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# Antibiotics and Acne Therapy

Azam Qureshi MD, Adam Friedman MD FAAD

George Washington Medical Faculty Associates, Department of Dermatology, Washington, DC

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**Abstract** Tetracyclines are the most commonly prescribed oral antibiotics for acne vulgaris and are often utilized for longer than the *American Academy of Dermatology* recommendation of 3–4 months due to patient preference for effective and persistent acne control. The importance of provider responsibility when prescribing these agents, the structural foundation for their efficacy, and the emergence of sarecycline were all important concepts discussed in a series of podcasts available at the *Journal of Drugs in Dermatology* online, including *Oral Antibiotics for Acne: Basic Concepts & Practical Considerations* hosted by Drs. Adam Friedman, Emmy Graber, and Mahmoud Ghannoum, as well as *New Developments in Tetracycline-Class Antibiotics* hosted by Drs. Adam Friedman and Chris Bunick. Practitioners must take great care to responsibly utilize this multifaceted class of agents, which have both antibiotic and anti-inflammatory properties conferred by structural modifications to their naphthacene core foundation. When used improperly, antibiotic resistance and cutaneous and gastrointestinal dysbiosis may occur. Emerging use of sarecycline, a narrow-spectrum tetracycline, is becoming increasingly favored in dermatology offices due to its reduced propensity to contribute to antibiotic resistance and dysbiosis and more favorable side effect profile in comparison to other commonly utilized broad-spectrum tetracyclines including doxycycline and minocycline.

## Introduction

"With great power, comes great responsibility." Uncle Ben's timeless adage may have originally been referring to superpowers conferred to his nephew, Spider Man, but the proverb also holds true for protecting humanity from another form of "Super Bug." Great responsibility must be exercised with every clinical decision made in medicine, especially upon prescribing antibiotics for acne, one of the most ubiquitous skin diseases affecting 85% of teenagers as well as many adults, with a cost of disease upwards of 3 billion dollars per year.[1] Current American Academy of Dermatology clinical guidelines recommend systemic antibiotics used in conjunction with topical therapy with benzoyl peroxide or a retinoid in management of moderate-severe acne and forms of inflammatory acne recalcitrant to treatment with topical therapy alone.[1] Tetracyclines are considered first-line, above macrolides and trimethoprim-sulfamethoxazole, and guidelines recommend limiting treatment course to 3–4 months in order to prevent development of antibiotic resistance and dysbiosis, or disruption of normal bacterial flora in places such as the gut and skin.[1]

The concept of antimicrobial stewardship was conveyed very eloquently by Dr. Emmy Graber, founder of the Dermatology Institute of Boston and Affiliated Clinical Instructor at Northeastern University, during her commentary in the *Oral Antibiotics for Acne: Basic Concepts & Practical Considerations* podcast available through the *Journal of Drugs in Dermatology* online (Figure 1). Dr. Graber, along with Dr. Mahmoud Ghannoum,

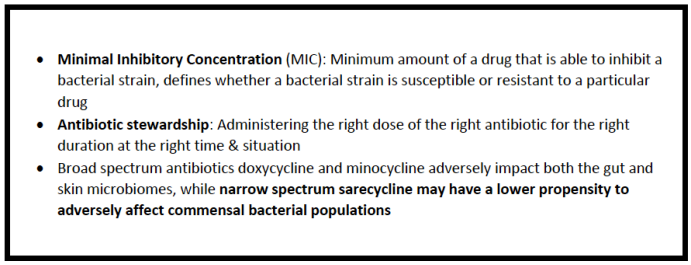


Figure 1. Pearls from *Oral Antibiotics for Acne: Basic Concepts & Practical Considerations* podcast featuring Dr. Adam Friedman, Dr. Emmy Graber, and Dr. Mahmoud Ghannoum.[2]

Professor in the Departments of Dermatology and Pathology and Director of the Center for Medical Mycology at Case Western Reserve University, discussed what dermatologists need to know when prescribing oral antibiotics for management of acne vulgaris.[2] Dr. Graber mentions that, in real life practice, patients tend to be on tetracyclines for longer than 3–4 months due to their preference for effective treatment with a quicker onset than other systemic treatment options such as isotretinoin and oral contraceptive pills.[2]

How do we explain tetracyclines' great power to keep acne at bay? Although no mutant spider was involved in their development, their structural foundation provides clues into their multifaceted approach to treating acne so effectively, as discussed by Dr. Chris Bunick, Associate Professor of Dermatology at Yale School of Medicine and expert in structural biology, in his commentary in the *New Developments in Tetracycline-Class Antibiotics* podcast available through the *Journal of Drugs in Dermatology* online (Figure 2).[3]

