

What rhinologists and allergists should know about the medico-legal implications of antibiotic use: a review of the literature

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Background: Antibiotics are commonly used in the management of both acute rhinosinusitis and acute exacerbations of chronic rhinosinusitis. With their common use, they have become the leading medication for litigation. It is crucial for the provider to be familiar with potential complications and the medico-legal ramifications of their use. The objectives of this review were to outline the existing data of the medico-legal implications of prescribing oral antibiotics.

Methods: An OVID search of the following terms was performed: antibiotics or antibacterial agents AND medico-legal, malpractice, jurisprudence, or informed consent. This search was then narrowed to English language articles and the titles and abstracts were searched for relevance.

Results: An OVID search identified 272 articles. This search was then narrowed, resulting in 13 articles that were relevant and included in the current review. Five articles involved database reviews of litigation associated with medications. Antibiotics were the most common medication

associated with litigation. Allergic reaction was the single most common reason for litigation.

Conclusion: Lawsuits associated with medications are disproportionately costly and antibiotics are the most common type of medication to result in litigation. Although the use of electronic medical records (EMRs) may decrease the frequency of these lawsuits, it is up to the physician to be familiar with the agents prescribed, their risks, and be vigilant regarding possible reactions. © 2014 ARS-AAOA, LLC.

Key Words:

antibiotics or antibacterial agents; medico-legal; informed consent; malpractice; jurisprudence

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Antibiotics are a staple in the treatment of both acute rhinosinusitis and acute exacerbations of chronic rhinosinusitis. Despite their common use, many providers are not familiar with the potential risks or the potential medico-legal ramifications of those risks.

The data supporting the use of antibiotics in acute rhinosinusitis and chronic rhinosinusitis is relatively sparse.

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There have been 2 Cochrane reviews evaluating the benefit of antibiotics for acute maxillary sinusitis.^{1,2} Both identified statistical improvements in those patients treated with antibiotics. They support the use of antibiotics, although the clinical significance of the improvements was difficult to define given the high rate of improvement of both groups. For chronic rhinosinusitis, a recent iterative review made the use of antibiotics an option (Level B evidence), given the balance of benefits to harm and a modest reduction in symptoms following antibiotic use.³

The authors have reported on the medico-legal aspects of corticosteroid use in sinusitis.⁴ The objectives of the current review were to outline the existing data of the medico-legal implications of antibiotics. In this work we discuss what is known about the risks to patients who consume them and to providers who prescribe them. We review the risks associated with antibiotic use, the issues associated with lawsuits, and how to educate patients so that providers can protect themselves in the event of litigation.

Complications of antibiotic use

Allergy

Allergic reactions and anaphylaxis are a common concern when prescribing antibiotics. The majority of these reactions, according to the European registry of recorded drug-induced severe anaphylaxis, were caused by penicillins, amoxicillin, and cephalosporins.⁵ This is not surprising considering penicillins and cephalosporins made up almost 60% of all antibacterial drugs sold in the United States in 2011.⁵ These reactions are Type I, immunoglobulin E (IgE)-mediated hypersensitivity reactions. The reported incidence of an “allergy” to an antibiotic such as penicillin is much higher than the IgE testing shows. In fact, studies with patients that have been labeled as having penicillin allergies have shown that between 0.3% and 3% of them truly have positive testing for a Type I hypersensitivity reaction.⁵

Additionally, the cross-reactivity between penicillin allergies and cephalosporin allergies are not as common as once believed. Initial studies from the 1960s and 1970s report a cross-reactivity rate of 8% to 18%. This may have been due to minor contamination of cephalosporins by penicillin from the manufacturing process. Until the 1980s, cephalosporins were chemically modified penicillins, leading to the minor contamination. More recent manufacturing involves synthetically synthesized cephalosporins, eliminating the risk of contamination.⁵ The cross-reactivity between the 2 types of antibiotics have been found to be due to structural similarity between R1 side chains rather than the beta-lactam ring as initially believed. The cross-reactivity is also related to the specific cephalosporin generation, with first-generation and second-generation cephalosporins having higher rates of cross-reactivity with penicillins. Current data suggests the true cross-reactivity to be between 1% and 2.55%.⁵

