

[Primary Care]



Antibiotic Precautions in Athletes

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Context: Antibiotics are the mainstay of treatment for bacterial infections in patients of all ages. Athletes who maximally train are at risk for illness and various infections. Routinely used antibiotics have been linked to tendon injuries, cardiac arrhythmias, diarrhea, photosensitivity, cartilage issues, and decreased performance.

Evidence Acquisition: Relevant articles published from 1989 to 2012 obtained through searching MEDLINE and OVID. Also, the Food and Drug Administration website was utilized.

Study Design: Clinical review.

Level of Evidence: Level 3.

Results: The team physician should consider alternative medications in place of the “drug of choice” when adverse drug effects are a concern for an athlete’s health or performance. If alternative medications cannot be selected, secondary preventative measures, including sunscreen or probiotics, may be needed.

Conclusion: Physicians choose medications based on a variety of factors to help ensure infection resolution while limiting potential side effects. Extra precautions are indicated when treating athletes with certain antibiotics.

Keywords: antibiotics; tendon injuries; antibiotic-associated diarrhea; photosensitivity; long QT

Team physicians treat musculoskeletal problems as well as medical conditions, including bacterial infections. Several considerations are appropriate when treating with antibiotics, including the specific pathogen, susceptibility, dosing frequency, mode of administration, and allergies. Special considerations should also be given to athletic participation and exercise patterns.

Athletes use oral antibiotics twice as frequently as age-matched controls (2.7% vs 1.3%),^{1,2} perhaps because physicians are quicker to prescribe antibiotics in hopes of helping the athlete return to play as soon as possible. Antibiotics can have unintended side effects. Tailoring a treatment plan for effective antibiotics that limit an athlete’s risk is paramount to the athlete’s safety and ability to continue exercise

TENDON INJURIES

Fluoroquinolones are broad-spectrum antibiotics that have bactericidal activity against a large number of both Gram-negative and Gram-positive bacteria. Because of their broad-spectrum coverage, by 2002, fluoroquinolones became the most commonly prescribed class of antibiotics for adults in the United States.²⁸ However, as fluoroquinolone use became

more widespread, adverse reactions related to these drugs have become apparent.¹⁰ The association between tendon injuries and fluoroquinolones has been receiving increased attention, most notably with the Achilles tendon.^{55,57} In 2008, the Food and Drug Administration reviewed the evidence and issued a black box warning regarding the increased risk for tendonitis and tendon rupture.²² The literature reports that patients taking fluoroquinolones have a 3 to 6 times increased risk of developing tendinitis or rupturing their Achilles tendon or an absolute risk of 7.74 per 100,000 days at risk and 3.2 per 1000 patient years.^{49,56}

One proposed mechanism of tendon injury in the central avascular portion of the Achilles tendon “watershed area” is the accumulation of free radicals during the inflammatory process secondary to antibiotic use.⁴⁶ These substances are toxic to tendon cells and can lead to necrosis.¹² With frequent use, there also appears to be histologic changes, including abnormal arrangement of tendon fibers, cystic changes, fibrotic changes, hypercellularity, edema, and neovascularization leading to a remodeling process that ultimately weakens the tendon matrix.¹²

Age and concomitant steroid use have been associated with Achilles tendon ruptures in patients using fluoroquinolones.^{12,22,57,61} In a case-crossover study performed by

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Wise et al, patients over the age of 60 who used corticosteroids were at the highest risk of developing Achilles tendinopathy and/or rupture as compared with the general population.^{49,55,56,61} This risk should be discussed with athletes, and alternative antibiotics might be considered if appropriate.^{20,57,61}

CARDIAC ARRHYTHMIAS

Cardiac effects from antibiotics may have significant consequences regarding participation and safety. Macrolides are a popular class of antibiotics used for a variety of mild to moderate bacterial infections. Macrolides and fluoroquinolones may be associated with increased risk of ventricular arrhythmia and cardiac arrest.⁶² There is a small increase in cardiovascular deaths with azithromycin use.⁴⁰ A review by the Food and Drug Administration has resulted in additional warnings for azithromycin.¹⁶ Prolongation of the QT interval by macrolides (erythromycin and clarithromycin) has been well established. These changes have also been seen in patients taking fluoroquinolones, especially moxifloxacin.^{40,42,44,53} A prolonged QT interval is linked to torsades de pointes, which can progress to a potentially fatal ventricular arrhythmia.⁶⁶

