Antibiotic resistance in dermatology: The scope of the problem and strategies to address it

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Antibiotic resistance is a growing health concern that has attracted increasing attention from clinicians and scientists in recent years. Although resistance is an inevitable consequence of bacterial evolution and natural selection, misuse and overuse of antibiotics play a significant role in its acceleration. Antibiotics are the mainstay of therapy for common dermatoses, including acne and rosacea, as well as for skin and soft tissue infections. Therefore, it is critical for dermatologists and physicians across all disciplines to identify, appropriately manage, and prevent cases of antibiotic resistance. This review explores dermatologic conditions in which the development of antibiotic resistance is a risk and discusses mechanisms underlying the development of resistance. We discuss disease-specific strategies for overcoming resistant strains and improving antimicrobial stewardship along with recent advances in the development of novel approaches to counter antibiotic resistance. (J Am Acad Dermatol 2022;86:1337-45.)

Key words: antibiotic resistance; antibiotics; general dermatology; infectious disease; medical dermatology; multidrug-resistant organisms.

INTRODUCTION

Antibiotics have only been in use since the 1940s, but recently, the emergence of antibiotic-resistant pathogens has exceeded the rate at which new drugs are discovered.[1] More than 70% of pathogenic bacteria are resistant to at least 1 antibiotic, and it is estimated that 2 million infections are caused by these pathogens every year, resulting in approximately 23,000 deaths.[2] The World Health Organization considers antibiotic resistance to be one of the most pressing issues facing medicine. Recognizing infections caused by resistant pathogens can guide the appropriate selection of antibiotic therapy. This review explores dermatologic conditions in which the development of antibiotic resistance is a risk and reviews disease-specific strategies and recent therapeutic advances to counter resistance.

INFLAMMATORY DERMATOSES

Inflammatory dermatoses, such as acne vulgaris, rosacea, and hidradenitis suppurativa (HS), are commonly treated with antibiotics. Although these dermatoses are not primarily infectious processes, dermatologists frequently prescribe antibiotics because of their inherent anti-inflammatory properties and to treat bacterial superinfections. Because of the prevalence and chronicity of these conditions, it is not surprising that dermatologists prescribe more antibiotics overall than physicians from other specialties.[3]

Acne vulgaris

Up to 75% of prescriptions written by dermatologists are for doxycycline and minocycline, which are frequently used to treat acne[4] because of their lipophilic properties that allow them to target the pilosebaceous unit.[5] Oral antibiotics are considered first-line treatment for moderate-to-severe inflammatory acne due to their quicker onset of action compared to topical treatment; however, selection pressure inducing antibiotic resistance in bacteria is a known consequence.[6] Treatment

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Funding sources: None.
IRB approval status: Exempt.

Accepted for publication September 10, 2021.

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Published online September 20, 2021.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2021.09.024

duration recommended by American Academy of Dermatology guidelines is 3-4 months because this limits the development of resistance and promotes stewardship.[7]

Other antibiotics with lower reported rates of resistance have been used, including trimethoprim-sulfamethoxazole, cephalexin, and azithromycin.[8-11] However, there are recent reports of increasing global resistance to trimethoprim-sulfamethoxazole among *Cutibacterium acnes* (formerly *Proprionibacterium acnes*), ranging from <5% in Colombia to 100% in China.[12] Key drivers of resistance include prolonged use of broad-spectrum antibiotics and the bacteriostatic nature of oral tetracyclines as well as topical erythromycin and clindamycin.[13-15] Studies have shown that over 50% of *C acnes* strains are resistant, with resistance rates being highest for erythromycin, followed by clindamycin, doxycycline, and tetracycline (Fig 1).[6,12]

CAPSULE SUMMARY

- Clinical consequences of antibiotic resistance include reduced treatment effectiveness and transmission of resistance to other bacteria.
- Combating resistance requires appropriate prescribing practices for dermatologic antibiotics, including shortening treatment duration, using narrow-spectrum antibiotics when feasible, and avoiding monotherapy. Resistance mechanisms, guidance on prescribing practices, and novel treatment modalities are reviewed.

