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REVIEW

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Antibiotics and Antimicrobial Resistance in Acne: Epidemiological Trends and Clinical Practice Considerations

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Antimicrobial resistance is an increasing public health problem worldwide. The interest of a focus on antimicrobial resistance in acne lies on the facts that acne vulgaris (acne) is the most common skin disease worldwide, that the bacterium *Cutibacterium acnes* (*C. acnes*, formerly *Propionibacterium acnes*) plays a key role in the pathogenesis of acne, while at the same time being part of the skin flora, and that antibiotics are commonly recommended for acne treatment. The overuse of topical and/or systemic antibiotics, the long treatment courses used for acne, and the availability of over-the-counter antibiotic preparations, have led to the worldwide emergence of resistant strains in acne patients. In this review, we discuss the epidemiological trends of antimicrobial resistance in acne, the need to avoid the perturbation of the skin microbiome caused by anti-acne antibiotics, and the clinical practice considerations related to the emergence of resistant strains in acne patients. In light of the increasing risk of antimicrobial resistance, raising concerns over the misuse of antibiotics, prescribing patterns can be a critical target for antibiotic stewardship efforts. Also, the selection of non-antibiotic therapies for acne, whenever possible, may offer significant advantages.

INTRODUCTION

Antimicrobial resistance is an increasing public health problem worldwide. The Centers for Disease Control (CDC) estimate that antimicrobial resistance infections cause one death every 15 minutes in the United States and antimicrobial resistance overall is a top three public health concern of the 21st century [1]. The interest of the focus on antimicrobial resistance in acne lies on the facts that acne vulgaris (acne) is the most common skin disease worldwide, that the bacterium *Cutibacterium acnes* (*C. acnes*) plays a key role in the pathogenesis of acne, while at the same time being part of a complex skin microbiome, and that antibiotics are commonly recommended for acne treatment.

Acne affects 80% of teenagers (of both sexes), while up to 50% of individuals (mostly female) may have acne in their adult life [2]. It may result in scarring and impact on the psychology and quality of life of patients [3]. Acne is a chronic inflammatory disease of the pilosebaceous units of the skin, located on sebaceous gland-rich body areas, such as the face and trunk (Figure 1) [4].

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Abbreviations: MIC, minimal inhibitory concentration; BPO, benzoyl peroxide; COC, combined oral contraceptives.

Keywords: antimicrobial resistance, antibiotic, acne, epidemiology, microbiome, *Cutibacterium acnes*, *Propionibacterium acnes*, infections

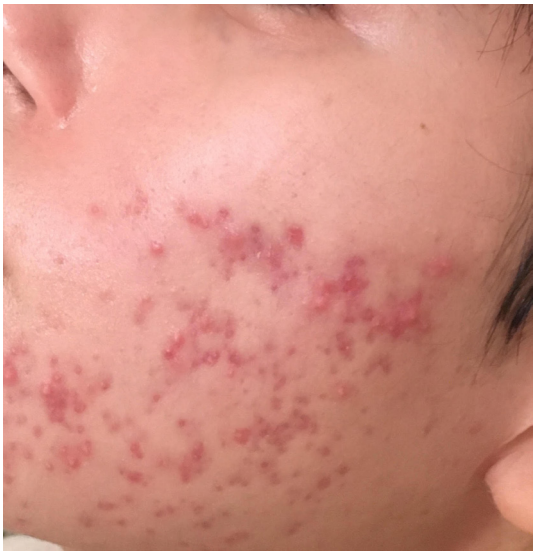

Figure 1. A patient with acne vulgaris on the face, presenting with inflammatory papules and pustules and atrophic scarring. The patient had been previously using topical antibiotics without improvement.

The major factors implicated in acne pathophysiology include disturbed sebaceous gland activity associated with hyperseborrhea and alterations in sebum fatty acid composition, follicular hyperkeratinization, changes in *C. acnes* (previously termed *Propionibacterium acnes* [5,6]) colonization, and dysfunction of the innate and adaptive immunity [4].

