

## Minocycline Hydrochloride: The Emerging Evidence of Its Therapeutic Value in Complicated Bacterial Infections

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**Abstract:** In order to address increasing antimicrobial resistance issues in combination with few new antimicrobial agents, minocycline has renewed interest for new uses in resistant, serious infections. Minocycline is a broad-spectrum antimicrobial with activity against Gram-positive and -negative bacteria, including aerobes and anaerobes as well as *Mycoplasma*, *Chlamydia*, *Rickettsia*, *Nocardia*, *Legionella*, and various spirochetes. Minocycline has many favorable attributes including good pharmacokinetic profile, high tissue penetration, intravenous and oral preparation, and negligible dose adjustments for patients with renal and hepatic dysfunction. In case studies, minocycline does display efficacy in the treatment of *S. aureus* skin and soft tissue infections, and has been used successfully in the management of patients with *S. aureus* endocarditis, including MRSA. Minocycline-rifampin impregnated catheters are efficacious in both preventing colonization of catheters as well as preventing bloodstream infections associated with catheter use. In Gram-negative infections, case reports have described the successful use of minocycline for pneumonia, hospital-associated and ventilator-associated type, and wound infections due to *A. baumannii* and *S. maltophilia*. In sexually transmitted infections, minocycline may be an attractive alternative to doxycycline in the treatment of nongonococcal urethritis and mucopurulent cervicitis. It has demonstrated efficacy in the treatment of neurosyphilis in those patients with penicillin allergies. As bacterial resistance issues continue to worsen, additional clinical evidence for the use of minocycline in complicated bacterial infections may arise, further integrating its place in therapy for these infections. Most of this evidence will likely come from case report, cohort, or observational studies since prospective randomized trials with minocycline will be difficult to perform.

**Keywords:** tetracyclines, resistance, complicated infections, bacteria

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## Introduction

Antimicrobial resistance in both Gram-positive and Gram-negative bacterial pathogens remains a concern for patients in hospital and community settings. These concerns are exacerbated with diminishing numbers of new antimicrobials being developed and approved for use.<sup>1</sup> Infections due to antimicrobial resistance carry significant consequences, increasing inpatient hospital costs per patient an estimated \$18588 to \$29069, extending hospital stay up to 12 days, and elevating mortality rates by 6.5%.<sup>2</sup> Antimicrobial resistance in the community setting is also occurring, which is particularly troubling given the aging population in the United States that is susceptible to infections with invasive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA).<sup>3</sup> Other microorganisms including *Enterococcus*, *Pseudomonas*, *Acinetobacter*, and *Enterobacteriaceae* (*E. coli*, *Klebsiella*, and others) are also notable bacterial pathogens possessing substantial resistance to numerous antimicrobials.<sup>4</sup>

In order to address increasing antimicrobial resistance issues with few new antimicrobial agents, increased interest has been placed on older antimicrobials for treating resistant infections. Fosfomycin, fluoroquinolones, amikacin, nitrofurantoin, and colistin are all older antimicrobials that have been examined as new treatment choices for antimicrobial resistant infections.<sup>5–7</sup> Minocycline is an example of this renewed interest for new uses in resistant infections. In particular, minocycline, a tetracycline antibiotic introduced in the 1960s, has been successfully used in the management of infections caused by MRSA and *Acinetobacter baumannii*.<sup>8</sup> As an oral agent, minocycline is especially attractive for treatment of susceptible MRSA as few oral regimens exist. Minocycline is a broad-spectrum antimicrobial with activity against Gram-positive and -negative bacteria including both aerobes and anaerobes as well as *Mycoplasma*, *Chlamydia*, *Rickettsia*, *Nocardia*, *Legionella*, and various spirochetes.<sup>9,10</sup> Interest in minocycline use for the treatment of invasive infections has recently been renewed since the re-introduction of the intravenous preparation into the US market in 2007. This review examines the use of minocycline for the treatment of complicated bacterial infections.

