



# Appropriate Use of Doxycycline for Skin and Soft Tissue Infection after Foot and Ankle Surgery: A Brief Review and Case Presentation

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## Abstract

This paper aims to provide a concise review of doxycycline, including a case report that provides an exemplar of a short-term application of this drug to a patient who developed skin and soft tissue infection of the lower extremity after elective surgery. Doxycycline appears to be benign but research suggests that it does have notable side effects and contraindications. A short duration of treatment is recommended after the risks and benefits of Doxycycline are carefully considered, and after the therapeutic guidelines provided by CDC, IDSA and WHO are reviewed. Studies have shown that Doxycycline is effective; however, it is not appropriate for every patient and increased reports of overuse have become a serious problem. Doxycycline should be used on organisms that are sensitive or suspected to be sensitive to it. Synthesis of the literature also suggests that dose and duration needs to be carefully examined. When used in outpatient therapy, use of Doxycycline prevents extended hospital stays, thus potentially reducing hospital-acquired infections and reduced costs for the hospital and the patient. Although it does have a broad antimicrobial coverage, patients should be transitioned to a narrow therapy following the discovery of sensitivity results.

**Keywords:** Doxycycline, Bone infection, Osteomyelitis, MRSA, Antibiotic stewardship program.

**Abbreviation:** MSSA- Methicillin-Susceptible *Staphylococcus Aureus*, PO-Per os or by mouth, OR-Operating Room, mcg/mL-Micrograms per Milliliter, mg/dL-Milligrams per Deciliter, mmol/L-Millimoles per Liter, MRSA-Methicillin-Resistant *Staphylococcus Aureus*, VRE-Vancomycin-Resistant *Enterococci*.

## Introduction

Doxycycline is a broad-spectrum antibiotic that remains one of the most inexpensive antibiotic regimens for treating soft tissue and bone infection in the human body. It belongs to a class of drugs called tetracyclines, discovered in 1948 [1]. Five tetracycline drugs are widely used today-oxytetracycline, tetracycline, demeclocycline, minocycline, and doxycycline-but only the last four are commercially available for patient use in the United States. Of these, doxycycline and minocycline are the most frequently prescribed in hospital and clinical settings [1]. We have used doxycycline in our clinical practice for patients who develop post-surgical skin infection and have found that judicious use of this drug for short courses in select patients can be beneficial.

## Applications

Due to doxycycline's broad spectrum of action, it is useful against many aerobic gram-positive and gram-negative bacteria. In addition, it has superb activity against atypical organisms including *Rickettsia* spp, *Borrelia* spp, *Coxiella burnetii*, *Treponema* spp, *Chlamydia* spp, *Mycoplasma pneumoniae*, *Plasmodium* spp, *Vibrio cholerae*, *Vibrio vulnificus*, *Brucella* spp, *Calymmatobacterium granulomatis*, *Leptospira*, *Burkholderia pseudomallei*, *Mycobacterium marinum*, and *Entamoeba histolytica* [3].

Although it does not have any effect on fungal and viral agents, it does provide excellent prophylaxis against protozoa that cause malaria. In addition, doxycycline provides anthelmintic activity; an eight-week course was found to reduce the growth of *Wolbachia* bacteria in the reproductive tracts of parasitic filarial nematodes, which reduces transmission of diseases such as elephantiasis [4].

## Absorption, Serum Concentration and Distribution

Absorption of doxycycline occurs in the small intestine and stomach. Its bioavailability is ~ 95% regardless of dosing with or without with food, and peak concentration occurs three hours after an oral dose. Its bioavailability decreases if the drug is taken with any agents (e.g. antacids) containing divalent and trivalent cations such as aluminum, calcium, iron, and magnesium. These cations chelate with tetracycline agents and reduce their concentrations in plasma [5]. The maximum serum concentration after an intravenous dose of doxycycline in an average patient occurs within 30 minutes. Peak concentrations range from 1.5 to 2.5 mcg/mL after a dose of 200 mg when taken by mouth, and from 4 to 10 mcg/mL for the same dose administered intravenously [5]. Doxycycline penetrates plasma fluid fairly well due to its excellent lipid solubility. It is known to penetrate soft tissue and bone, which makes it an excellent antibiotic for organisms, e.g. *Staphylococcus aureus* and *Streptococcus* spp that cause infection of these tissues. The drug has been found at therapeutic levels in vitreous humors, tears,



sinuses, lungs, digestive and biliary tracts, and kidneys. Its excretion takes place primarily in the intestine, while about 20% is excreted by the kidneys via glomerular filtration [6-10].