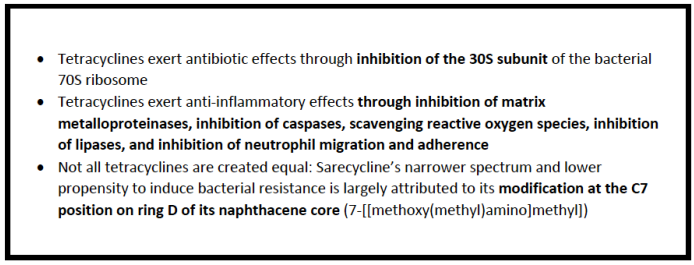


Figure 2. Pearls from *New Developments in Tetracycline-class Antibiotics* podcast featuring Dr. Adam Friedman and Dr. Chris Bunick.[3]

Tetracycline structure is based on a napthacene core, which consists of 4 interconnected phenol rings upon which other building blocks are added to create various specific tetracyclines.[3] The 4-ringed structure has both a polar (hydrophilic) side and a hydrophobic side.[3] Ultimately, these antibiotics bind to the 30S subunit of the 70S bacterial ribosome, with the polar aspect of the compound allowing for binding to the ribosomal RNA. During protein synthesis, a charged tRNA molecule binds into the A-site (amino-acyl or acceptor site) on the ribosome, located in the 30S subunit. This tRNA contains an anticodon stem loop sequence that recognizes the mRNA codon within the ribosome and being presented at the A-site. This A-site is a critical recognition site where tetracyclines bind and prevent the tRNA from coming in and creating codon-anticodon matches with the mRNA, thereby effectively halting bacterial protein translation.[4]

Aside from bacteriostatic antibiotic effects, tetracyclines also generate anti-inflammatory effects. Tetracyclines reduce inflammation by ways of multiple mechanisms, as discussed by Dr. Bunick.[3,4] First, they inhibit matrix metalloproteinases (MMPs), which serve to digest aspects of the extracellular matrix, and lead to tissue destruction and inflammation.[4] By blocking MMPs, they indirectly block serine protease activity by protecting serine protease inhibitors from digestion.[4] They also inhibit caspases both directly and through inhibition of gene expression, thereby

serving as an anti-apoptotic role.[4] Tetracyclines also scavenge reactive oxygen species, a function enabled by their structure consisting of phenol rings, which absorb free oxygen radicals, forming phenolic radicals.[4] Furthermore, they also inhibit lipases, along with neutrophil migration and adherence, thereby functioning in a number of diverse roles to counter inflammation.[4]

Given tetracycline-class antibiotics' unrivaled multidimensional approach to combat acne, it is important to consider the possible downsides of overuse, aside from possible direct side effects including but not limited to gastrointestinal upset, headaches, photosensitivity, teratogenicity, and esophagitis. Development of a Super Bug, or multi-drug resistant bacteria, is not only a villain-worthy for our friendly neighborhood Spider Man, but also unfortunately presents a real non-fictional threat. Recent data supports the imminence of this threat, while conveying that rates of tetracycline resistance varies greatly among different cultures and populations.[5,6] In a recent cohort of 50 Israeli patients, 19.4% of *Cutibacterium acnes (C. acnes)* isolates were resistant to doxycycline, and 11.1% were resistant to minocycline.[5] Another study published the same year investigating rates of tetracycline resistance in *C. acnes* isolates in Jordanian patients demonstrated a doxycycline resistance rate as high as 37% with a minocycline resistance rate as low as 3%.[6]

Dr. Graber summarizes antimicrobial stewardship as "the right dose of the right antibiotic, for the right duration, at the right time." As we have already discussed the guidelines regarding the indications for and duration of treatment, let's now redirect our focus to the dosing and choice of drug. For Dr. Graber and many other dermatologists, sub-antimicrobial dosing, or dosing under the "minimum inhibitory concentration" (MIC), is a useful strategy. Dr. Ghannoum discusses the concept of MIC, which is the lowest tested concentration of a specific antimicrobial that is effective in inhibiting an isolate's growth.[7] This determination is facilitated by automated instrument systems or manual testing methods, which expose the isolated organisms to a series of concentrations of the antimicrobial of interest.[7] The lowest concentration in which bacterial growth is inhibited is recorded as the associated MIC for the isolated organisms treated by the specific antimicrobial of interest.[7] These are assembled into susceptibility summaries, and provided to practitioners with culture reports, often simplified into a binary scale of "resistant" or "susceptible" based on thresholds of MICs. Dosing below the MIC – doxycycline 20mg twice daily, for example – is a strategy utilized by many dermatologists to prevent against development of antimicrobial resistance.