## Properties

Minocycline is a second-generation tetracycline antibiotic introduced in 1967 possessing the central four-ring carbocyclic scaffold shared by tetracyclines with molecular modifications that have yielded a longer half-life, improved oral absorption, and stability against many tetracycline resistance mechanisms. Minocycline exhibits significant lipophilic character, allowing for excellent penetration to various tissues, particularly central nervous system tissues. Similar to other tetracyclines, minocycline is a bacteriostatic antimicrobial with an intracellular antibacterial target. Entry into the cell is mediated by an energy-dependent process and chelation of the minocycline molecule to divalent cations occurs readily.<sup>11,12</sup> Minocycline inhibits protein synthesis through reversibly binding the 30S ribosomal subunit to prevent association with aminoacyl-tRNA (transfer RNA), creating a magnesium-minocycline chelation complex.<sup>9,11</sup>

The pharmacokinetic characteristics of minocycline are listed in Table 1. Following oral administration, minocycline is quickly and nearly completely absorbed with bioavailability approaching 100%; coadministration of minocycline with food does not alter the achieved maximum concentration or the area under the concentration-time curve (AUC).<sup>13,14</sup> Unlike other tetracyclines, the absorption of minocycline is largely unaltered by the presence of divalent cations, including iron, calcium, magnesium, and aluminum.<sup>9,10</sup> Minocycline serum levels of 2.3–3.5 µg/mL are achieved and maintained with a single 200 mg oral loading dose followed by 100 mg oral maintenance doses given every twelve hours.<sup>9</sup>

**Table 1.** Pharmacokinetic parameters of oral and intravenous minocycline doses of 100 mg every 12 hours.<sup>8,21</sup>

Pharmacokinetic parameter	Route	
	Oral	Intravenous
F (%)	95–100	100
C <sub>max,ss</sub> (mg/L)	2.3–3.5	1–4
AUC <sub>ss</sub> (hr*mg/L)	32–50	32–50
V <sub>d</sub> (L/kg)	1.17	1.17
Protein binding (%)	75	75
Urinary recovery (%)	5–12	5–12
Fecal recovery (%)	20–35	20–35

**Abbreviations:** F, bioavailability;  $t_{1/2}$ , terminal half-life; C<sub>max,ss</sub>, maximum concentration at steady state; AUC<sub>ss</sub>, area under the concentration-time curve at steady state; V<sub>d</sub>, volume of distribution.



The volume of distribution of minocycline is approximately 1.17 L/kg.<sup>15</sup> Minocycline distributes well to the cerebrospinal fluid (CSF) as it possesses the highest partition coefficient of all tetracyclines at physiologic pH.<sup>16</sup> CSF levels are approximately 30% that of serum levels in subjects with non-inflamed meninges.<sup>17</sup> Penetration into the lung, sputum and other respiratory secretions is also substantial.<sup>18</sup>

The half-life of minocycline is 12–16 hours, likely lengthened by distribution to tissues and protein binding (75%–85%).<sup>9</sup> Minocycline is metabolized to at least six metabolites with some of the metabolites possessing antimicrobial activity.<sup>8</sup> Elimination of minocycline largely occurs through the hepatobiliary and gastrointestinal tract.<sup>19</sup> Renal and hepatic function do not substantially impact the elimination of minocycline.<sup>20</sup>

Pharmacodynamically, minocycline is best gauged by the AUC to minimum inhibitory concentration (MIC) ratio when considering dosing. Available data in MRSA isolates reveal that an AUC/MIC of 33.9 achieves bacteriostatic effect and a ratio of 75.9 achieves a one log decrease in bacterial density. These AUC/MIC targets are attainable since dosing minocycline at 100 mg twice daily achieves an AUC/MIC of 200 in highly susceptible organisms (MIC  $\leq$  0.25).<sup>21</sup> In organisms with MICs  $>$  2 mg/L, it is difficult to achieve these target AUC/MIC values with standard dosing.