### Mechanism of Action and Resistance

Doxycycline is a bacteriostatic agent that passively diffuses into cells and is also known to use energy-dependent active transport systems. When inside the cell, it reversibly binds the 30s ribosomal subunits a position and blocks the binding of the aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex. As a result protein synthesis is inhibited and leading to a bacteriostatic effect [11]. Resistance to doxycycline unlike some other antibiotics does not result from a chemical change in the drug but rather from decreased influx or increased efflux from the microbial cell [11]. The genes conferring resistance are carried in transferrable elements, e.g. plasmids and transposons; organisms carrying these elements can provide cytoplasmic protection that allows the microbial ribosome to carry out normal protein synthesis despite an increase in intracellular drug concentrations [11,12].

### Safety

Doxycycline is generally well-tolerated by patients; however, it has notable potential adverse effects. The most common are esophageal erosion and photosensitivity (reported as a 10% risk), but only 130 such cases were described between 1966 and 2003 [13]. It is safe to assume that hundreds of millions of doxycycline prescriptions were written in this time frame, and the rate of these adverse reactions is thus vanishingly small. Other side effects can be prevented with the use of simple precautions. Some unusual side effects include photoonycholysis, various skin eruptions, Stevens-Johnson syndrome, a Jarisch-Herxheimer reaction and benign intracranial hypertension [13].

Liver disease and hepatotoxicity do occur with other tetracyclines, but have not been observed for doxycycline [14]. Compared to other drugs in its class, doxycycline causes nausea and vomiting at a lower frequency [15]. Dose-related gastrointestinal effects may include diarrhea that subsides once the regimen is stopped. Prolonged use may result in fungal or bacterial superinfection, including *Clostridium difficile*-Associated Diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months post-treatment [14].

### Contraindications

Doxycycline should not be given to patients who have experienced severe allergic reaction or hypersensitivity to tetracyclines. The World Health Organization states that maternal use of doxycycline should be avoided if possible, but that a single dose or short-term use is probably safe; there is a possibility of dental staining and inhibition of bone growth in fetuses and breastfeeding infants, as well as among children given doxycycline before the age of 8 (WHO 2002). Many patients with impaired kidney function can take doxycycline without dose adjustment, but in cases of severe hepatic impairment, such an adjustment may be necessary [15].

### Efficacy

There have been reports of increased resistance to doxycycline in various parts of the world. Resistance has been most commonly reported in *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Bacteroides* spp and *Gonococcus* spp. The drug continues to be effective against atypical organisms [16].

### Drug interaction

The use of doxycycline should be avoided in patients taking warfarin, as concomitant use increases the anticoagulant effect of warfarin in the body, which increases patient bleeding risk [17]. Doxycycline is also thought to reduce the metabolism of warfarin by reducing cytochrome p450 action in hepatocytes, increasing the amount of free warfarin in the blood [18]. Doxycycline can be used by women in combination with oral contraceptives; a meta-analysis by Archer, et al. concluded that

available scientific and pharmacokinetic data do not support the hypothesis that antibiotics-with the exception of rifampin-lower the efficacy of oral contraceptives [2,15].

### Dosing

Accepted guidelines recommend the empiric use of antibiotic therapy to target likely pathogens while cultures are in progress [5]. In cases of non-purulent skin infection and cellulitis, a diagnosis should be made based on clinical observation; culture is not required in these cases, as most cellulitis and erysipelas is caused by group A, B, C, and G beta-hemolytic streptococci and Methicillin-Susceptible *Staphylococcus Aureus* (MSSA) [5]. However, in cases of purulent, draining abscesses, the recommendation is to drain the abscess in the hope that symptoms will resolve and obtain gram stain and culture of the purulent material to identify the microorganisms involved [19]. Doxycycline, 200 mg PO followed by 100 mg PO every 12 hours for 7-14 days is the recommended outpatient treatment [5].

### Case Presentation

A 63-year-old patient with a 10-year history of type 2 diabetes, chronic kidney disease, Charcot arthropathy of the left foot, prior osteomyelitis of the left heel bone, and an extensive ulceration that led to the exposure of tibial bone distally. We performed multiple irrigation and debridement on the wound and applied bioengineered skin substitute to allow epithelialization of the ulcer base. We also obtained bone and soft tissue specimen for pathology and microbiological analysis. The patient was transferred to a long-term acute care hospital the same day. A week after surgery, she presented to the emergency room with a temperature of 101°C, a respiratory rate of 19, a heart rate of 68, a WBC count of 12,000/mm<sup>3</sup>, and 5% band cells. Her blood pressure was 124/80, her lactic acid was 1 mmol/L, her BUN was 30 mg/dL, and her serum creatinine was 4 mg/dL. She complained of pain and seropurulent drainage around the medial aspect of the soleus pin site.