In addition to drug-resistance, another important consideration upon prescribing oral antibiotics for acne is gut and cutaneous dysbiosis. The "right drug" Dr. Graber refers to is one preferably of narrow spectrum, as opposed to broad-spectrum agents, such as doxycycline and minocycline, which indiscriminately kill beneficial commensal organisms, thereby contributing to dysbiosis. In fact, recent work showed that minocycline treatment for acne disturbs not only the gut microbiome but also the skin microbiome, with significant decreases in *Lactobacillus salivarious*, *Bifidobacterium adolescentis*, and *Bifidobacterium breve* in gut microbiota, and significant skin microbiota decreases in *Staphylococcus epidermidis* and *Prevotella nigrescens* and enrichments in *Bifidobacterium longum* and *Leuconostoc mesenteroides*.[10] This effect is not trivial, as microbial dysbiosis can precede both gastrointestinal and skin disease, such as *Clostridium difficile* colitis and atopic dermatitis.[8,9] Currently, there is only one narrow-spectrum antibiotic approved for acne, and this is sarecycline.[2,3,11,12]

The successes of sarecycline are again explained by its structure, as recently described by Dr. Bunick working along with Dr. Yuri Polkinoff at the University of Illinois, Chicago, with findings recently published in the Proceedings of the National Academy of the Sciences.[3,11] Drs. Bunick and Polkinoff studied multiple x-ray crystal structures of sarecycline bound to the 70S ribosome of *Thermus thermophilus*.[11] Specifically, they found a biochemical basis for sarecycline's action, through its modification at the C7 position on ring D of its napthacene core (7-[[methoxy(methyl) amino]methyl] group or C7 moiety), which is the longest and largest of any tetracycline drug.[11] They determined that sarecycline binds at the same spot of 30S ribosomal subunit, but the C7 moiety extends into the mRNA channel, and interacts with the A-site mRNA codon, slowing down movement through the channel and disrupting codon-anticodon interactions.[11] This direct interaction with mRNA at the A-site is a mechanism not observed with other tetracyclines.[11] Furthermore, the C7 moiety on sarecycline interferes with tetM (by way of proline 509 and valine 510 on domain IV), keeping it from binding to the ribosome.[11] This molecular interaction is of clinical significance, as resistance to tetracyclines can be due to drug efflux pumps or ribosomal protection proteins like tetO or tetM.[13-15] The ribosomal protection proteins induce a conformational change in the drug-binding pocket of the ribosome, thereby preventing re-binding of the tetracycline antibiotic as the ribosome progresses, translating the mRNA.[13-15] Due to sarecycline's specific interactions, tetM cannot get close enough to dislodge the tetracycline antibiotic.[11] Drs. Bunick and Polkinoff concluded that this unique C7 chemical modification makes sarecycline both narrower spectrum and with a lower propensity to contribute to antimicrobial resistance while providing targeted attack of *C. acnes* and minimal activity against Gram-negative bacteria.[3,11,12]

Further beneficial effects of sarecycline provide explanation to its growing use in management of acne. Beyond the advantages above, this narrow-spectrum agent also has also shown to have a lower propensity to cause headaches and other vestibular disturbances, likely due to its reduced ability to cross the blood brain barrier.[3] Furthermore, sarecycline works as early as 3 weeks into the treatment course, has good data for truncal acne, is approved down to 9 years of age, and is supported by American Dental Association for its lack of dental staining risk.[12]

As our care for acne continues to advance into the 21st century, we must continue to responsibly treat patients while interpreting data from the past, which has shown us that not all tetracyclines are made the same. Doxycycline, minocycline, and sarecycline

are all distinct chemical entities with different mechanisms of action. Sarecycline, the newest in the tetracycline class, is relatively narrow spectrum with reduced propensity to contribute to both dysbiosis and antimicrobial resistance and has other favorable characteristics that make it a preferable choice drug for longer-term management of acne. Further investigation should be carried out, however, especially in regard to pharmacogenetics and pharmacogenomics, to determine which agent may be best for specific subsets of patients.

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