Bacterial resistance to tetracyclines is most commonly mediated by tetracycline resistance (*tet*; 33 genes) and oxytetracycline resistance (*otr*; three genes). Nineteen of these genes encode for efflux pumps while eight encode for ribosomal protection proteins (RPPs).<sup>22</sup> A third resistance mechanism, the *tet(X)* gene, allows for enzymatic alteration of tetracyclines, but its prevalence has not been studied.<sup>8</sup> Bacterial chromosomal mutation does not commonly generate tetracycline resistance. Most *tet* genes are encoded on mobile genetic elements to allow for easy gene transfer between bacterial species, leading to common resistance to tetracyclines. Additionally, multiple resistance genes are often found in a single mobile genetic element, further exacerbating resistance problems.<sup>22</sup>

Minocycline susceptibility breakpoints per the Clinical and Laboratory Standards Institute (CLSI)

guidelines have remained stable and are presented for multiple pathogens in Table 2. Most organisms including *Staphylococcus* spp, *Enterococcus* spp, Enterobacteriaceae, and Non-enterobacteriaceae have a minocycline susceptibility breakpoint of  $\leq$ 4 mg/L.

## Clinical Studies and Case Reports

### MRSA infections

The use of minocycline for treatment of MRSA infections is evidenced in case reports and case series, but not prospective clinical trials. In case studies, minocycline does display efficacy in the treatment of MRSA skin and soft tissue infections.<sup>23,24</sup> Additionally, a retrospective review of MRSA infections confirmed minocycline as a non-vancomycin, non-linezolid option in MRSA skin and soft tissue infections.<sup>25</sup> Minocycline has been used successfully in the management of patients with *S. aureus* endocarditis, including MRSA endocarditis.<sup>26,27</sup> Minocycline has also shown utility in the treatment of MRSA osteomyelitis.<sup>28</sup> Minocycline in combination with rifampin was successful in treating severe MRSA infections.<sup>29</sup> Minocycline is an attractive alternative for the management of MRSA infections as it is one of the few antimicrobial agents that may be used orally in these clinical cases.

### Central nervous system infections

Minocycline penetrates the central nervous system quite effectively given its high partition coefficient and lipophilic character. For these reasons, it has been used successfully in older studies for the management of bacterial meningitis outbreaks.

An outbreak of sulfonamide-resistant *Neisseria meningitidis* among 8721 men at a military base was halted following three confirmed meningitis cases with the use of 100 mg minocycline twice daily for five days. A second outbreak due to the arrival of new recruits was subsequently managed by the same minocycline regimen to prevent further dissemination.<sup>30</sup> Similar results were reported in reducing carrier rates of unvaccinated army recruits at a second site of outbreak. Rifampin was administered prophylactically to 389 recruits, reducing carriage by 78% while minocycline was administered to 1151 recruits, reducing carriage by 62%. Notably, five highly resistant rifampin strains were detected

**Table 2.** Minocycline minimum inhibitory concentration (MIC) CLSI breakpoints according to organism classification.

Minocycline susceptibility	<i>Staphylococcus spp</i> <sup>1</sup> (mg/L)	<i>Streptococcus spp</i> (mg/L)	<i>Enterococcus spp</i> (mg/L)	Enterobacteriaceae (mg/L)
Susceptible	≤4	≤2	≤4	≤4
Intermediate	8	4	8	8
Resistant	≥16	≥8	≥16	≥16

following rifampin prophylaxis while no minocycline resistance was uncovered. Additionally, four weeks following prophylaxis, carriage rates in both groups rose by approximately 30%, indicating that both minocycline and rifampin prophylaxis is not durable over time.<sup>31</sup> Minocycline is an effective prophylactic agent for *N. meningitidis* meningitis.