Eady et al[16] showed that use of erythromycin promotes the development of resistant *C acnes* and is associated with therapeutic failure. Another study demonstrated an increase in the risk of upper respiratory infections when treated with topical or oral antibiotics.[6] In antibiotic-treated patients, resistance has also been found to extend to commensal flora such as *Staphylococcus aureus* and *Streptococcus pyogenes*.[17-20]

Consensus guidelines from the Global Alliance recommend against topical and systemic antibiotic monotherapy in the treatment of acne.[21] Instead, benzoyl peroxide is recommended in combination with antibiotics and/or topical retinoids because of its bactericidal properties, favorable safety profile, and no known associated resistance.[22-24]

Sarecycline, a narrow-spectrum tetracycline-class drug, was approved by the United States Food and Drug Administration (FDA) in 2018 for the treatment of moderate-to-severe inflammatory acne in patients as young as age 9 years.[25] Sarecycline is an oral aminomethylcycline with a stable modification at C7 moiety that exhibits antibacterial activity against *C acnes*, including isolates with high-level resistance to erythromycin (Fig 2).[26,27] *C acnes* strains have displayed a low propensity for the development of resistance to sarecycline, with spontaneous mutation frequencies being 10^{-10} at 4 to 8 × minimum inhibitory concentration.[28] Compared to broad-spectrum tetracyclines, sarecycline better preserves the gut microbiome through reduced activity on enteric gram-negative bacilli.[27] In 2 phase 3 studies that evaluated the safety and efficacy of sarecycline for patients with moderate-to-severe acne, significant reduction in inflammatory lesion count was observed as early as week 3.[25] Significant improvement in truncal acne was reported in both trials, and few treatment-related adverse effects were observed.[25] A recent study has shown that unlike other tetracyclines, sarecycline inhibits the bacterial ribosome in part by directly binding to the messenger RNA. Although sarecycline has not been studied for the treatment of infections, it has demonstrated *in vitro* activity against methicillin-resistant *Staphylococcus aureus* (MRSA).

Topical minocycline can also be used for moderate-to-severe acne. Its mutant protection concentration ranged from 0.06 to 1 μg/mL, meaning there is a low likelihood of resistance associated with its use.[29] A related porcine ear study assessed the concentration of topical minocycline in both the epidermis and dermis and found a mean concentration of 3.5 μg/mL, a value more than 1000-fold higher than the mutant protection concentration.[30] However, minocycline is a broad-spectrum antibiotic, and cutaneous dysbiosis has been reported with its use in acne.[31] Another treatment option that has been used is a subantimicrobial dose (40 mg) of doxycycline due to its inherent anti-inflammatory properties.[32] However, recent evidence suggests that subantimicrobial concentrations can select for resistant bacteria through various mechanisms.[33-35]

Nonantimicrobial acne treatment options to help mitigate the development of resistance are listed in Table I.[7,36-38]

Rosacea

The treatment course for rosacea with oral antibiotics is generally limited to 4-8 weeks. Similar to acne, several clinical trials have demonstrated the safety and efficacy of a subantimicrobial dose (40 mg) of doxycycline in its treatment.[39] Oral

Abbreviations used:

HS: hidradenitis suppurativa
MDR: multidrug-resistant
MRSA: methicillin-resistant *Staphylococcus aureus*
SSTI: soft tissue infection
VRE: vancomycin-resistant enterococci

tetracyclines can be combined with topical metronidazole for greater efficacy.[4] Sarecycline demonstrated efficacy in papulopustular rosacea in a pilot study.[40] The local concentration of topical minocycline foam 1.5% was found to be above the mutant protection concentration, making it another treatment option.[41] Various treatment alternatives are listed in Table I.