Prolongation of the QTc (corrected QT interval) on electrocardiogram can be important in the consideration for participation in competitive sports. Criteria for participation with congenital long QT syndrome were outlined at the 36th Bethesda Conference⁶⁵ and by the European Society of Cardiology in its 2005 guidelines.³⁰ The conference currently defines the upper limit to >470 ms in men and >480 ms in women,⁶⁵ while the European Society of Cardiology recommends further evaluation in men with QTc intervals >440 ms and women with >460 ms.³⁰ Drug-induced prolongation of the QTc can carry substantial risk.⁶⁶ While the mean increase in the QT interval with fluoroquinolones is approximately 3 to 6 ms and is thought to have little clinical significance, it may place patients at an increased risk for ventricular arrhythmias,⁴⁷ especially those with long QT syndrome. Since electrocardiogram testing is used in organized competitive sports, even mild prolongation of the QTc could confuse evaluation, delay participation, and cause limitations or possibly disqualification. Antibiotic use close to or at the time of testing should be addressed during history. A prolonged QT interval may resolve over time and not necessitate extensive cardiac evaluation.^{25,40}

Most athletes will not undergo formal evaluation before participation in athletics and may have other risk factors that put them at risk for arrhythmia with concomitant use of antibiotics (Table 1).⁶²

ANTIBIOTIC-ASSOCIATED DIARRHEA

Antibiotic-associated diarrhea (AAD) is a common adverse reaction with many antibacterials, with rates ranging from 5% to 39%.^{31,51} Diarrhea can start acutely or up to 3 to 4 weeks after the initiation of antibiotic therapy. Antibiotics disrupt the normal intestinal microflora, leading to

Table 1. Risk factors for arrhythmia with concomitant use of antibiotics⁶²

Organic heart disease
Congenital long QT syndrome
Ischemic heart disease
Congestive heart failure
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Myocarditis
Metabolic abnormalities
Hypokalemia
Hypocalcemia
Hypomagnesaemia
Bradycardia
Atrioventricular and sinoatrial blocks
Drug-related factors
Actions on cytochrome P450 enzymes
Polypharmacy
Female preponderance
Hepatic impairment

proliferation of pathogenic microorganisms (eg, *Clostridium difficile*) or impairment of the metabolic function of the microflora.^{11,34,38} Broad-spectrum antibiotics, especially those that affect *Enterobacteriaceae* and anaerobic bacteria (eg, aminopenicillins, cephalosporins, clindamycin), are likely to have a significant effect on the normal flora, as well as antibiotics with a high intraluminal concentration in the intestinal tract.^{11,23} Risk factors for AAD include duration, repeated use, and combination of antibacterial therapies.^{11,34} The dosage and route of antibiotics are usually not risk factors; exceptions are erythromycin and beta-lactams^{11,60} (Table 2). The prevalence of AAD in children is 11%, with amoxicillin-clavulanate (23%), erythromycin (16%), cephalosporins (9%), macrolides (9%), trimethoprim-sulfamethoxazole (6%), and penicillin G and V (3%).⁵⁴

Two ways to minimize the risk of AAD is to limit the duration of treatment to a minimum and use a narrow-spectrum antibiotic.³² Another method may be the use of probiotics. Some studies showed that *Saccharomyces boulardii* can prevent AAD,²⁶ while others showed no difference.²⁷ One study showed that probiotics did not help with acute diarrhea

Table 2. Rates of antibiotic-associated diarrhea from multiple studies

Antibiotic	Rate, %
Clindamycin ⁹	15-30
Azithromycin ¹¹	18
Erythromycin ¹¹	45
Amoxicillin-clavulanic acid ¹²	11.60
Levofloxacin ¹²	1.30
Clarithromycin ¹⁸	5.60
Doxycycline ²¹	4-52

but rather helped prevent delayed-onset diarrhea.²¹ A sensitivity analysis found that only 2 probiotic strains could prevent AAD: *S. boulardii* and *Lactobacillus rhammosus*.³⁵ A Cochrane review showed that probiotics are effective in preventing AAD in children (relative risk, 0.49); the number needed to treat to prevent 1 case of AAD was 10.²⁴

PHOTOSENSITIVITY

Common photosensitizers in the athlete population include tetracyclines, fluoroquinolones, and sulfonamides.^{37,59} Photosensitivity can be either phototoxic after a single dose or photoallergic, which is immunologically mediated and requires re-exposure.^{15,37} Many drugs can cause both reactions. Clinical presentation resembles an exaggerated sunburn with clear delineation of sun-exposed areas.³⁷ Photosensitivity can increase the risk of skin cancer from sunburn.^{4,15,37}

Tetracyclines are commonly prescribed for acne vulgaris and other common infections that occur in high school and college athletes. Doxycycline has the highest incidence of photosensitivity (20%), while minocycline rarely causes photosensitivity.⁵⁸ The effect can be seen within 2 weeks of the onset of treatment and is dose dependent.⁶³ Doxycycline is also known to cause photo-onycholysis, with onset in as few as 8 days⁶⁴; these changes generally resolve spontaneously after 3 to 4 months.³⁹ Although minocycline generates less photosensitivity than other tetracyclines, it can cause reversible or irreversible hyperpigmentation in 2% to 15% of cases.^{18,48}