### Catheter-associated bacteremia

A large, randomized, multicenter, prospective clinical trial assessed the use of antimicrobial-impregnated catheters in preventing both catheter colonization and catheter-associated bloodstream infections in high-risk adult patients, as defined as adult patients with central venous catheters that were expected to remain in place for at least three days. Eight hundred and sixty-five patients were randomized to receive triple lumen catheters impregnated with either minocycline-rifampin or chlorhexadine-silver sulfadiazine. Blood cultures were obtained as warranted by clinical suspicion. Following removal of catheters, the catheter tips and subcutaneous portions were cultured for bacterial growth. Seven hundred and thirty-eight catheters yielded culture results for evaluation; 7.9% (28 of 356) of minocycline-rifampin catheters were colonized compared to 22.8% (87/382) of chlorhexadine-silver sulfadiazine catheter ( $P < 0.001$ ); 0.3% (1 of 356) of minocycline-rifampin catheters were associated with bloodstream infections compared to 3.4% (13 of 382) of chlorhexadine-silver sulfadiazine catheters. Minocycline-rifampin impregnated catheters are efficacious in both preventing colonization of catheters as well as preventing bloodstream infections associated with catheter use.<sup>32</sup>

A meta-analysis evaluated the use of numerous antimicrobial central venous catheters in preventing both microbial colonization and catheter-associated bloodstream infections. Thirty-four randomized clinical trials

were included in the evaluation. Of the central venous catheters evaluated, only minocycline-rifampin and chlorhexadine-silver sulfadiazine catheters reduced colonization (odds ratio [OR]: 0.39 [95% CI: 0.27–0.55], OR: 0.51 [0.42–0.61], respectively) and reduced catheter-associated bloodstream infections (OR: 0.29 [0.16–0.52], OR: 0.68 [0.47–0.98], respectively). Additionally, minocycline-rifampin outperformed chlorhexadine-silver sulfadiazine catheters in reducing colonization and preventing catheter-associated bloodstream infections (OR: 0.34 [0.23–0.49], OR: 0.18 [0.07–0.51], respectively).<sup>33</sup>

### *Stenotrophomonas maltophilia*

*Stenotrophomonas maltophilia*, formerly identified as *Pseudomonas maltophilia* or *Xanthomonas maltophilia*, is a Gram-negative aerobic bacillus that is commonly implicated as an opportunistic pathogen, particularly in cystic fibrosis patients, and may also cause community-acquired infections.<sup>34</sup> *S. maltophilia* is often resistant to numerous antimicrobials including  $\beta$ -lactams, fluoroquinolones, and aminoglycosides among others.<sup>35</sup> A review of available literature sought to identify antimicrobials that may be used for *S. maltophilia* infections beyond co-trimoxazole, the first line agent for these infections. This review revealed reports of forty-nine patients treated with antimicrobials other than co-trimoxazole. While the majority of patients were treated with a fluoroquinolone- or  $\beta$ -lactam-based regimen, one patient with *S. maltophilia* pneumonia was successfully treated with minocycline.<sup>36</sup>

In vitro susceptibility testing of minocycline demonstrates that most clinical isolates of *S. maltophilia* are susceptible to minocycline, often with no resistance being documented.<sup>37,38</sup> Previous clinical successes coupled with in vitro susceptibilities suggest that minocycline may be useful in the management of



Non-Enterobacteriaceae <sup>2</sup> (mg/L)	<i>Haemophilus</i> spp (mg/L)	<i>Neisseria meningitidis</i> (mg/L)	<i>Neisseria gonorrhoeae</i> (mg/L)
≤4	≤2	≤2	≤0.25
8	4	–	0.5–1
≥16	≥8	–	≥2

**Notes:** <sup>1</sup>Includes methicillin-resistant *Staphylococcus aureus*; <sup>2</sup>Includes *Pseudomonas* spp, *Acinetobacter* spp, *Burkholderia* spp, and *Stenotrophomonas maltophilia*.

*S. maltophilia* infections, particularly in combination with other antimicrobials.