HS

Topical clindamycin and oral tetracyclines are first-line therapy for HS with a typical treatment duration of 12-16 weeks.[42] Combination regimen with oral clindamycin and rifampicin for a 10-week duration is commonly used; however, this duration was arbitrarily derived, and treatment beyond 10 weeks has been suggested.[43] Daily administration of parenteral ertapenem is a safe and effective alternative for refractory disease.[44]

A 2010-2015 cross-sectional analysis of HS patients demonstrated a significantly higher prevalence of clindamycin-resistant *S aureus* in patients using topical clindamycin compared to patients using no antibiotics.[45] Moreover, a 2019 study by Bettoli et al[46] found that 84.7% of bacterial cultures from HS patients harbored resistance against tetracyclines. This suggests that topical antibiotic monotherapy may accelerate the development of resistance. Therefore, it is recommended that antibiotics be used as adjunctive therapy with other management options, including chlorhexidine or benzoyl peroxide wash, adalimumab, smoking cessation, weight loss, and other nonantimicrobial treatments (Table I).[36-38]

INFECTIONS RELEVANT TO DERMATOLOGISTS

Skin and soft tissue infections

Among hospitalized patients, the prevalence of skin and soft tissue infections (SSTIs) is estimated to be 7%-10%.[47] Hospital-acquired SSTIs are commonly caused by resistant pathogens, with *Staphylococcus*, *Pseudomonas*, and *Enterococcus* species posing the biggest threat.[48,49]

MRSA: *Staphylococcus aureus*. SSTIs begin with bacterial invasion into areas of microtrauma to the skin. Bacterial surface proteins bind to extracellular matrix proteins and allow bacteria to proliferate on the damaged tissue.[50] Individuals with skin barrier dysfunction, as in atopic dermatitis, are susceptible to secondary skin colonization with *S aureus*, including MRSA.[34] The incidence of community-acquired MRSA SSTIs has been increasing.[50-52] One study reported a 17% increase in the proportions of MRSA in *S aureus* isolates over a 3-year period in a community dermatology setting.[53]

Treatment options for MRSA infections include mupirocin, vancomycin, trimethoprim-sulfamethoxazole, linezolid, tetracyclines, tigecycline, and ceftaroline.[48,51,52] However, MRSA strains with resistance to these drugs have been identified, further complicating management.[52-54] Mupirocin, the topical antibiotic most widely used against MRSA SSTIs, was first introduced in 1985; since then, reported resistance rates have ranged from 1% to 81%.[55] Another topical agent used in MRSA SSTIs is fusidic acid, and although it is not approved by the FDA, its associated risk of resistance is typically very low.[56]

Retapamulin, a topical antimicrobial used for impetigo, was studied in a small pilot randomized trial. Children who received retapamulin-decolonizing therapy had a significantly lower rate of MRSA colonization and higher rate of clearance than those who received placebo at 1 week post decolonization.[57] Chronic use of dilute bleach baths has also been shown to decrease the severity of atopic dermatitis in patients with secondary MRSA infections.[58] One study found that twice-weekly bleach baths in conjunction with hygienic measures compared to hygienic measures alone led to a 21% and 17% reduction in MRSA SSTIs, respectively, although the difference was not statistically significant.[59] A study by Huang et al[60] showed that topical chlorhexidine for MRSA skin decolonization resulted in a 37% reduction in MRSA-positive clinical cultures.

Antibiotic resistance in MRSA is often mediated through de novo mutations in genes such as *mecA*.[48,52] MRSA resistance to tetracyclines occurs through alteration of the ribosomal subunit binding target, active drug efflux, or reduced drug uptake, frequently mediated through mutations in the *tet*(k) gene.[61,62]

Pseudomonas aeruginosa. *Pseudomonas aeruginosa* is a common cause of SSTIs, from hot-tub folliculitis to diabetic foot infection.[48] Roughly 13% of nosocomial infections caused by *P aeruginosa* are resistant to at least 1 antibiotic, whereas some strains are resistant to nearly all antibiotics.[48,63] The significant adaptability of *P aeruginosa* to antibiotics

