Oral Antibiotics in Dermatology: A Practical Overview with Clinically Relevant Correlations and Management Suggestions

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Introduction

Oral antibiotics are frequently prescribed in dermatology practice, with their use related to treatment of both cutaneous infections and noninfectious inflammatory dermatologic disorders [1, 2]. Representing approximately 20% of all prescriptions written within the dermatology specialty, dermatologists prescribe more oral antibiotics per type of practitioner than any other medical specialty, including primary care; the majority of these oral antibiotic prescriptions are for treatment of noninfectious inflammatory dermatoses, such as acne and rosacea [1, 3, 4]. It is important to note that unlike treatment of most bacterial infections which usually respond to appropriate antibiotic therapy within a few to several days, antibiotic treatment of inflammatory skin disorders (such as acne and rosacea) is usually prolonged over a few to several months [1, 3–6]. Consistent with the common use of oral antibiotic agents to treat inflammatory skin disorders, oral tetracyclines comprise approximately three-fourths of all oral antibiotics prescribed by dermatologists, especially doxycycline and minocycline [1].

The goal of this chapter is not to serve as an encyclopedic review of all oral antibiotics that may be used for treatment of dermatologic conditions as a very thorough and recent review is already available [3]. Rather, the objectives of this chapter are to discuss specific oral antibiotic therapies that are commonly used in dermatology and to provide a practical overview on optimal antibiotic use for uncomplicated superficial cutaneous infections and noninfectious inflammatory dermatoses. *Emphasis is placed on the more frequently used antibiotic treatments* of *more commonly encountered cutaneous disorders*, such as superficial staphylococcal and streptococcal infections and facial inflammatory dermatoses (e.g., acne, rosacea, perioral dermatitis). Summary statements are provided for oral antibiotics that are used less frequently in outpatient dermatology, such as rifampin, clindamycin, linezolid, tedizolid, and dapsone.

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Oral Penicillin Derivatives and Oral Cephalosporins

Dermatologic Applications of Oral Penicillins

The beta-lactamase-resistant oral penicillins and oral cephalosporins are adaptable for treatment of many uncomplicated bacterial skin infections caused by susceptible organisms. These agents are not generally recommended for treatment of common inflammatory facial dermatoses such as acne and rosacea, primarily due to concerns related to antibiotic resistance [1, 3, 7–9]. Of the oral beta-lactamase-resistant penicillins, dicloxacillin exhibits the most favorable pharmacologic and pharmacokinetic properties, with therapeutic activity against methicillin-sensitive *Staphylococcus aureus* (MSSA); these agents are not recommended for treatment of methicillin-resistant *S. aureus* (MRSA) [3]. The same is true for amoxicillin-clavulanate, which incorporates a beta-lactamase inhibitor (clavulanic acid) in combination with amoxicillin. Amoxicillin offers superiority over ampicillin, a structurally similar oral aminopenicillin antibiotic, demonstrating greater gastrointestinal (GI) absorption, lower incidence of diarrhea, adaptability to co-administration with food, and resistance to beta-lactamase when combined in the same tablet/capsule with clavulanic acid [3]. Isoxazolyl penicillins offer good coverage against both *Streptococcus pyogenes* and MSSA, which are associated with a variety of

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Table 46.1 Clinically relevant information with selected oral antibiotics used in dermatology