Acne is a non-infectious disease and *C. acnes* that is implicated in its pathogenesis, is a commensal bacterium, ie, a member of the normal skin microbiota and an inhabitant of all humans' skin [7]. Dysbiosis, defined as changes in the skin microbiota, has been implicated in various skin diseases, including acne, eczema, and chronic wounds [8]. In acne, similar relative abundance of *C. acnes* on the skin of patients and controls have been shown, however distinct "acnegenic" *C. acnes* phylotypes and a loss of *C. acnes* phylotype diversity are highly associated with acne [9-12]. In the complex pathways of acne pathophysiology, *C. acnes* acts on all the implicated key cell types, namely keratinocytes, immune cells, and sebocytes. "Acnegenic" *C. acnes* strains may modulate the differentiation of keratinocytes and increase local inflammation, supporting its key role in the development of inflammatory acne lesions as well as the formation of the microcomedo in the early stages of acne, while it has also been implicated in lipogenesis and sebum production from sebocytes (Figure 2) [7,13-15]. In addition, the effect of *C. acnes* on dermal fibroblasts was recently demonstrated in acne. Reactive adipogenesis – a process in which skin fibroblasts can undergo localized proliferation and differentiation into a preadipocyte lineage in response to bacteria stimuli – was shown in human acne lesions, while *C. acnes* induced reactive adipogenesis via TLR2 in mice. Adipocytes in turn mount an innate immune defense response that may contribute to acne pathophysiology [16].

Antibiotics have been traditionally used as treatments for acne, mainly due to their anti-inflammatory properties, resulting in clinical improvement of the disease. However, the overuse of topical and/or systemic antibiotics, the long treatment courses used for acne, and the availability of over-the-counter (OTC) antibiotic preparations in some countries, has led to the worldwide emergence of resistant strains [17,18]. In this review, we will discuss the epidemiological trends of antimicrobial resistance in acne, the need to avoid the perturbation of the skin microbiome caused by anti-acne antibiotics, and the clinical practice considerations related to the emergence of resistant strains in acne patients.

C. ACNES RESISTANCE IN ACNE: WHY AND HOW

The emergence of *C. acnes* resistance coincided with the introduction of topical antibiotic formulations in the 1970s [17]. The clinically relevant resistance of *P. acnes* to antibiotics, was first documented in 1983, in the US, in patients who were not responding well to oral antibiotic treatment [19]. In the past and over the years, various antibiotics have been extensively used in acne, including topical clindamycin and topical erythromycin, oral trimethoprim-sulfamethoxazole, oral macrolides, oral tetracyclines, amoxicillin, and cephalexin [20,21].

Since acne is treated at the outpatient setting, prescribing patterns are a critical target for antibiotic stewardship efforts. There are scarce data on the prescription practices concerning the duration of antibiotic treatment for acne. Although current acne guidelines recommend restricting the duration of oral antibiotics to up to 3 months [22], the reported length of antibiotic treatment in clinical practice is significantly longer [23]. In a study from the US MarketScan Commercial Claims and Encounters database (2008-2010) of 29,908 patients that were prescribed oral antibiotics for acne, the majority of courses were more than 3 months; 64% were treated for more than 3 months, including 17% treated for more than 6 months [23]. Another US retrospective study of 137 patients with acne (2005-2014), reported an average duration of 331 days for oral antibiotic use before isotretinoin. Only 15.3% of patients were prescribed antibiotics for 3 months or less, while the remaining majority received extended courses of oral antibiotics for 6 months or more. These results highlight the overuse and late recognition of antibiotic failure for these patients with severe inflammatory or nodulocystic acne [24].