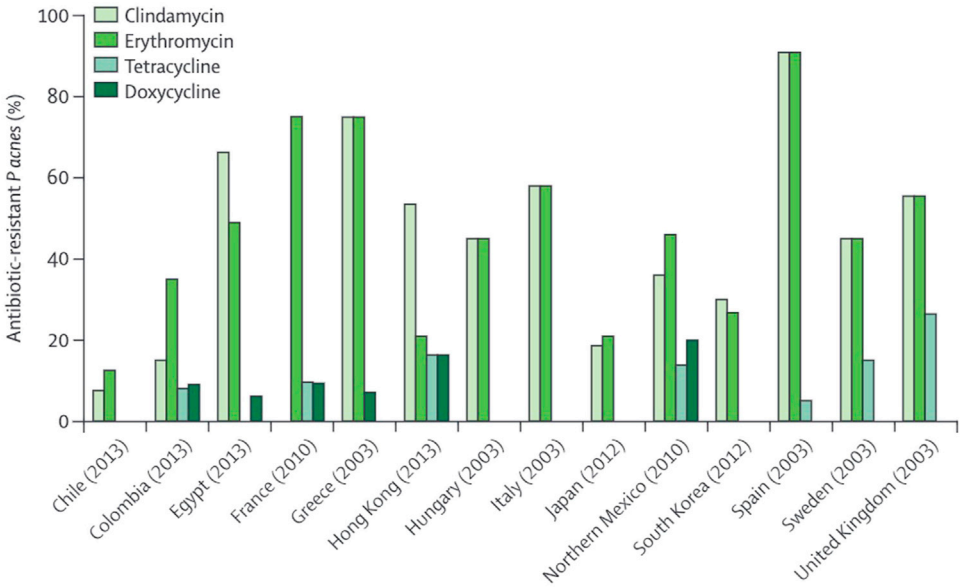

Fig 1. Topical and oral antibiotic-resistant *Cutibacterium acnes* isolated from acne patients in different countries. (Reproduced from Walsh TR, Efthimiou J, Dréno B. Systematic review of antibiotic resistance in acne: an increasing topical and oral threat. *Lancet Infect Dis*. 2016;16(3):e23-e33, with permission from Elsevier.) *P acnes*, *Propionibacterium acnes*.

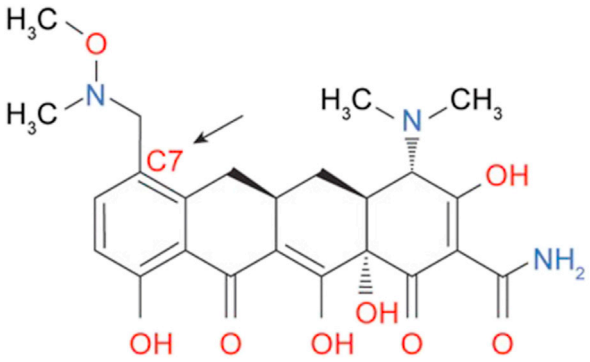

Fig 2. Structure of sarecycline, with the sarecycline modification at C7 (*red arrow*).[27] The positions marked at C7 have been modified to potentially overcome tetracycline resistance mechanisms and to change bacterial ribosome binding. (Modified from http://www.chemspider.com/Chemical-Structure.28540486.html and Zhanel G, Critchley I, Lin LY, Alvandi N. Microbiological profile of sarecycline, a novel targeted spectrum tetracycline for the treatment of acne vulgaris. *Antimicrob Agents Chemother*. 2019;63(1):e01297-18.)

has been attributed partly to its large genome of 5-7 Mbps, which increases the likelihood of genomic rearrangements.[64] Resistance is conferred through beta-lactamase production, efflux-mediated and porin-related resistance, and target site modification.[63]