On clinical examination, the area appeared to contain scant purulent drainage and moderate erythema to the surrounding skin extending 5 cm<sup>2</sup> around the pin site, and it exhibited increased warmth. An x-ray of the tibia/fibula of her left leg showed the implant was intact in the original position without any loosening, but with no acute findings related to the soft tissue and bony structures. The patient was discharged the same day with a script for doxycycline 100 mg, by mouth, twice a day for seven days and a period sufficient to allow culture results and finalize a recommendation for narrow-spectrum antibiotic therapy. She presented to the clinic one week later for a post-operative visit. The erythema surrounding the pin tract site had resolved, with no drainage noted. She reported no pain, and her labs and vitals were found to be normal.

### Discussion

A short course (seven days) of doxycycline was appropriate in this case based on the guidelines of the Infectious Diseases Society of America, which recommends a brief course of systemic antimicrobial therapy for patients with soft tissue and skin infections following clean operations on the trunk, head and neck or extremities who also have systemic signs of infection [19]. Our patient's prior history of osteomyelitis culture-positive for *Staph aureus* rendered a broad-spectrum antibiotic most appropriate. Our selection was based on the patient's existing medical conditions; doxycycline is generally safe for patients with impaired renal function, and no dose adjustment was necessary. In addition, doxycycline can be administered on an outpatient basis, reducing healthcare costs and preventing other bacterial infections associated with inpatient treatments (e.g. MRSA or VRE). The excellent bioavailability and bone penetration of doxycycline helped the patient recuperate while waiting for culture and sensitivity results to arrive [19]. We were unable to find information on the safety of long-term (longer than three months) doxycycline use in the foot and

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ankle literature. However, we found that some providers use lower doses of doxycycline for an extended period to treat acne. It was not clear what Schlagenhauf consider an “extended period” and “lower dose” as the information was not provided in the book [20]. Besides, no documented cases of hepatotoxicity were found associated with prolonged use of doxycycline in a single reported case-control study. However, Schlagenhauf indicated that doxycycline does interact with other drugs. For example, antacids may reduce the serum level. Older literature indicates that the concurrent use of doxycycline with estrogen-containing birth control pills causes decreased contraceptive efficacy. However, there have been few reports of contraceptive failure when doxycycline is used concurrently [21]. Further, the current literature does show that doxycycline can be used concurrently without leading to an increased rate of contraceptive failure [21].

As far as the soft tissue infection in the foot and ankle is concerned, timely administration of antibiotics can be an effective therapy in cases like this, and can save lives in cases of sepsis. However, physicians tend to overprescribe the antibiotics, whether it is at a dentist's office, an emergency medicine setting, or a family physician. This increased antibiotic use is a troubling phenomenon. It has been reported that ~20-50% of antibiotic prescriptions for inpatient care, and 25% of those for outpatient care, are clinically unnecessary [22]. Overuse poses clear threats, including increased resistance, increased healthcare costs, and above all, an increased risk of serious adverse events with no clinical benefit to patients [22].

In our case, we used our clinical judgment first and foremost to decide if the antibiotic was needed in the patient's case, or if the patient could benefit from its use. Then we decided to find what current literature shows about safety and efficacy and proceeded to prescribe a dose that we felt was therapeutic for the patient. Additionally, we followed facility-specific treatment recommendations. This is a program that exists in most hospitals as part of an antibiotic stewardship program that has the goal of appropriate pharmacy-driven infection- and syndrome-specific antibiotic prescription [22]. One of its goals, in our view, is to curtail the rampant prescription of antibiotic regimens. We spoke with a pharmacist who educated us about safety profile, indications, and interactions so that we could improve patient outcomes, reduce microbial resistance, and decrease the spread of infections caused by multidrug-resistant organisms.

## Conclusion

Doxycycline is well-suited for certain applications, especially soft-tissue and bone infections. However, antibiotic overuse carries the risk of adverse reactions and antibiotic resistance. Therefore, the risks/rewards and contraindications must be weighed in each specific case. In cases such as the one presented here, the benefits of avoiding hospital-acquired infections, lower cost, and compatibility with existing health conditions outweigh the risks. Healthcare providers must follow evidence-based guidelines in deciding whether to prescribe antibiotics, and if appropriate, which antibiotic to prescribe.

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