TABLE 1. Odds of developing a *Clostridium difficile* infection following exposure to various antibiotics based on class⁸

Antibiotic	Odds ratio for developing a <i>C. difficile</i> infection	95% confidence interval
Clindamycin	20.43	8.50–49.09
Fluoroquinolones	5.65	4.38–7.28
Cephalosporins	4.47	1.60–12.50
Penicillins	3.25	1.89–5.57
Macrolides	2.55	1.91–3.39
Sulfonamide/trimethoprim	1.84	1.48–2.29
Tetracyclines	0.91	0.57–1.45

Antibiotic-associated diarrhea

Antibiotic-associated diarrhea (AAD) is a commonly encountered side effect of antimicrobial therapy. A distinct subtype of AAD is pseudomembranous colitis, which is characterized by colonic mucosal necrosis and pseudomembrane formation. *Clostridium difficile* is the pathogen responsible for antibiotic-associated pseudomembranous colitis caused by disruption of the normal colonic flora due to the antibiotic ingestion.⁶ *C. difficile* is an anaerobic, spore-forming, Gram-positive bacillus that can produce toxins A and B, which are thought to mediate this disease process.

C. difficile infection is defined as at least 3 unformed stools in 24 hours and a positive stool test for *C. difficile* toxin or endoscopic evidence of pseudomembranous colitis.⁷ Disease severity can range dramatically from an asymptomatic colonization to fulminant colitis requiring surgical therapy. The morbidity associated with infection is reported to be as high as 80% with mortality rates up to 8%.⁶ The incidence of *C. difficile* colitis has increased from 0% in 1990 to 3.2% in 2000.⁶

The most common risk factor for acquiring *C. difficile* colitis is prior exposure to antibiotics. A recent meta-analysis of 8 studies, including over 30,000 patients showed that antibiotic usage led to a significantly higher risk of developing community-acquired *C. difficile* infection compared to patients with no antibiotic exposure.⁸ When evaluating specific antibiotic class, clindamycin had the greatest risk of a *C. difficile* infection, followed by a fluoroquinolone, cephalosporins, penicillins, and macrolides, then sulfonamide/trimethoprim had the lowest risk. Tetracyclines were not associated with an increased risk of *C. difficile* infection⁸ (Table 1).

There have been extensive studies evaluating the protective effects of probiotics in preventing *C. difficile*-associated diarrhea and infection. Several randomized trials and meta-analyses have shown reduction in the incidence of *C. difficile* infections in patients taking probiotics compared to placebo.⁷ A Cochrane review reported that probiotics reduced the risk of *C. difficile*-associated diarrhea by 64%, as well as reduced the risk of developing AAD. The review evaluated secondary outcomes and found a decreased risk of developing side effects from antibiotics such as abdominal cramping, nausea, flatulence, and taste disturbance.⁹ Interestingly, although the study identified a reduction in *C. difficile*-associated diarrhea, there was no difference in the incidence of *C. difficile* infection. The authors hypothesize that this may suggest the probiotics may be more effective at limiting the extent of infection or preventing the symptoms of infection rather than inhibiting the actual colonization and infection.⁹ The authors conclude that probiotics are safe and effective at reducing the rate of *C. difficile*-associated diarrhea, AAD, and the side effects of antibiotics in the immunocompetent patient.

Fluoroquinolone-induced tendon damage

In 2008, the U.S. Food and Drug Administration (FDA) came out with a boxed warning regarding the risk of tendonitis and tendon rupture with the use of fluoroquinolones.¹⁰ The purpose of this boxed warning was to draw providers' attention to the continued report of tendon issues occurring in patients using fluoroquinolone antibiotics. These antibiotics include ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin. The Achilles tendon is the most commonly involved, but the rotator cuff, biceps, and thumb and hand tendons can also be affected. Patients over the age of 60 years, those taking corticosteroids, and those who have had solid organ transplants are at higher risk. The warning also points out that the risk for injury does not end with the completion of the therapy; patients have reported problems months after the antibiotic was stopped. Of note, this warning only applied to systemic use of the fluoroquinolones, not eye or ear drops.