Enterococcus. Vancomycin resistance is a major concern in enterococcal infections, with an estimated incidence of 30%.[48] Resistance occurs due to bacterial synthesis of abnormal peptidoglycan, leading to a decreased affinity of vancomycin for the target peptide.[65] Vancomycin-resistant enterococci, especially *Enterococcus faecalis* and *Enterococcus faecium*, are difficult to treat because these organisms are resistant to multiple classes of antibiotics. The introduction of linezolid, quinupristin/dalfopristin, daptomycin, and tigecycline provided a temporary solution, but increasing resistance to these agents has been reported.[61,66,67] A recent study found that 100% of vancomycin-resistant enterococci isolates are susceptible to daptomycin, 81% to linezolid, 75% to tigecycline, and 20% to quinupristin/dalfopristin.[68]

Novel antibiotics for treatment-resistant SSTI. To address the high incidence of multidrug-resistant (MDR) bacteria in SSTIs, new generations of oxazolidinone and glycopeptide antibiotics have been developed recently, with promising results (Table II).[69]

Oxazolidinones inhibit protein synthesis and include linezolid and the newer tedizolid. Tedizolid has broad-spectrum activity against vancomycin-resistant enterococci and gram-positive pathogens, including MRSA.[70,71] Recent clinical trials have demonstrated that tedizolid is noninferior to linezolid and is a promising alternative for linezolid-resistant bacteria with fewer adverse effects.[72]

Glycopeptide antibiotics inhibit cell wall synthesis and include vancomycin, teicoplanin, telavancin,

Table I. Therapeutic alternatives for inflammatory dermatoses to combat antibiotic resistance

Inflammatory dermatosis	Treatment modality	Drug
Acne vulgaris	Retinoids	Isotretinoin
		Topical retinoids
	Hormonal therapies	Spironolactone[7]
		Oral contraceptive pills[7]
		Topical clascoterone
Rosacea	Topicals	Azelaic acid
		Sulfur preparations
	Antihelminthics	Ivermectin
		Permethrin
Hidradenitis suppurativa	Retinoids	Isotretinoin
		Acitretin
	Topicals	Chlorhexidine
		Resorcinol
	Steroids	Topical triamcinolone acetonide
		Oral prednisone
		Intralesional steroids
	Antiandrogens	Spironolactone[36]
		Finasteride
		Oral contraceptive pills
		Metformin[37]
	Immunomodulators	Colchicine
		Cyclosporine
		Methotrexate
	Biologics	Adalimumab
		Etanercept[38]
		Infliximab[38]
		Anakinra[38]
		Ustekinumab[38]

ramoplanin, and decaplanin. Two novel second-generation lipoglycopeptide antibiotics, dalbavancin and oritavancin, have been approved to treat SSTIs caused by susceptible gram-positive organisms.[71]

Other recently approved treatment options for SSTIs involving MDR *P aeruginosa* include novel cephalosporins like cefiderocol, aminoglycosides like plazomicin, and combination therapies, including cephalosporins paired with beta-lactamase inhibitors.[71,73–79]

Leprosy

Leprosy, or Hansen's disease, is caused by *Mycobacterium leprae* or *Mycobacterium lepromatosis*. The first-line drugs include dapsone and rifampin for paucibacillary disease and dapsone, rifampin, and clofazimine for multibacillary disease. A World Health Organization surveillance study found that 8% of *M leprae* strains were resistant to rifampin, dapsone, and/or ofloxacin.[80] Resistance to rifampin, due to missense mutations in the *rpoB* gene, is concerning, as it is the most effective drug against *M leprae*.[81] For rifampin-resistant cases, clarithromycin, minocycline, and quinolones may be of benefit. The development of antibiotics for leprosy has been mostly stagnant, apart from bedaquiline (TMC207), which is currently in phase 2 clinical trial for the treatment of multibacillary leprosy.