Fluoroquinolones are also photosensitizers.⁵² There are a variety of mechanisms, including free radical formation and reactive oxygen species.⁵² Fortunately, the worst offenders (nalidixic acid and similar generation quinolones) in this class are less commonly used or unavailable in the United States.⁵⁸ Ciprofloxacin is often used for a variety of conditions, including urinary tract infection. The incidence of photosensitivity with ciprofloxacin is 1% to 4%,⁵⁰ while levofloxacin carries a lower risk of 0.2%.^{14,29,58}

Sulfonamides, especially sulfamethoxazole, can cause a number of cutaneous reactions, including photosensitivity and the more severe Stevens-Johnson syndrome.^{37,52,58} The incidence of cutaneous reactions is between 1:1000 and 1:100,000 and can occur within 3 days of treatment.⁵²

If an athlete is participating in outdoor events, it is best to avoid photosensitizing antibiotics. If use cannot be avoided, use of sun-protective clothing and broad-spectrum sunscreen should be emphasized.

BONE, CARTILAGE, AND TEETH

Tetracycline and its derivatives cause intrinsic staining of the oral cavity and teeth of children during osteogenesis and odontogenesis.⁴³ Hence, tetracyclines are contraindicated in pregnant women and in children under the age of 8 years because of their teratogenic effects on bone and tooth development in the fetus and because staining is more prevalent in growing children.^{13,19,43} Tetracyclines also cause hyperpigmentation of the skin, thyroid, nails, sclera, conjunctiva, and bone.⁴³

The prevalence of tetracycline staining in the oral cavity is 3% to 6%.^{3,6} Staining can also occur on the long bones of the body.⁴¹ Minocycline treatment of severe acne, which is sometimes used for extended periods of treatment, can cause dental and hard palate staining.^{3,6} This cosmetic concern should be explained as a rare but potential side effect of treatment. Staining is caused by chelation of iron and the formation of insoluble deposits in skin, hair, and bone.^{3,8} This staining is reversible in bone, as humans remodel 10% of their skeleton annually.^{3,17} The staining of teeth, however, is permanent, as teeth do not remodel. In an animal study, fluoroquinolones caused articular cartilage damage during growth in lambs; there was no change in growth velocity.⁴⁵ One study on human cadavers was inconclusive.³⁶

FATIGUE OR DECREASED PERFORMANCE

Antibiotics may cause fatigue or affect an athlete's performance.³⁵ However, it is difficult to discriminate the effects of the antibiotic or the illness itself. A study comparing tetracycline, ampicillin, and trimethoprim-sulfamethoxazole to a placebo in 50 healthy male military trainees found that there were no differences in muscle enzyme activity, muscle strength, VO₂ max, and subjective fatigue after 3 days of treatment.⁹ However, since most antibiotic treatment courses last longer than 3 days, it is possible that longer courses could cause a negative effect. Higher fatigue scores have been reported with a greater number of antibiotic courses and total use of antibiotics.⁷ In a side effect review of doxycycline and minocycline, somnolence was found in 1.2% with doxycycline, with weakness or fatigue with minocycline in 23%.⁴⁸

CONCLUSION

There are no "perfect" antibiotics, and it may be impossible to avoid all side effects. AAD and tendon injuries may hinder performance, while prolongation of the QT interval may be more serious.



Clinical Recommendations

SORT: Strength of Recommendation Taxonomy

A: consistent, good-quality patient-oriented evidence

B: inconsistent or limited-quality patient-oriented evidence

C: consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Clinical Recommendation	Strength of Recommendation Taxonomy (SORT) Grades
Fluoroquinolones should be discouraged in patients over 60 years on corticosteroids, if appropriate alternatives are available, to reduce risk of tendon injury. ^{12,22,49,55,56,57,61}	A
Fluoroquinolones should be avoided in athletes unless medically necessary. ^{20,57,61}	C
Recent or current antibiotic use must be considered during electrocardiogram screening when long QT syndrome is suspected. ^{16,40,42,44,53,62}	B
Antibiotics that may prolong the QT interval should be used with caution in the athletic population.	C
The risk of antibiotic-associated diarrhea can be minimized by limiting the duration of treatment and using narrow-spectrum antibiotics. ^{11,32}	A
<i>Saccharomyces boulardii</i> and <i>Lactobacillus rhamnosus</i> may reduce the risk of antibiotic-associated diarrhea. ^{21,24,26,33}	B
If an antibiotic with a high risk of photosensitivity is used in an outdoor athlete, sun-protective clothing and sunscreen should be used to prevent sunburn. ^{5,37,52,58}	A

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