The exact incidence or etiology of fluoroquinolone-associated tendon issues are not known. Published reports estimate the incidence between 0.14% to 0.4% in healthy patients.¹¹ Renal impairment and transplant have been associated with higher incidence, up to 15.6%, presumably due to impaired clearance of the fluoroquinolone and higher blood levels. The mechanism of damage has been hypothesized through clinical reports and animal studies. Clinical reports have identified degenerative lesions on the tendons, fissures, edema, and necrosis, whereas animal studies have demonstrated oxidative damage, edema, and alterations of the tenocytes from the quinolones.¹¹

As mentioned in the FDA boxed warning, there are certain risk factors that can increase the risk of quinolone-induced tendon damage. There is debate in the literature regarding certain factors, such as obesity and gender; however, most of the studies consistently show increased age to be related to increased risk of tendon damage, as well as concurrent corticosteroid use and renal impairment.¹²

Others

Additional risks of antibiotics include cardiac arrhythmias, gastritis, increased sun sensitivity, colitis, and others. Although a complete assessment of possible complications associated with antibiotics use is beyond the scope of this review, we have listed common side effects/complications in Table 2.

Scope of litigation

An OVID search of the following terms: antibiotics or antibacterial agents AND medico-legal, malpractice, jurisprudence, or informed consent revealed 272 articles. The search was narrowed to English language and the titles and abstracts were searched for repeats and relevance. This narrowed the search down to 13 articles, which were

obtained and reviewed in detail. Ultimately, 5 articles were relevant to the current review.

Several studies have reviewed specific litigation brought against providers or episodes that had the potential to be involved in litigation. The first study discussed several reports from the 1970s and early 1980s from insurance companies.¹³ The overwhelming theme was that a significant number of claims were due to medications, with side effects of said medications leading to the claims.

The National Association of Insurance Commissioners, the state officials that oversee the insurance industry, reported their malpractice claims in 1976. This showed that adverse effects of drugs resulted in 4.5% of claims with over one-half due to allergic reactions. The therapeutic categories of drugs that led to the most claims included penicillin, which was responsible for 9.6% of claims, whereas antibiotics in general were 7.5% of claims.¹³

In 1977 the California Medical Association and the California Hospital Association reviewed over 20,000 patient charts looking for both claims filed, as well as events that had the potential for compensation but were not filed. This allows more accurate representation of the extent of events that occur in the healthcare systems. They found that drugs caused 18.8% of events, with tetracycline being responsible for 3%.¹³

The Risk Prevention Department of the Medical Inter-Insurance Exchange of New Jersey reviewed their cases identified as having "an error as a significant cause of the suit and closed with a payment to the plaintiff" between 1977 and 1988.¹⁴ Their review identified 337 files with allergic reactions, resulting in 34 cases with over \$1 million in indemnity payments. There were 6 deaths, 5 of which were due to an allergy to penicillin and 1 to an allergy to ibuprofen. The complaints specifically stated that the allergy was noted in the patient's chart; however, the provider never reviewed the chart, admitted to overlooking the record, or failed to read the discharge summary of previous hospitalizations. Treatment with antibiotics included 73 files and over \$5 million in indemnity payments. The errors listed included failure to order a culture and sensitivity, treatment with the wrong antibiotics (based on failure to follow up on a culture, or failure to order the correct antibiotic based on cultures), failure to reevaluate when the infection did not respond, failure to prescribe an antibiotic, and prescribing a lower dose than required.