Drug	Usual dose	Comments
CEPHALEXIN	250–500 MG QID	Pharmacokinetic profile for skin not as favorable as cefdinir due to very short half-life and rapid renal clearance
		Not active against MRSA
CEFDINIR	300 MG BID	More prolonged tissue levels within skin than cephalexin
	600 MG DAILY	Not active against MRSA
AZITHROMYCIN	500 MG DAILY on first day followed by 250 MG DAILY on days 2 through 5	Dosage to left recommended for uncomplicated skin infections caused by susceptible bacteria
		Selective use for acne or rosacea; after initial loading dose may use 250 mg two to three times per week
DOXYCYCLINE	150–200 MG DAILY (infection)	Lower doses may be equally effective in rosacea
	150–200 MG DAILY (acne)	Enteric-coated and small tablet (scored) formulations reduce GI side effects
	20 MG BID or 40 MG DAILY with modified-release capsule (rosacea)	Administer with food to reduce GI upset
	50–200 MG DAILY (rosacea)	Avoid lying down flat after ingestion
		Photoprotection recommended
		Severe intractable cephalgia/visual disturbances/nausea and vomiting warrant evaluation for presence of papilledema
		Take doxycycline at least 1–2 h before oral ingestion of iron
MINOCYCLINE	100–200 MG DAILY (infection)	Caution about vestibular side effects; most likely to occur within first few days
	100–200 MG DAILY (acne)	Acute vestibular side effects reduced with weight-based dosing (using ER tablet) for acne
	1 MG/KG DAILY using extended-release (ER) tablet formulation (acne)	Drug hypersensitivity syndrome (DHS) most often occurs within the first 2–8 weeks after starting therapy; flu-like symptoms, facial edema, hepatotoxicity common; systemically may present with interstitial pneumonitis as predominant finding; watch for delayed development of autoimmune thyroiditis weeks to months after resolution of lupus-like syndrome that develops most often after months to years of use, usually without any skin changes, with polyarthralgias/arthritis of small peripheral joints (fingers/hands) most common; ANA* positive with several other autoantibodies potentially positive on serologic testing
		Monitor patients with cutaneous and/or mucosal dyspigmentation; may present as blue scars, blue lunula, gray or blue color of skin and/or mucosa (oral, ocular), brown macular discoloration often on legs
		Severe intractable cephalgia/visual disturbances/nausea and vomiting warrant evaluation for presence of papilledema
		Take minocycline at least 1–2 h before oral ingestion of iron
TRIMETHOPRIM-SULFACETAMIDE	160 MG/800MG BID (infection) (double-strength [DS] tablet)	Use for MRSA suggested if patient has failed or is unable to use doxycycline or minocycline
		Use for acne in selected cases that have failed other therapies and patient not a candidate for or refusing oral isotretinoin
		Lower dose may be effective in selected cases of acne; may use BID or DAILY
		Watch for potential signs of emerging DHS, Stevens-Johnson syndrome, and toxic epidermal necrolysis especially in the first few months after starting therapy
		Consider baseline and periodic monitoring of complete blood cell counts if to be administered for prolonged duration (acne)
CIPROFLOXACIN	500–750 MG BID	Take ciprofloxacin/fluoroquinolone agent at least 1 h before and not within 4 h after ingestion of dairy foods (i.e., milk, yogurt), fortified cereals, antacids, and/or vitamin/mineral supplements as failure to do so results in reduced GI absorption of the drug; this predisposes to antibiotic treatment failure

cutaneous bacterial infections encountered in the outpatient setting; the natural penicillins (penicillin G, penicillin V) are not active against MSSA or MRSA [3]. All oral penicillins primarily undergo renal elimination, with the exception of oxacillin [3]. Dosing of selected major oral penicillins used in outpatient dermatology is depicted in Table 46.1.

Adverse Effects Associated with Oral Penicillins

Hypersensitivity reactions, such as anaphylaxis/anaphylactoid reactions, are probably the major adverse effects (AEs) encountered clinically when prescribing oral penicillin derivatives. The diverse range of severity encompasses

morbilliform skin eruptions to urticarial reactions to fatal or near-fatal anaphylaxis [3]. From a clinical perspective, it should be considered that all penicillins may cross-react. Therefore, if a patient is truly allergic to a penicillin (or cephalosporin) antibiotic, especially with a severe allergic reaction, avoidance of other penicillin and cephalosporin agents is recommended [3]. Other AEs associated with oral penicillins are antibiotic-associated diarrhea and *C. difficile*-associated colitis (much less common than the former); more serious AEs such as hemolysis, blood dyscrasias, and seizures are most commonly associated with high-dose parenteral administration of specific penicillin derivatives [3]. Assuming the clinical benefit is felt to outweigh the potential risks of therapy during pregnancy, the oral penicillins are generally rated as pregnancy category B [3, 10].