Regarding prescribing patterns among physicians, a

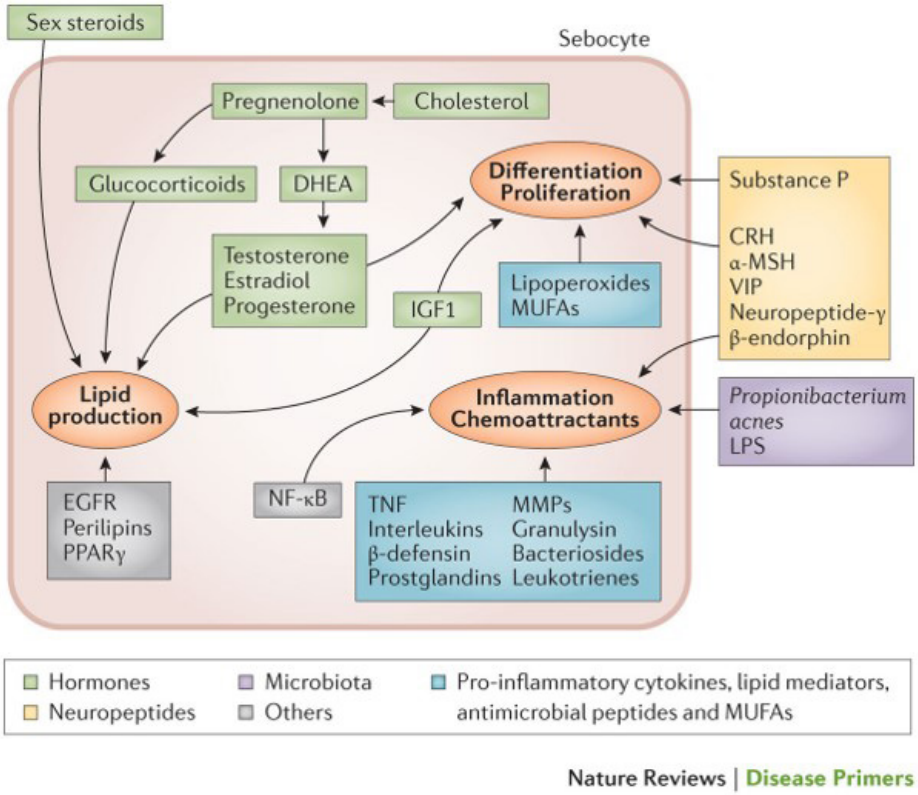

Figure 2. **Pathophysiological processes involved in acne vulgaris**. The pathogenesis of acne involves several processes including sebum production, and sebocytes differentiation, proliferation, and inflammation. These processes are regulated by circulating sex hormone levels as well as locally synthesized hormones, neuropeptides, the microbiota and pro-inflammatory cytokines, lipid mediators, antimicrobial peptides, and monounsaturated fatty acids (MUFAs). α-MSH, alpha-melanocyte-stimulating hormone; CRH, corticotropin-releasing hormone; DHEA, dehydroepiandrosterone; EGFR, epidermal growth factor receptors; IGF-1, insulin-like growth factor 1; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; PPARγ, peroxisome proliferator-activated receptor-γ; TNF, tumor necrosis factor; VIP, vascular intestinal polypeptide. (Reproduced with permission from: Moradi Tuchayi S et al. [4])

US study in data from the National Ambulatory Medical Care Survey (NAMCS) (1996-2005) reported that erythromycin was prescribed more frequently by pediatricians (in 7.2% of visits for acne) compared to dermatologists (2.8%) [25]. Another US study investigated prescribing patterns of systemic therapies among dermatologists and non-dermatologists of 572,630 patients treated for acne using the OptumInsight Clinformatics DataMart (2004-2013) [26]. Over the 10-year study period, there was no significant change in the mean duration of therapy among dermatologists and non-dermatologists, while one-third of both physician groups prescribed courses of oral antibiotics that exceeded 6 months in duration [26]. An internet questionnaire survey of 201 dermatologists and 147 family physicians in Turkey (2018) showed that there were concerns over antibiotic resistance from 88.5% of dermatologists and 79.5% of family physicians, highlighting a group of physicians that does not report concerns on this issue. Also, 23.9% of dermatologists and 31.9% of family physicians "had no idea" of the highest rate of resistance among antibiotics [27]. These findings underscore the need to raise awareness of the risk of antimicrobial resistance in health providers.