Errors in writing the prescriptions and failure to communicate were each included in the review given the relatively high damages and relative ease of prevention. The recommendations of the manuscript include heeding the patients' warnings regarding allergies and consider the pharmacist as a consultant. Additionally, the authors strongly encourage maintaining a current list of all drugs, doses, dates prescribed, and date discontinued, as well as current allergies. Although it is easy to assume, in the current age of electronic medical records (EMRs), that these errors could not happen due to the inherent safeties in the system, but

TABLE 2. Potential side effects of common antibiotics per Micromedix® 2.0

Amoxicillin
Dermatologic: rash (greater than 1%)
Gastrointestinal: diarrhea (overall, greater than 1%; <i>Helicobacter pylori</i> therapy, 7% to 8%), nausea (greater than 1%), vomiting (greater than 1%)
Neurologic: headache (<i>Helicobacter pylori</i> therapy, 6% to 7%; extended-release tablets, 1%)
Reproductive: vulvovaginitis, mycotic (extended-release, 2%)
Amoxicillin/clavulanate potassium
Dermatologic: diaper rash (3.5% to 6%), rash (1.1% to 3%)
Gastrointestinal: diarrhea (2.9% to 14.5%), loose stool (1.6% to 9%), nausea (up to 3%), vomiting (up to 2.2%)
Reproductive: mycosis (3.3%), vaginitis (1%)
Other: candidiasis (1.4%)
Ciprofloxacin
Cardiovascular: cardiorespiratory arrest (up to 1%), myocardial infarction (up to 1%), prolonged QT interval, syncope (up to 1%), torsades de pointes
Dermatologic: rash (up to 1.8%), photosensitivity (up to 1%), Stevens-Johnson syndrome (up to 1%), toxic epidermal necrolysis (up to 1%)
Gastrointestinal: diarrhea (1.6% to 4.8%), nausea (2.5% to 4%), vomiting (1% to 4.8%), <i>Clostridium difficile</i> diarrhea (up to 1%), gastrointestinal hemorrhage (up to 1%), pancreatitis (up to 1%), pseudomembranous enterocolitis
Hematologic: agranulocytosis, aplastic anemia, bone marrow depression, hemolytic anemia, leukopenia (0.4%), pancytopenia (0.1%), thrombocytopenia
Hepatic: hepatic necrosis (up to 1%), hepatitis (up to 1%), hepatotoxicity, liver failure
Immunologic: immune hypersensitivity reaction (up to 1%)
Musculoskeletal: myasthenia gravis, exacerbation, rupture of tendon, tendinitis
Neurologic: headache (oral extended-release tablets, 3% ; IV, greater than 1%), raised intracranial pressure, seizure (up to 1%)
Ophthalmic: retinal detachment
Psychiatric: depression (up to 1%), psychotic disorder (up to 1%)
Renal: acute renal failure (up to 1%), hemorrhagic cystitis (up to 1%)
Levofloxacin
Cardiovascular: cardiac arrest (0.1% to 1%), prolonged QT interval, torsades de pointes, ventricular tachycardia (0.1% to 1%)
Dermatologic: erythema multiforme, Stevens-Johnson syndrome
Endocrine metabolic: hypoglycemia (0.1% to 1%)
Gastrointestinal: diarrhea (ophthalmic, 1% to 2% ; oral or IV, 5%), nausea (ophthalmic, 1% to 2% ; oral or IV, 7%)
Hematologic: aplastic anemia, pancytopenia, thrombocytopenic purpura
Hepatic: hepatitis, liver failure
Immunologic: anaphylactoid reaction, immune hypersensitivity reaction (0.1% to 1%)
Musculoskeletal: myasthenia gravis, exacerbation, rupture of tendon, tendinitis (0.1% to 1%)
Neurologic: dizziness (3%), headache (ophthalmic, 8% to 10% ; oral or IV, 6%), insomnia (4%), peripheral neuropathy, seizure (0.1% to 1%)
Ophthalmic: retinal detachment
Renal: acute renal failure (0.1% to 1%)
Moxifloxacin
Cardiovascular: prolonged QT interval (oral/IV, 0.1% to less than 1%), torsades de pointes
Dermatologic: rash (oral/IV, 0.1% to less than 1%), Stevens-Johnson syndrome, Toxic epidermal necrolysis
Gastrointestinal: diarrhea (oral/IV, 6%), nausea (oral/IV, 6.9%)

(Continued)