Dermatologic Applications of Oral Cephalosporins

Cephalosporins are beta-lactamase-resistant agents that have been divided into "generations" depending primarily on their spectrum of antibiotic activity; the first-generation cephalosporins, cephalexin and cefadroxil, and the third-generation cephalosporin, cefdinir, exhibit the most favorable antibacterial activity among oral cephalosporin agents against MSSA and non-enterococcal streptococci, with some activity against certain Gram-negative organisms [3, 11]. With the exception of cefdinir, which exhibits favorable antibacterial activity against MSSA and non-enterococcal streptococcal pathogens, it is generally accepted that second-, third-, fourth-, and fifth-generation cephalosporins exhibit increased activity against Gram-negative pathogens and lesser activity against Gram-positive pathogens, with many agents available for parenteral use only. Notably, individual differences in antibacterial coverages exist among specific agents in all generations [3, 11].

From a practical perspective, two oral cephalosporins that are commonly used in dermatology to treat uncomplicated cutaneous bacterial infections caused by susceptible pathogens are cephalexin and cefdinir. As with other cephalosporins, these agents are inactive against *Pseudomonas* spp. including *P. aeruginosa*, and unlike cefaclor (a second-generation agent), they are not active against *Haemophilus influenzae* [3, 11]. Cephalexin is best absorbed from an empty stomach, rapidly undergoes renal excretion, and warrants oral administration three to four times daily due primarily to its short serum half-life [3]. Unlike oral cephalexin, cefdinir exhibits a longer serum half-life and more prolonged persistence in the skin after oral administration, with favorable antibiotic activity against MSSA and *S. pyogenes* with twice daily or once daily administration [3, 11, 12].

Oral cephalosporins are often used in dermatology practice to treat uncomplicated superficial cutaneous infections caused by MSSA or non-enterococcal streptococci, such as folliculitis, cellulitis, and furunculosis [3, 11]. Other selected uses of oral cephalosporins that may be helpful in certain clinical situations include treatment of *H. influenzae* cellulitis with cefaclor and treatment of selected cases of gonorrhea or Lyme borreliosis with cefuroxime axetil [3].

Dosing of selected major oral cephalosporins used in outpatient dermatology is depicted in Table 46.1.

Adverse Effects Associated with Oral Cephalosporins

Hypersensitivity and urticarial skin reactions are reported to occur in 1–3% of patients treated with cephalosporin antibiotics, inclusive of both oral and parenteral administration [11]. Potential cross-reactivity/cross allergenicity between penicillins and cephalosporins has been noted to occur in anywhere from 1 to 10% of patients [3]. Overall, oral cephalosporin antibiotics are very well tolerated; GI toxicity such as nausea, vomiting, or diarrhea may occur, with antibiotic-associated colitis noted to be rare with oral formulations [3]. Vaginal candidiasis may occur in some cephalosporin-treated patients [3, 11]. Serum sickness-like reaction has been occasionally reported in association with oral cefaclor use, especially in children [13]. More serious AEs, such as hematologic toxicities, are infrequent and are usually seen in association with parenteral cephalosporin use [3].

Oral Macrolides and Azalide Agents

Dermatologic Applications of Macrolide and Azalide Agents

Macrolides and azalides are compounds that are structurally very similar; the major oral macrolide antibiotics used in dermatology are erythromycin and clarithromycin, with azithromycin being the major azalide agent [3, 14]. Oral erythromycin use for the treatment of acne, and also for treatment of commonly encountered superficial cutaneous staphylococcal bacterial infections, has been limited due to the prominent emergence of erythromycin-resistant causative organisms (i.e., *P. acnes* in acne; *S. aureus* in superficial cutaneous infections) [1, 4, 8, 14–17]. Clarithromycin is equally absorbed from the GI tract when administered with or without food, while azithromycin is absorbed better in the absence of food (1–2 h before food ingestion) [3]. Azithromycin elimination is predominantly via hepatic metabolism, while clarithromycin is primarily eliminated by renal excretion [3].

Oral macrolide/azalide agents *have* demonstrated efficacy for a variety of uncomplicated superficial cutaneous infections caused by susceptible bacteria, including folliculitis, infected wounds/skin ulcers, and cellulitis; MRSA is not responsive to macrolide or azalide therapy [3, 17, 18]. Other mucocutaneous infections that may be treated with macrolide/azalide agents include Lyme disease, erythrasma, erysipeloid, and several sexually transmitted diseases (STDs; non-gonococcal urethritis, syphilis, chancroid, lymphogranuloma venereum) [3, 19–21]. Azithromycin has demonstrated efficacy in the treatment of cat scratch disease, donovanosis, human and animal bites caused by *Pasteurella* spp. and *Eikenella* spp., and urethritis or cervicitis caused by *N. gonorrhea* or *C. trachomatis* [3, 19, 20]. Clarithromycin has demonstrated efficacy in the treatment of leprosy and atypical mycobacterial skin infections caused by a variety of *Mycobacterium* spp. [3, 19–22]. Both azithromycin and clarithromycin are active against *H. influenzae*, *Treponema pallidum*, *Toxoplasma gondii*, and *Borrelia burgdorferi* [3].