### Acinetobacter species infections

The management of infections due to *A. baumannii* with minocycline has been reported through case reports. Minocycline successfully treated traumatic wound infections due to *A. baumannii* in seven of eight patients, with the eighth patient discontinuing due to treatment-limiting side effects.<sup>39</sup> Ventilator-associated pneumonia in four patients was treated with minocycline, with three patients improving with minocycline and other antimicrobials and one patient failing minocycline treatment due to poor prognosis.<sup>40</sup>

### *Nocardia* infections

Evidence supporting the use of minocycline to treat *Nocardia* infections is largely limited to case reports in available literature. Several *Nocardia* species demonstrate susceptibility to minocycline upon in vitro testing.<sup>41–43</sup> Numerous case reports demonstrate successful treatment of *Nocardia* infections, particularly pulmonary nocardiosis, with minocycline in transplant patients including kidney, liver, bone marrow, and heart transplants.<sup>44–46</sup> Minocycline has also shown utility in the clinical management of *Nocardia* brain abscesses.<sup>47,48</sup> In these cases, minocycline, in combination with a third generation cephalosporin, may be chosen for patients with a sulfa allergy or treatment failure.<sup>49</sup> Notably, case reports of central nervous system *Nocardia* dissemination following pulmonary nocardiosis treated with minocycline do exist, but have not demonstrated favorable outcomes for using minocycline in this infection type.<sup>50</sup> The evidence from these studies suggests that minocycline is inadequate for the management of disseminated nocardiosis.

### Sexually transmitted infections

A prospective, double-blinded, randomized clinical trial evaluated doxycycline and minocycline in the management of nongonococcal urethritis and mucopurulent cervicitis. One hundred thirty-three patients were treated with doxycycline (100 mg twice daily for seven days) and 120 patients were treated with minocycline (100 mg every night for seven days). The percentages of patients achieving clinical cure between doxycycline and minocycline were similar (85% vs. 89%, respectively, [95% CI: –7%–16%]) while vomiting (7% vs. 0%, respectively,  $P = 0.004$ ) and gastrointestinal adverse events (39% vs. 18%, respectively,  $P < 0.001$ ) occurred more frequently with doxycycline treatment.<sup>51</sup> Minocycline may be an attractive alternative to doxycycline in the treatment of nongonococcal urethritis and mucopurulent cervicitis as it is equally effective and has a low incidence of adverse reactions.

A case series described the use of minocycline for the treatment of neurosyphilis in three patients with penicillin hypersensitivity that declined penicillin desensitization. These patients received 100 mg of minocycline for fourteen consecutive days per month for a total treatment length of nine months. Minocycline treatment led to prompt resolution of clinical signs and symptoms of neurosyphilis (within one month) in all patients and conversion of the Venereal Disease Research Laboratory (VDRL) test to negative occurred at six months for two patients while the third was adherent to minocycline therapy for only the first three months.<sup>52</sup> Minocycline may be a therapeutic option in the treatment of neurosyphilis in those patients with penicillin allergies.

### Miscellaneous infections

Casereports demonstrate the use of minocycline in other infection types. In conjunction with chloramphenicol,



minocycline was used to treat vancomycin-resistant *Enterococcus faecium* endocarditis following treatment failure with other antimicrobials including quinupristin-dalfopristin.<sup>53</sup> There is also a single case report of successful chronic staphylococcal osteomyelitis treatment with minocycline following failure of extended therapy with other antimicrobials.<sup>54</sup>

## Safety

Minocycline is largely well tolerated by patients, although toxicities do occur. Particularly, minocycline use is most commonly associated with gastrointestinal and central nervous system adverse events. Additionally, adverse events are more common with higher minocycline doses and longer courses of therapy.