The molecular basis for resistance was first shown in the United Kingdom to be caused by point mutations in genes coding the 23S subunit in ribosomal RNA (rRNA) for erythromycin and 16S subunit in rRNA for tetracycline [28]. The same mutations were replicated in strains from the US, Australia, France, Japan, and Germany [29]. Cross resistance between erythromycin and clindamycin has been associated to point mutations in genes encoding the 23S subunit of rRNA, which give resistance to Macrolide-lincosamide (clindamycin)-streptogramin B (MLS) antibiotics [30]. Tetracycline resistance in *C. acnes*, in most cases, is associated with a mutation in the 16S rRNA of the small ribosomal subunit at *E. coli* equivalent base 1058 (G to C transition) [31]. MLS antibiotic resistance in *C. acnes* has been reported to be also mediated by an acquired Corynebacterium transposon Tn5432 carrying the erm(X) resistance gene [32]. The transposon-based

Table 1. Antimicrobial resistance of *C. acnes* in acne patients in Europe and UK, in the published literature (1990-2022). Studies including at least 100 patients are shown.

Study, period	Country	Acne patients, n	Any antibiotic resistance, n (%)	Clin, n %	Ery, n %	Azi, n %	Doxy, n %	Mino, n %
Ross [46], 1999-2001	Total	622						
	UK	106	NR	50%	50%	NS	NR	0
	Greece	150	NR	75%	75%	NS	NR	0
	Hungary	68	51%	45%	45%	NS	NR	0
	Italy	128	NR	58%	58%	NS	NR	0
	Spain	92	94%	91%	91%	NS	NR	0
	Sweden	120	NR	45%	45%	NS	NR	0
Coates [17], 1991-2000	UK	4274	1991:34.5% 1997: 64% 2000:55.5%	1991:20% 1997: 48% 2000: 43%	1991: 29% 1997: 57.6% 2000: 54%	NR	NR	NR
Dumont-Wallon [47], 2010	France	273	NR	NS	75.1%	NS	100% * (26 patients)	NS
Bettoli [48], 2000-2004	Italy	1206 patients (1146 Priopionibacteria isolates)	56.5%	40.9%	49.8%	NS	NS	0.6%
Oprica [49], 1999-2000	Sweden	130 patients (280 *C. acnes* isolates)	24.6%	NR	NR	NS	NS	NS

NR: not reported, NS: not studied, Clin: clindamycin resistance, Ery: erythromycin resistance, Azi: azithromycin resistance, Doxy: doxycycline resistance, Mino: minocycline resistance.
* Only strains resistant to tetracycline were tested with doxycycline.

erm(X) resistance determinant accounted for 8.9% of MLS-resistant isolates in six European countries in the study of Ross et al. [32].

The minimal inhibitory concentration (MIC) is the lowest concentration *in vitro* of an antibiotic that will prevent growth of a microorganism [18]. Recommendations for the interpretation of antibiotic susceptibility testing for anaerobes, have been provided by the Clinical and Laboratory Standard Institute (CLSI) [33]. Also, the European EUCAST guidelines for antibiotic susceptibility testing have provided relevant critical MIC breakpoints [34]. A MIC above the breakpoint value is defined as resistance.