Although not considered a first-line agent, oral azithromycin has been used in selected cases to treat both acne and rosacea [1, 3, 7, 9, 14, 23–28]. Due to its prolonged persistence in cutaneous tissue, a variety of intermittent regimens have been suggested with oral azithromycin for acne and rosacea [3, 7–10, 14, 24–28]. Due to the marked global prevalence of *P. acnes* strains resistant to erythromycin, the use of this agent for the treatment of acne has diminished; oral erythromycin is also associated with a higher potential for GI upset than azithromycin and clarithromycin and is associated with some potentially significant drug-drug interactions with an enhanced risk of systemic toxicity when co-administered with certain other drugs (i.e., cyclosporine, carbamazepine) [1, 3–5, 7–9, 15, 29]. Dosing of selected major oral macrolide/azalide agents used in outpatient dermatology is depicted in Table 46.1.

Adverse Effects Associated with Oral Macrolide and Azalide Agents

The most predominant AEs associated with oral macrolide/azalide use are GI disturbances associated with erythromycin and metallic taste associated with clarithromycin [3, 14, 19]. Cardiac conduction abnormalities, including QT prolongation and torsades de pointes, have been associated primarily with systemic erythromycin use, with risk factors including higher age, high dosage, rapid administration, and history of cardiac disease [3]. Animal data support that macrolides/azalides can induce reactive oxygen species formation, mitochondrial membrane permeabilization, mitochondrial swelling, and cytochrome C release in cardiomyocyte mitochondria providing some plausible scientific explanation for cardiac conduction changes and arrhythmias, including QT prolongation and torsades de pointes [30]. Sporadically reported AEs potentially associated with these agents have been fixed drug eruption, leukocytoclastic vasculitis, and hypersensitivity reactions with clarithromycin and hearing loss, angioedema, and hypersensitivity syndrome with azithromycin [3, 14, 19].

Oral Tetracyclines

Dermatologic Applications of Tetracycline Agents

Tetracycline agents are the most frequently utilized antibiotics in dermatology, representing approximately 75% of all oral antibiotics prescribed by dermatologists in the ambulatory practice setting; they are used to treat a broad range of cutaneous infections and even more commonly for noninfectious inflammatory dermatoses such as acne, rosacea, and perioral dermatitis [1, 3, 7, 8, 14]. Currently, doxycycline and minocycline are the most commonly prescribed tetracycline agents in the USA, with the majority of their use for facial inflammatory dermatoses (acne, rosacea, perioral dermatitis); these two agents offer advantages over tetracycline, including greater GI absorption, greater activity against *P. acnes*, lower prevalence of *P. acnes* resistance, reduced frequency of administration, and less binding within the GI tract by co-ingested metal ions found in dairy products, vitamin/mineral supplements, and antacids [1, 3, 4, 8, 9, 14, 29, 31].

Because of their broad range of antibiotic activity against MRSA and a diverse array of bacterial pathogens and spirochetes, doxycycline and minocycline are commonly used to treat a wide variety of cutaneous infections, including uncomplicated MRSA infections, several STDs, and Lyme disease [1, 3, 17, 21]. The biologic properties of tetracyclines which include anti-inflammatory effects unrelated to antibiotic activity appear to contribute therapeutically to their established efficacy for treatment of acne, rosacea, perioral dermatitis, and other noninfectious inflammatory and bullous skin disorders [2, 3, 14, 32, 35]. These biologic/anti-inflammatory properties unrelated to antibiotic effects include inhibition on neutrophil migration, diminished production of neutrophil chemoattractants by *P. acnes*, inhibition of matrix metalloproteinases associated with derma matrix degradation and modulation involving collagen and elastic tissue (e.g., collagenase, gelatinase), scavenger effect on reactive oxygen species, downregulation cytokines involved innate immune response, and inhibition of protein kinase C-associated granuloma formation [2, 3, 14, 32–35]. Sub-antibiotic dosing of doxycycline is

achieved with the use of doxycycline 20 mg twice daily or with once daily administration of a specific modified-release 40 mg capsule formulation (doxycycline-MR) which is approved in the USA for treatment of papulopustular rosacea [34, 35].