Novel approaches to countering antibiotic resistance: microbiome, precision, and phage therapy

Ongoing trials are confronting the challenge of treating MDR bacteria in 2 ways: (1) modifying existing antibiotics to improve potency and efficacy and (2) developing narrow-spectrum agents that inhibit different bacterial pathways or structures. However, antimicrobial drug development is a long and complex process, so alternative methods are being explored.

One promising avenue is the modulation of the skin microbiome. Researchers have found that treatment of acne with isotretinoin dramatically alters the composition of the skin microbiome. Patients who achieved remission had microbiome profiles closely resembling that of normophysiologic skin.[82] These findings open the possibility of treating dermatoses through direct manipulation of the skin microbiome via live biotherapeutic products or transplantation of human skin microbiota. A recent phase I/II trial demonstrated the feasibility of the latter by performing human skin microbiota transplantation in patients with atopic dermatitis.[83]

Another alternative is precision treatment, which targets key virulence determinants of specific pathogens while sparing host microbiota. Succinic acid, isolated from *Staphylococcus epidermidis*, effectively inhibits growth of *C acnes*. Similarly, lugdunin, isolated from *Staphylococcus lugdunensis*, removes *S aureus* from the nasopharynx. These small molecule inhibitors exhibit their bactericidal effects through iron-sulfur cluster assembly, RnpA-mediated RNA degradation, and other means.[84]

A third alternative is phage therapy, which uses bacteriophages to infect and lyse bacteria.[85] Recent studies have reported successful use of personalized bacteriophage therapy in patients with infections complicated by MDR *Acinetobacter baumannii*.[86,87] In dermatology, there is increasing interest in phage therapy against *C acnes* in the treatment of refractory acne.[88]

CONCLUSION

Because of frequent antibiotic use, dermatologists will encounter patients who harbor resistant

Table II. Novel antibiotic therapies against specific target pathogens

Antibiotic	Class	Mechanism of action	Target pathogens
Tedizolid	Oxazolidinones	Protein synthesis inhibitor; prevents formation of initiation complex	Broad-spectrum activity against VRE and MRSA
Dalbavancin	Glycopeptides	Cell wall biosynthesis inhibitor; prevents transpeptidation	Susceptible gram-positive organisms, including MRSA, *Streptococcus* sp, and *Enterococcus faecalis* (vancomycin-susceptible)
Oritavancin	Glycopeptides	Cell wall biosynthesis inhibitor; prevents transpeptidation	Susceptible gram-positive organisms, including MRSA, *Streptococcus* species, and *Enterococcus faecalis* (vancomycin-susceptible)
Sarecycline	Tetracyclines	Protein synthesis inhibitor; prevents formation of initiation complex	Narrow-spectrum activity against gram-positive organisms, including *Propionibacterium acnes* and MRSA, and reduced activity against gram-negative bacilli
Ozenoxacin	Quinolones	DNA gyrase and topoisomerase IV inhibitor; prevents DNA replication	Broad-spectrum activity against methicillin-, mupirocin-, and ciprofloxacin-resistant strains of *Staphylococcus aureus*
Bedaquiline	Diarylquinolines	Mycobacterial ATP synthase inhibitor; prevents energy production	Susceptible, MDR, and XDR strains of *Mycobacterium tuberculosis*
Delamanid	Nitroimidazoles	Methoxy-mycolic acid and keto-mycolic acid synthesis inhibitor; prevents formation of mycobacterial cell wall	In vitro activity against *Mycobacterium tuberculosis* and other nontuberculous mycobacteria, including *Mycobacterium kansasii* and *Mycobacterium bovis*

ATP, Adenosine triphosphate; *MDR*, multidrug-resistant; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *VRE*, vancomycin-resistant enterococci; *XDR*, extensively drug-resistant.

bacteria. Both an understanding of the pathogens involved in these conditions and awareness of the available antimicrobial options will guide effective treatment design. Prudent prescribing practices in addition to ongoing research will continue to advance our efforts in battling antibiotic resistance.

Conflicts of interest

None disclosed.

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