RECOMMENDATIONS ON THE USE OF ORAL ANTIBIOTICS FOR ACNE IN CURRENT GUIDELINES

The concern over antimicrobial resistance has shaped the current recommendations in international guidelines for the treatment of acne. Current European guidelines (2016) limit their recommendation for systemic antibiotics for acne, to doxycycline and lymecycline, to a treatment period of 3 months [22]. Also, considering the risk of antimicrobial resistance, topical antibiotics should preferably be avoided as monotherapy [22]. In the current US guidelines (2016), doxycycline and minocycline are more effective than oxytetracycline. In addition, although oral erythromycin and azithromycin can be effective in treating acne, their use should be limited to those who cannot use the tetracyclines (ie, pregnant women or children <8 years of age) [20]. Also, the use of systemic antibiotics, other than the tetracyclines and macrolides, is discouraged because there are limited data for their use in acne [20]. In current guidelines, the recommendations for oral antibiotics for acne, are based considering their effectiveness for acne, the risk of antimicrobial resistance, as well as their safety profile. In the US guidelines 2016, Canadian guidelines 2015, the UK NICE guidelines 2021, and the European guidelines 2016, doxycycline and lymecycline should be selected in preference to minocycline. The reasoning was the similar effectiveness across tetracyclines but the more frequent severe adverse events with minocycline [20,22,35,36].

More recently, sarecycline, a narrow-spectrum tetracycline derivative, was approved by the US FDA for moderate-to-severe acne vulgaris [37], after the guidelines were issued. The topical use of nadifloxacin for acne treatment has been questioned, considering the risk of antimicrobial resistance with the use of a broad-spectrum quinolone [38]. Along the same lines, a call was made by Sardana et al. to restrict the use of oral azithromycin for acne. The logic for this statement was based on the absence of regulatory approval of azithromycin for acne in US and Europe, the risk of resistance to azithromycin [39-42], the indications of azithromycin for other important diseases (including respiratory tract infections, tick-borne infections, donovanosis, cat-scratch disease, toxoplasmosis, urethritis, and cervicitis) and evidence showing that azithromycin is not superior to doxycycline or minocycline for acne [43-45].

ANTIMICROBIAL RESISTANCE IN ACNE: EPIDEMIOLOGICAL TRENDS

Worldwide efforts have struggled to describe resistant patterns in *C. acnes* and other bacteria isolated from acne patients. Epidemiological data on antimicrobial resistance in acne mainly refer to the emergence of *C. acnes* resistant strains due to antibiotic treatment for acne. The frequency of antimicrobial resistance in patients with acne in Europe and the UK, reported in published studies from 1990 to 2022, is summarized in Table 1 [17,46-49]. Of note, there are no national prevalence data for any country. The UK study of Coates et al. is the largest study on antibiotic-resistant propionibacteria, including 4,274 acne patients spanning 10 years (1991-2000). The frequency of resistant propionibacteria to any antibiotic rose from 34.5% in 1991 to 55.5% in 2000. Resistance to erythromycin was most prevalent and resistance to clindamycin was slightly lower, while resistance to tetracycline was less common [17]. The multicenter study by Ross et al. reported the frequency of resistance of *C. acnes* in Europe and the UK from 1999 to 2001 [46]. This study is important as it reports resistance patterns across various countries using a common, standard methodology and thus including a fairly homogeneous sample. It is also the largest study from Europe and the UK including 622 patients. A limitation is that it reported resistance for clindamycin and erythromycin and not for doxycycline (Table 1). The prevalence of resistant propionibacteria was lowest in Hungary (50.8%) and highest in Spain (93.6%). Resistance to tetracycline was lower compared to clindamycin or erythromycin in all the countries, and no isolates resistant to tetracycline were detected in Hungary or Italy [46]. The multicenter French study by Dumont et al. reported resistance of Propionibacteria to doxycycline in all the 26 patients that were also resistant to tetracycline [47] (Table 1). The frequency and patterns of antimicrobial resistance of *C. acnes* in acne patients in other countries, including Jordan, Japan, Israel, Egypt, Korea, Colombia, Hong Kong, Singapore, and China, are shown in Table 2 [41,42,50-59]. Overall, there are higher rates of clindamycin and erythromycin resistance and lower rates of doxycycline resistance of *C. acnes*. Azithromycin resistance has been scarcely studied; two studies in China reported similarly high rates of azithromycin- and erythromycin-resistance in their sampled

Table 2. Antimicrobial resistance of *C. acnes* in acne patients in other countries, in the published literature (1990-2022). Studies including at least 100 patients are shown.