The high lipophilicity of minocycline and doxycycline allows for concentrations in the skin, including the sebum-rich pilosebaceous unit [3, 4, 14, 31]. Co-ingestion of minocycline or doxycycline with iron may markedly reduce GI absorption; however, intake with food or with other metal ions has a more modest effect on impairing GI absorption [3, 29]. Doxycycline is primarily excreted via the GI tract; however, renal impairment prolongs the serum half-life of other tetracycline agents [3]. An extended-release (ER) tablet formulation of minocycline is available, specifically indicated only for treatment of acne and not for cutaneous infections, which allows for a slower drug accumulation, lower maximum drug concentration, and decrease in systemic drug exposure over time; minocycline-ER is dosed based on weight, with a target dose of 1 mg/kg/day [36]. Weight-based dosing of minocycline-ER has been shown to reduce the potential for acute vestibular side effects associated with minocycline use, such as vertigo [37].

For the purpose of clarification, the words doxycycline and minocycline refer to dosing and formulations that provide both the antibiotic and biologic properties and can be used to treat cutaneous infections; minocycline-ER and doxycycline-MR refer to formulations that are used to treat inflammatory acne and papulopustular rosacea, respectively, and not for cutaneous infections. Dosing of selected major oral tetracycline agents used in outpatient dermatology is depicted in Table 46.1.

Doxycycline and minocycline are the predominant tetracycline agents currently used by dermatologists in the USA [1, 2, 8, 14]. The predominant use of these agents in dermatology is for acne and rosacea, including primarily papulopustular rosacea, but also for ocular rosacea and granulomatous rosacea [1, 3, 4, 8, 14]. For acne and papulopustular rosacea, their use is continued usually over at least a few months in order to gain adequate control of the eruption, allowing for transition to topical therapy alone to sustain control of the disorder and reduce continued risk of antibiotic resistance [1, 3, 4, 7–9, 14, 23]. Sub-antibiotic dose doxycycline is amenable for more prolonged treatment of papulopustular rosacea, including as monotherapy, due to lack of antibiotic selection pressure and avoidance of emergence of antibiotic-resistant bacterial strains; data for use in acne are limited but may be beneficial in some cases of mild to moderate acne severity, especially with more prolonged use over at least 6 months [1, 5, 32, 34, 38–40].

Importantly, doxycycline and minocycline are frequently used to treat uncomplicated cutaneous MRSA infections and are commonly utilized as first-line therapy, with incision and drainage incorporated when cutaneous abscess is present [3, 17, 18, 41, 42]. Doxycycline is considered the treatment of choice for rickettsial infections such as Rocky Mountain spotted fever and African tick bite fever, and for lymphogranuloma venereum, and is also used for spirochete infections, including primary syphilis (second line), early Lyme disease, yaws, and pinta [3, 21]. Tetracyclines are no longer considered to be a therapeutic option for uncomplicated or disseminated gonorrhea, and use of any tetracycline agent for granuloma inguinale, despite initial improvement or clearance, has been associated with a high risk of therapeutic failure [3, 21]. Minocycline or doxycycline have been used successfully for treatment of cutaneous *M. marinum* infections (e.g., fish tank granuloma), used preferably at maximum dose (200 mg/day) and ideally for durations of at least 12–16 weeks [3, 22]. Management of other atypical mycobacterial infections is dependent on type of organism, severity/extent of disease, and immunologic status of the patient, with many cases involving combination therapy with other agents; further details on management have been reviewed elsewhere [3, 22].

Tetracyclines have been sporadically reported in small studies and case reports to be effective, alone and/or in combination with other agents, in the treatment on several noninfectious dermatologic disorders, including immunobullous disorders (e.g., bullous pemphigoid; combination with niacinamide), sarcoidosis (minocycline, doxycycline), pityriasis lichenoides et varioliformis acuta (tetracycline), pityriasis lichenoides chronica (tetracycline, minocycline), pyoderma gangrenosum (minocycline), oral lichen planus (doxycycline, minocycline), cetuximab-related acneiform eruption (minocycline and topical tazarotene), and hidradenitis suppurativa [2, 3, 32, 43, 44]. Minocycline is considered to be first-line therapy for confluent and reticulate papillomatosis [2, 3].