TABLE 2. Continued

Hematologic: agranulocytosis, aplastic anemia, hemolytic anemia, pancytopenia, thrombocytopenia (oral/IV, 0.1% to less than 1%)
Hepatic: hepatic necrosis, hepatitis, liver failure
Immunologic: anaphylactoid reaction, immune hypersensitivity reaction
Musculoskeletal: myasthenia gravis, exacerbation, rupture of tendon, tendinitis
Neurologic: dizziness (oral/IV, 3%), headache (oral/IV, 4.2%), peripheral neuropathy, seizure
Ophthalmic: dry eyes (ophthalmic, 1% to 6%), reduced visual acuity (ophthalmic, 1% to 6%), retinal detachment
Renal: acute renal failure (oral/IV, 0.1% to less than 1%)
Respiratory: extrinsic allergic alveolitis
Other: serum sickness due to drug
Cephalexin
Dermatologic: rash
Immunologic: immune hypersensitivity reaction
Gastrointestinal: diarrhea
Cefuroxime
Eosinophilia
Cefprozil
Dermatologic: diaper rash (1.5%)
Gastrointestinal: diarrhea (2.9%), nausea (3.5%)
Hepatic: ALT/SGPT level raised (2%), AST/SGOT level raised (2%)
Immunologic: superinfection (1.5%)
Reproductive: pruritus of genital organs (1.6%), vaginitis (1.6%)
Cefdinir
Gastrointestinal: abdominal pain (0.8% to 1%), diarrhea (4% to 19%), nausea (0.2% to 3%)
Reproductive: Candida vaginitis (0.3% to 4%)
Doxycycline
Dermatologic: rash (4%), photosensitivity
Gastrointestinal: diarrhea (3.3% to 5%), nausea (8% to 13.4%), vomiting (8.1%)
Musculoskeletal: myalgia (6.4%)
Reproductive: bacterial vaginosis (3.3%)
Respiratory: nasopharyngitis (5%)
Azithromycin
Dermatologic: injection site reaction (3.1% to 6.5%)
Gastrointestinal: abdominal pain (adult, 1.9% to 14%; pediatric, 2% to 4%), diarrhea (adult, 4.3% to 12%; pediatric, 7% to 10%), flatulence (5%), nausea (adult, 3% to 14%; pediatric, 4%), vomiting (adult, up to 13%; pediatric, 11% to 14%)
Hepatic: increased liver enzymes (less than 1% to 6%)
Neurologic: headache (up to 5%)
Ophthalmic: abnormal vision (5%)
Clarithromycin
Gastrointestinal: abdominal pain (1% to 7.5%), diarrhea (1.6% to 15%), disorder of taste (0.4% to 18.9%), indigestion (up to 3.8%), nausea (3% to 28.3%), vomiting (1% to 24.5%)

(Continued)

TABLE 2. Continued

Neurologic: headache (up to 9%)
Hepatic: hepatitis (greater than or equal to 1%)
Sulfamethoxazole/trimethoprim
Dermatologic: rash, urticaria
Gastrointestinal: loss of appetite, nausea, vomiting
Clindamycin
Dermatologic: morbilliform eruption
Gastrointestinal: abdominal pain, diarrhea, nausea

ALT = alanine aminotransferase; AST = aspartate aminotransferase; IV = intravenous; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamate pyruvate transaminase.

those safeties require up-to-date information in order for them to be effective.

A review performed by the Physician Insurers Association of America (PIAA), published in 1993, studied lawsuit data provided by the liability insurance companies within their association. They reviewed 117,000 claims and found that medication errors were the second most frequent reason for claims against physicians, and almost all of the errors that lead to lawsuits were avoidable.¹⁵ The study identified 393 medication error claims, with over \$47 million paid in indemnity, for an average payment of over \$120,000.¹⁵ Antibiotics were the most common drug class implicated at 14% of claims and 7 deaths. Although not specifically outlined, many of the errors were allergy-related. The most common errors listed in the litigation were as follows: the failure to note a documented allergy; most appropriate drug not used; drug inappropriate for medical condition; inadequate medical history; and failure to read medical record.¹⁵