Study period	Country	Acne patients, n	Any antibiotic resistance, n (%)	Clin, n (%)	Ery, n (%)	Azi, n (%)	Doxy, n (%)	Mino, n (%)
Moon [54], 2011	Korea	100 (30 *C. acnes* isolates)	11 (36.7)	30%	26.7%	NS	2 (6.7)	3 (10)
Mendoza [55],2005, 2006	Colombia	100	40%	15%	35%	NS	9%	1%
Tan [57], 2007	Singapore	262 (174 *C. acnes* isolates)	14.9%	7.5%	10.3%	NS	3.4%	1.7%
Yang [58], 2014	Singapore	149 (45 *C. acnes* isolates)	15 (33%)	15 (33%)	14 (31%)	NS	10 (22%)	NS
Luk [56], 2009	Hong Kong	111 (86 *C. acnes*)	47 (54.7)	53.5%	18 (20.9)	NS	14 (16.3)	14 (16.3)
Abdel-Fattah [53], 2011-2012	Egypt	98 patients	NR	66%	49%	5%	6%	NS
Akhawaja [50], 2020	Jordan	100	55%	59%	73%	NS	37%	3%
Aoki [51], 2013-2018	Japan	212 patients (127 *C. acnes* isolates)	NR	2013: 37.5% 2018: 56.5%	2013: 46.9% 2018: 60.9%	NS	2013: 0 2018: 4.3%	2013: 0 2018: 0
Zhu [41], 2015-2017	China, Kunming	375 patients (227 *C. acnes* isolates)	NR	55.5%	57.7%	58.6%	1.3%	NS
Fan [42], 2014	China, multicenter	364 patients (312 C. *acnes* isolates)	NR	NR	47.8%	47.8%	0.3%	0
Zhang [59], 2016-2017	China, Shanghai	100 (63 *C. acnes* isolates)	NR	18 (28.6%)	31 (49.2%)	NS	NS	0

NR: not reported, NS: not studied, Clin: clindamycin resistance, Ery: erythromycin resistance, Azi: azithromycin resistance, Doxy: doxycycline resistance, Mino: minocycline resistance.