Adverse Effects Associated with Oral Tetracycline Agents

Tetracycline is no longer commonly used in dermatology due to need for greater frequency of administration, higher prevalence of *P. acnes*-resistant strains than doxycycline and minocycline, less predictable GI absorption with higher chelation by co-administered metal ions in foods (e.g., milk, yogurt, fortified cereals) and vitamin/mineral supplements, and intermittent problems with supply and manufacturing [3–5, 7–9, 14, 29, 31].

The most common AEs associated with doxycycline use are dose-related phototoxicity and GI side effects ("pill esophagitis") [3, 8, 9, 14]. The former may be obviated by

ultraviolet light (i.e., sun) avoidance and broad-spectrum sunscreen use, and the latter mitigated by administration with food and use of an enteric-coated formulation or the small tablet formulation of doxycycline [3, 14, 45].

Minocycline is associated with acute vestibular side effects (vertigo, dizziness, tinnitus) in some patients, which develops early on after starting therapy, and may be obviated by use of minocycline-ER weight-based therapy if treating acne [3, 9, 14, 37]. Cutaneous and mucosal hyperpigmentation may also occur with use of minocycline, especially with more prolonged durations of use [3]. Multiple cases of drug hypersensitivity syndrome (DHS; drug reaction with eosinophilia and systemic symptoms [DRESS]) have been reported in association with minocycline use; patients commonly present within 2–6 weeks after initiation of therapy with flu-like symptoms, diffuse erythema, pharyngitis, facial swelling, and systemic effects such as hepatitis and/or pneumonitis and/or delayed autoimmune thyroiditis [3, 8, 9, 14, 46, 47]. Systemic lupus-like syndrome and autoimmune hepatitis have also been associated with minocycline use, usually occurring after chronic administration over months to years, although some cases may occur earlier [3, 9, 46].

Sporadic reports of benign intracranial hypertension (BIH; pseudotumor cerebri) have been reported with use of tetracycline agents, including tetracycline, minocycline, and doxycycline [3, 7–9, 14]. Affected patients may present with intractable cephalgia, diplopia, photophobia, nausea, and/or vomiting. If BIH is suspected, the suspected agent should be discontinued, and ophthalmologic evaluation is recommended to evaluate for presence of papilledema.

Oral Trimethoprim-Sulfamethoxazole

Dermatologic Applications of Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP-Sulfa) is well absorbed after oral administration with biotransformation of both components partially by hepatic metabolism and the remainder dependent on renal excretion (20–60% of parent compounds excreted unchanged) [3]. The antibacterial activity of TMP-Sulfa includes MRSA, MSSA, several streptococcal stains, and some *Pseudomonas* spp. other than *P. aeruginosa* [3]. In dermatology, TMP-Sulfa is used selectively as an alternative agent for refractory inflammatory acne and for treatment of uncomplicated cutaneous MRSA infections [3, 7–9, 14, 25, 41, 42, 48]. Use of TMP-Sulfa in combination with incision and drainage proved to be superior in achieving clearance of uncomplicated MRSA-induced skin abscesses than incision and drainage alone [49]. Dosing of oral trimethoprim-sulfamethoxazole used in outpatient dermatology is depicted in Table 46.1.

Adverse Effects Associated with Oral Trimethoprim-Sulfamethoxazole

Due to the potential for TMP-Sulfa to induce rare yet severe AEs that are often associated with significant morbidity or mortality, use of this agent warrants careful consideration of the anticipated therapeutic benefits versus possible risks along with dedicated patient education. Less severe cutaneous reactions which often occur within the first few weeks of use in up to 5% of immunocompetent patients include morbilliform eruptions, urticaria, fixed drug eruption, and pruritus [3]. The most concerning AEs associated with use of TMP-Sulfa are cutaneous reactions and hematologic effects [3, 46, 48]. TMP-Sulfa may induce DHS (DRESS), Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN), usually manifesting within 2–6 weeks after starting therapy; approximately 30% of cases of SJS/TEN are induced by sulfonamide antibiotics, most often TMP-Sulfa [46, 48]. The risk of TEN associated with the use of TMP-Sulfa in adults is estimated overall to be 2.6/100,000 exposures, increasing to 8.4/100,000 exposures in HIV-infected individuals [3, 46, 48]. The development of flu-like symptoms, "hives," painful skin, "sore throat," or mouth "sores" reported by the patient warrants discontinuation of therapy and clinical assessment as these findings may suggest the onset of DRESS or SJS/TEN. Onset of a very severe "sore throat" may suggest the presence of agranulocytosis.

