Acinetobacter pneumonia successfully treated with minocycline intravenous have been reported by 4 different groups of authors (Table 2). Although the reports are descriptive, often lack specific details, frequently involve use of minocycline intravenous in combination with other antibiotics,
### Table 2. Summary of Clinical Experience With Minocycline for Treatment of Infections Caused by *Acinetobacter*

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Outcomes Evaluated</th>
<th>Results</th>
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<tr>
<td><strong>Pneumonia</strong></td>
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<tr>
<td>Wood et al [18]</td>
<td>Retrospective case series VAP Critically ill trauma patients MDR <em>Acinetobacter baumannii</em> n = 4 All sensitive to tetracycline Monotherapy (n = 2) and combination therapy (n = 2) Minocycline 100 mg intravenous every 12 h Treatment duration ranged from 10 to 20 d</td>
<td>Success was defined as negative follow-up BAL and clinical improvement. If follow-up BAL was unavailable, then success was defined as clinical improvement and survival until hospital discharge. Failure was defined as death due to VAP complications or persistent positive BAL culture without clinical improvement.</td>
<td>All 4 patients achieved success. Three patients had a negative follow-up BAL. One patient did not have a follow-up BAL.</td>
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<tr>
<td>Chan et al [19]</td>
<td>Retrospective study VAP Trauma center Carbapenem-resistant <em>Acinetobacter</em> n = 19 Minocycline 200 mg, then 100 mg intravenous every 12 h (or 200 mg orally or per tube every 12 h) Overall average treatment duration = 13.3 d</td>
<td>Clinical response, defined as improvement and resolution of signs and symptoms of VAP, or microbiologic eradication from follow-up BAL or sputum culture</td>
<td>Clinical response to minocycline intravenous: 15/19 (78.9%) Clinical response to minocycline oral: 14/17 (82.5%) Overall clinical response to minocycline-based regimens: 29/36 (80.6%) Overall clinical response regardless of specific antibiotic therapy: 42/55 (76.4%)</td>
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<tr>
<td>Jankowski et al [20]</td>
<td>Retrospective case series Intensive care unit patients MDR <em>Acinetobacter baumannii</em> n = 3 Minocycline 100 mg intravenous every 12 h Treatment duration ranged from 10 to 13 d</td>
<td>Successful clinical outcome was defined as the absence of or partial resolution of clinical and laboratory parameters of infection. Successful microbiologic outcome was defined as documented or presumed eradication.</td>
<td>Successful clinical outcome: n = 2/3 Successful microbiologic outcome: n = 3/3</td>
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<tr>
<td>Bishburg et al [21]</td>
<td>Retrospective study Hospitalized patients <em>Acinetobacter baumannii</em> n = 2 Minocycline 100 mg intravenous every 12 h (allowed transition to minocycline oral therapy to complete the course) Treatment duration ranged from 5 to 18 d</td>
<td>Clinical improvement Hospital discharge</td>
<td>Both patients demonstrated clinical improvement and were discharged from the hospital.</td>
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<td><strong>Skin and soft tissue infections with or without osteomyelitis</strong></td>
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<td>Jankowski et al [20]</td>
<td>See tabular description above</td>
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<td>Successful clinical and microbiologic outcome</td>
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<td>Bishburg et al [21]</td>
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<td><strong>Bacteremia</strong></td>
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<td>Griffith et al [22]</td>
<td>Retrospective study Traumatic wound infection with presumptive osteomyelitis MDR <em>Acinetobacter calcoaceticus</em> complex n = 8 Sensitive to minocycline: n = 3 Susceptibility to minocycline not available: n = 5 Minocycline 100 mg orally twice daily Treatment duration ranged from 4 to 7 wk</td>
<td>Success was defined as no further evidence of infection as determined by symptoms, physical exam, and laboratory evaluation (leukocyte count, erythrocyte sedimentation rate, and C-reactive protein).</td>
<td>Successful outcome: n = 7/8</td>
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<tr>
<td>Jankowski et al [20]</td>
<td>See tabular description above</td>
<td>See tabular description above</td>
<td>Successful clinical and microbiologic outcome</td>
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Abbreviations: BAL, bronchoalveolar lavage; MDR, multidrug-resistant; VAP, ventilator-associated pneumonia.
and often involve copathogens, the published experiences with the use of minocycline intravenous for treatment of MDR Acinetobacter pneumonia are in general favorable and consistent. Moreover, minocycline penetrates rapidly and substantially into lung tissues, as well as sputum [28–30]. Whether nonantibiotic, anti-inflammatory properties characteristic of tetracyclines are involved in the overall therapeutic activity of intravenous minocycline for MDR Acinetobacter infections is unclear [14].

Experience with minocycline intravenous for treatment of skin and soft issue infection and bacteremias caused by MDR Acinetobacter is much more limited. In addition, consideration of intravenous to oral step-down minocycline therapy is supported by Chan et al’s previously discussed successful use of this strategy in the setting of VAP, as well as by the aforementioned favorable results achieved by Griffith et al with minocycline oral for treatment of several traumatic wound infections with bone involvement [19, 22].

Given the lack of options available for treating MDR Acinetobacter infections, it is reasonable to consider use of any agent(s) testing active against a particularly resistant strain of this organism, including minocycline intravenous. Due to the possibility of obtaining discordant results among tetracycline agents, in vitro susceptibility testing with Acinetobacter should include minocycline. The availability of CLSI susceptibility breakpoints with Acinetobacter and minocycline allows accurate reporting of minocycline susceptibility results in the clinical setting.

Increasing clinical experience is accumulating with minocycline intravenous monotherapy and as a component of combination therapy for MDR Acinetobacter infections, especially pneumonia. The role of minocycline intravenous for treatment of MDR Acinetobacter infections is likely to continue to evolve with the availability of additional clinical and microbiologic data. The existing minocycline intravenous indication for treatment of Acinetobacter infections, the encouraging clinical results discussed herein, and the generally favorable safety profile of minocycline intravenous warrant its serious consideration for treatment of serious MDR Acinetobacter infections.

Notes

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