The Risk Management Foundation of the Harvard Medical Institution analyzed the malpractice claims between 1990 and 1999.¹⁶ Of the 129 cases involving medication-related claims, antibiotics were the most common class of medication, accounting for 12 cases or 9% of all claims. Ten of the 12 antibiotic-associated cases were considered to be “preventable.” The “preventable” nature of the error had significant implications in the defense as well as the indemnity payments. Of the closed cases with verdicts, 16% of the preventable cases were ruled for the defense, whereas 60% of the nonpreventable cases were ruled for the defense. Of the settled cases, 59% of the preventable vs 6% of the nonpreventable cases were settled for the plaintiff. The mean indemnity payment for all preventable claims was \$332,000, whereas the mean payment of the nonpreventable claims was \$30,000.¹⁶ Of note, it was estimated that computerized physician order entry could have prevented 40% of the inpatient and 35% of the outpatient “preventable” events.

The Ophthalmic Mutual Insurance Company published their series of claims that dealt specifically with ophthalmology-related lawsuits.¹⁷ In this review, they

found that the average indemnity payment for a medication error was \$115,000 compared to \$95,000 for all other types of claims. Additionally, medication errors were costlier to defend. Antibiotics were 1 of the most common medications implicated in the claims. Prescriptions for medications to a patient with a documented allergy to that medication was 1 of the most common causes for medication error claims.

Preventing complications and litigation

There are several things, as suggested in the literature, that practitioners can do to help avoid complications and litigation (Table 3). Despite the relatively low incidence of a true hypersensitivity reaction to a medication, it is recommended that practitioners heed the patients’ warnings regarding allergies. Current lists of drugs, doses, dates prescribed, dates discontinued, and allergies are all essential

TABLE 3. Common plaintiff allegations related to antibiotic therapy

Allergy
Provider never reviewed the chart; failure to note a documented allergy; failure to read medical record
Inadequate medical history
Failure to order a culture and sensitivity
Most appropriate drug not used (based on culture)
Failure to follow up on a culture
Failure to reevaluate when the infection did not respond
Failure to prescribe an antibiotic
Prescribed a lower dose than required
Errors in writing the prescription
Communication failure between physician and patient
Providers did not review potential complications of antibiotics with patient

and should be updated at every visit. Documentation of past tolerances of antibiotics is also an important. Finally, consulting the hospital or local pharmacist regarding medication interactions, patient medication tolerance, and allergies is also good practice. Providers should communicate effectively with patients regarding past reactions and/or tolerances to antibiotics and document these conversations. Providers should consider providing patient education material addressing antibiotics.

Limitations

This type of review is limited in several ways, similar to the limitations of the steroid medico-legal review.⁴ These include an inability to provide total numbers of lawsuits or true incidences of lawsuits and the inability of the reviews to address the appropriateness of the claims discussed.¹⁵ The reviews included here are all from the pre-modern, pre-EMR era. The impact of the EMR is not known. Presumably it will lower the incidence of prescribing a medication that is contraindicated based on an allergy, but that again depends on the completeness of the EMR.

Conclusion

In this review, we have attempted to provide an overview of the existing data as to the medico-legal aspects of antibiotic use. Unfortunately, these data are relatively sparse,

TABLE 4. Steps to help avoid litigation

Heed patient warnings on allergies
Update current medications at each visit
Update current allergies at each visit
Document past tolerances to medications
Discuss the rationale for using medication if reported allergy; eg, past tolerance despite listed allergy
Consult pharmacist if questions
Keep good documentation of conversations
Be familiar with complications and side effects of the various antibiotics
Consider patient educational materials

making specific conclusions challenging to articulate. Providers must use their best judgment in the appropriate care of their patients. Be vigilant regarding allergic reactions. Make sure this is documented and up to date. Ideally, clinicians should discuss the rationale for antibiotics and explain the material risks and potential side effects. Answer any questions that may arise and involve the patient in the decision-making process. Document this discussion and the patient's decision in the medical record. Consider providing educational material for the patient to read and review (Table 4). 

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