A diverse array of hematologic reactions can occur at any point during therapy with TMP-Sulfa, including thrombocytopenia, neutropenia, agranulocytosis, aplastic anemia, and pure red cell aplasia [3, 48]. TMP-Sulfa should be used cautiously in patients with folate deficiency or in those with megaloblastosis [3]. If long-term treatment with TMP-sulfa is anticipated, baseline and periodic monitoring of complete blood cell counts may be prudent; however, there are no specific monitoring recommendations [3].

Oral Fluoroquinolones

Dermatologic Applications of Oral Fluoroquinolones

There are several oral fluoroquinolones available in the marketplace, with ciprofloxacin and levofloxacin the most commonly prescribed [3]. Fluoroquinolones are concentration-dependent antibiotics, are well absorbed from the GI tract with or without food (with the exception of norfloxacin), and are predominantly eliminated via renal excretion (with the exception of moxifloxacin) [3, 50–52]. Importantly, administration within 1 h before or 4 h after ingestion of metal ions found in dairy products (e.g., milk), fortified cereals, antacids, and vitamin/mineral supplements markedly reduce the GI absorption of most fluoroquinolones, including ciprofloxacin [3, 29, 50–52].

The antibacterial spectrum of fluoroquinolones is primarily against Gram-negative organisms including *P. aeruginosa*, with variable activity against Gram-positive bacteria; in vitro and clinical activity against *S. aureus* (including MRSA) and *S. pyogenes* has been reported with some fluoroquinolones; however, emergence of resistance is often rapid, especially with *S. aureus* (including MRSA) [3, 17, 18, 41, 42]. Ciprofloxacin exhibits antibacterial activity against *Bacillus anthracis*; ciprofloxacin and levofloxacin demonstrate activity against *Mycobacterium* spp., including *M. fortuitum*, *M. kansasii*, and *M. tuberculosis* [3].

The ability of fluoroquinolone agents to achieve high concentrations in the skin supports their use for treatment of uncomplicated cutaneous infections caused by Gram-negative bacterial pathogens, such as infected ulcers, folliculitis (including hot tub folliculitis caused by *P. aeruginosa*), cellulitis, toe web space infections, lower extremity ulcers in diabetic patients, and abscesses [3, 50, 51]. Ciprofloxacin has the greatest activity against *P. aeruginosa* compared to other fluoroquinolones, is a treatment of choice for cutaneous anthrax, and may be used as a second-line agent for treatment of chancroid and granuloma inguinale [3, 21]. Dosing of oral fluoroquinolones used in outpatient dermatology is depicted in Table 46.1.

Adverse Effects Associated with Oral Fluoroquinolones

The most common AEs associated with use of fluoroquinolones are GI related, including nausea, vomiting, and diarrhea [3, 51, 52]. A diverse array of CNS side effects have also been reported with these agents, including cephalgia, dizziness, sleep disturbance, seizures, hallucinations, and depression [3, 52]. Avoidance of fluoroquinolones in children is recommended due to concerns about impairment in cartilage formation [3]. Multiple cases of tendonitis and tendon rupture have been reported associated with fluoroquinolone use, may be delayed in onset, and appear to be associated with risk factors such as corticosteroid use, increased age, sports-related physical activity, renal failure, diabetes, rheumatologic disease, and history of tendinopathy [3, 53]. Hypersensitivity reactions, including anaphylaxis/anaphylactoid reactions, and photosensitivity, have been reported with fluoroquinolones, including ciprofloxacin [3, 51, 52].