A systematic review of available literature examined case reports and clinical trials that identified adverse events associated with minocycline use from 1966 to August 2003, yielding eleven clinical trials ( $n = 788$  patients) and 333 adverse events reported through case reports.<sup>55</sup> In clinical trials, commonly reported adverse events associated with minocycline use were largely associated with the gastrointestinal tract (nausea, vomiting, diarrhea) and central nervous system (dizziness, vertigo, vestibular disturbances). Central nervous system adverse events were largely mild and often transient, but yielded discontinuation rates of 1.7% to 8.8%. Headache, weakness, fatigue, and visual disturbances also occurred. Of the adverse events reported through case reports, those occurring at a rate of at least five percent include lupus-like syndrome (28%), hyperpigmentation of skin, nails, or bones (15%), vestibular effects (11%), hepatitis or hepatic dysfunction (9%), pseudotumor cerebri (5%), and hypersensitivity (5%).

A study of eighty-three subjects receiving minocycline for *N. meningitidis* prophylaxis further highlighted vestibular toxicities commonly associated with minocycline use.<sup>56</sup> Dosing among these subjects was variable, but 76% experienced one vestibular toxicity (dizziness, vertigo, nausea, or vomiting). Thirty-eight percent experienced other gastrointestinal symptoms (loss of appetite or diarrhea). While minocycline is efficacious in meningitis prophylaxis, it does carry toxicity concerns with use. Other research mirrors these findings of common vestibular toxicities, but also notes high rates of discontinuation of

minocycline, approaching 80%, when these toxicities occur as well as fast resolution (within 48 hours) when minocycline is discontinued.<sup>57</sup>

A double-blind, clinical study compared the incidence of minocycline adverse effects on the basis of gender.<sup>58</sup> Forty-five subjects (18 men, 27 women) were administered 100 mg of minocycline twice daily for five days. While the men in treatment group were larger in weight, vestibular side effects occurred more commonly in the women receiving minocycline than men receiving minocycline (70.4% vs. 27.8%, respectively,  $P < 0.005$ ). The female subjects in this study had higher serum minocycline concentrations, probably related to lower weight, that help to explain the increased incidence of adverse reactions.

Importantly, minocycline, or any other tetracycline, is not recommended for use in pregnancy or children under the age of eight years due to tooth discoloration from this antibiotic class in these age groups and during fetal development.<sup>59</sup>

## Conclusions

Minocycline is an older antibiotic that has seen increased utility in the modern clinical setting, where growing bacterial resistance issues remain challenging. Recent reviews show successful use of minocycline in treating MRSA infections.<sup>8</sup> Two arenas of use are well defined where minocycline displays efficacy: prevention of catheter-associated bacteremia and meningitis prophylaxis. Evidence for minocycline use in other serious infections is more limited to case reports without strong clinical study evidence. Nonetheless, minocycline may be a therapeutic option in *Stenotrophomonas*, *Nocardia* (not disseminated pulmonary type) and *Acinetobacter spp.*, as well as some sexually transmitted infections. Excellent central nervous system penetration, a long half-life, allowing for once-to-twice daily dosing, and conversion from intravenous to oral regimens make minocycline an attractive option when considering antimicrobial selection. Unlike other oral tetracyclines, oral minocycline does not interact with food or cationic supplements. Additionally, it is one of two oral agents along with linezolid in the treatment of MRSA infections. As bacterial resistance issues continue to worsen, additional clinical evidence for the use of minocycline in complicated bacterial infections may arise, further solidifying a place in therapy with minocycline for these infections.



Many barriers exist to conducting prospective, randomized studies with minocycline in complicated infections. First, infection types such as CNS infections, endovascular, or deep-seated infections are difficult studies to perform due to the relatively low occurrence of patients compared to other conditions and the time needed to enroll sufficient numbers. Also, multi-drug resistant pathogens, where minocycline therapy would be of high interest, are often treated with a number of antibiotics, so evaluating minocycline clinical effectiveness against these strains is difficult. Ultimately there is a scarcity of funding to investigate clinical efficacy of older antibiotics such as minocycline. In the absence of such trials, the best evidence for use of minocycline in complicated infections will have to come from case control and observational studies statistically designed to control for confounding variables.

## Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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