Summary Points with Selected Oral Antibiotics

- Oral clindamycin is sometimes utilized to treat cutaneous MRSA infections; however, resistance to this agent may be prevalent in some communities [3, 17, 41, 42]. The D zone test should be utilized by laboratories to confirm that inducible resistance to clindamycin is not present as cross-resistance may occur when *S. aureus* strains are erythromycin-resistant [3, 42].
- Rifampin is sometimes used in combination with other oral antibiotics, such as clindamycin or TMP-Sulfa for treatment of MRSA infections. Monotherapy with rifampin is avoided due to rapid emergence of resistance [3, 41, 42].
- Rifampin is potent enzyme inducer resulting in increased metabolism of several other drugs. This can result in reduced therapeutic effects of the drugs undergoing enhanced metabolic clearance. An illustrative example is decreased efficacy of oral contraceptives resulting in breakthrough bleeding and/or unintended pregnancy [3, 29].
- Oral linezolid, an oxazolidinone antibiotic, exhibits complete oral bioavailability and has activity against multidrug-resistant MRSA, vancomycin-resistant staphylococci, penicillin-resistant streptococci, and vancomycin-resistant enterococci; with regard to MRSA therapy, its use should be reserved for cases that have failed other agents including doxycycline, minocycline, TMP-Sulfa, clindamycin/rifampin, and/or vancomycin [3].
- Oral tedizolid is a newer oxazolidinone antibiotic that exhibits properties similar to those of linezolid; however, some in vitro microbiologic evaluations have suggested that tedizolid may be active against some staphylococcal and enterococcal strains that are resistant to linezolid and/or vancomycin [54–56]. Tedizolid, administered 200 mg once a day for 6 days, has been shown to be equivalent in efficacy to linezolid, given 600 mg every 12 h for 10 days [54–56]. Tedizolid is recommended for the treatment of adult patients with cutaneous infections caused by susceptible Gram-positive bacteria, including MSSA, MRSA, several streptococcal bacterial strains including *S. pyogenes*, and *Enterococcus faecalis* [54, 56]. As with linezolid, this agent is reserved for cases that have failed other agents

General Management Considerations with Oral Antibiotic Therapy

- Although product labeling with some oral antibiotics includes general and non-specific statements suggesting periodic laboratory monitoring, there are no specific published laboratory monitoring guidelines with penicillins, cephalosporins, macrolides/azalides, tetracyclines, and fluoroquinolones [3, 8, 9, 14, 52].
- Other than with rifamycin antibiotics, such as rifampin, there is no definitive evidence that oral antibiotics (including penicillins, cephalosporins, macrolides, tetracyclines, fluoroquinolones) reduce the efficacy of combination oral contraceptives [3, 29]. Population-based data suggest that such interactions do not appear to occur; however, it is not possible to totally exclude the potential for such interactions if the potential risk is low. Physicians

are encouraged to suggest to patients to utilize additional precautions to prevent pregnancy.

- Dermatologic conditions where oral antibiotic use is not usually needed are inflamed epidermal cysts and chronic venous leg ulcers; oral antibiotic therapy has not been shown to accelerate healing of noninfected venous ulcers; however, colonization with drug-resistant bacteria is promoted [17].
- More recent published guidelines on perioperative antibiotic prophylaxis and studies evaluating the risk of postsurgical infection after dermatologic surgical procedures have resulted in a definite shift away from routine perioperative administration of prophylactic antibiotics [17]. The reader is encouraged to refer to published guidelines in order to review recommendations in detail as several clinical scenarios may need to be considered [57–60].
- The use of oral antibiotics is discussed in guidelines and "consensus" publications that address the management of both acne and rosacea [1, 7, 23, 61, 62]. These are suggested as further reading to those clinicians who regularly treat patients with these common dermatologic disorders.
- Treatment of moderate and severe acne with oral antibiotic therapy should always be coupled with a rational topical regimen; the goal is to discontinue oral antibiotic therapy once adequate suppression of new acne lesion development is achieved, with topical therapy continued to sustain the therapeutic benefit [1, 3–5, 7–9, 14–16, 23].
- As the pathophysiology of rosacea has not been associated with the presence of causative bacteria, an antibiotic effect is not believed to be needed in order to achieve improvement of papulopustular rosacea [62, 63]. It is suggested that when oral therapy for papulopustular rosacea is felt to be warranted, that sub-antibiotic dose doxycycline be on azelaic acid, ivermectin, in order to avoid antibiotic selection pressure and emergence of antibiotic-resistant bacterial organisms [1, 3, 5, 62, 64].

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