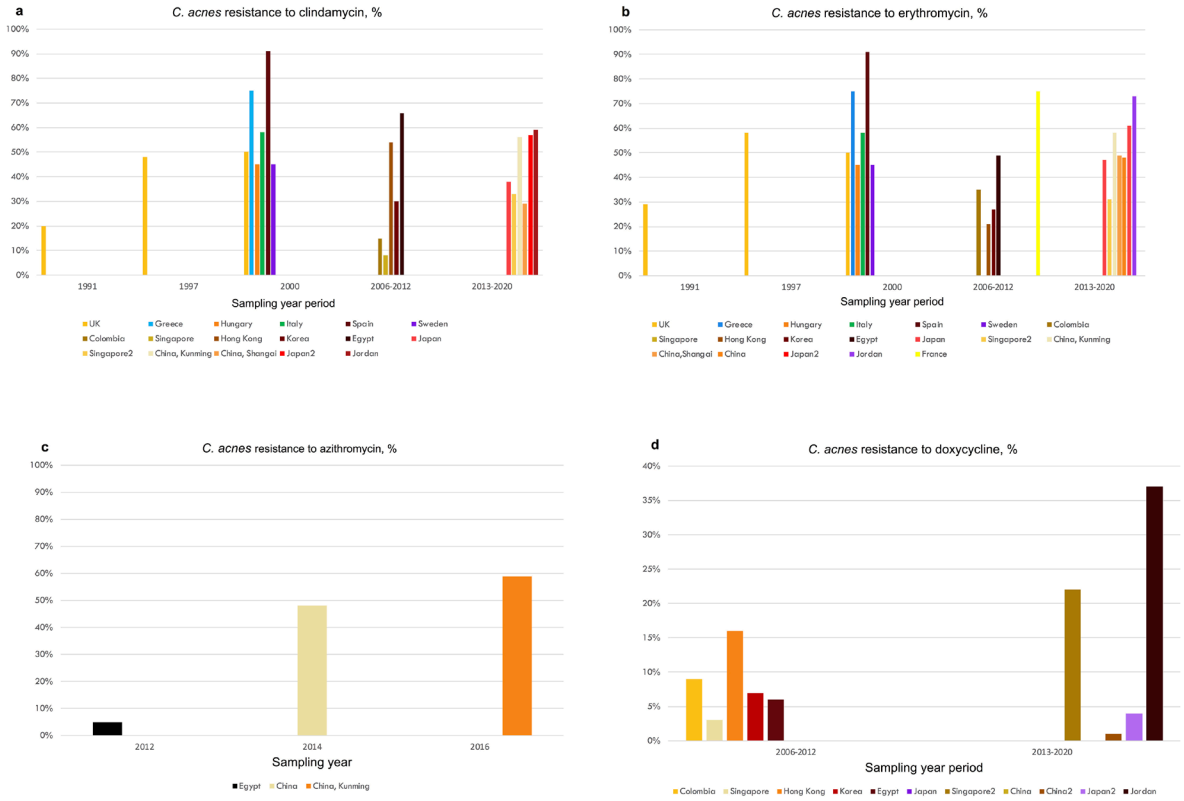

Figure 3. **The frequency of antimicrobial resistance of *C. acnes* in acne patients in various countries, for A. clindamycin, B. erythromycin, C. azithromycin, D. doxycycline**. (Data is derived from Tables 1 and 2. For a study period lasting more than one year, the median year value is shown. Minocycline is not shown as its use is discouraged compared to doxycycline for acne in current guidelines).

patients [41,42]. On the other hand, a study in Egypt found low rates of azithromycin resistance despite high rates of resistance to erythromycin [53]. In addition, a study in 49 acne patients in northern Mexico, reported that 82% showed resistance to azithromycin [40], while a study in 52 *C. acnes* strains isolated from 80 patients in India reported 100% resistance to azithromycin [39]. The frequency of antimicrobial resistance of *C. acnes* to clindamycin, erythromycin, azithromycin, and doxycycline in various countries, is shown in Figure 3 (a-d). Figure 4 is a schematic diagram of the reported frequency of *C. acnes* resistance (to any antibiotic) over time. Reports from different studies are difficult to compare directly as results may vary depending on the chronological setting, prior acne treatments, sampling techniques, the body location sampled, and the methodology used to identify *C. acnes* strains [60] and to define resistance. However, resistance rates vary across countries even when the same methodology was used, reflecting – at least in some part – true differences due to varying antibiotic prescribing practices [46].

There are also reports of the antimicrobial resistance in other bacteria isolated from acne patients. In a study in Jordan, 35% of isolated *S. aureus* and 25% of *S. epidermidis* strains were resistant to an antibiotic tested [50]. In a study in Korean acne, patients reported high rates of resistance of *S. epidermidis* to tetracycline (31%), doxycycline (27%), clindamycin (33%), and erythromycin (58%) [54].

Another French study in 1,472 hospitalized (mostly orthopedics) patients reported that all *Cutibacterium* strains were susceptible to amoxicillin, ceftriaxone, vancomycin, and moxifloxacin. Fifteen percent of *C. acnes* strains were resistant to erythromycin and 4.1% were resistant to clindamycin, while 2.2% were resistant to tetracycline [61].

THE FINE EQUILIBRIUM OF THE SKIN MICROBIOME: DO NOT DISTURB!

The microbiota consists of an aggregate of microorganisms, including bacteria, archaea, protists, fungi, and

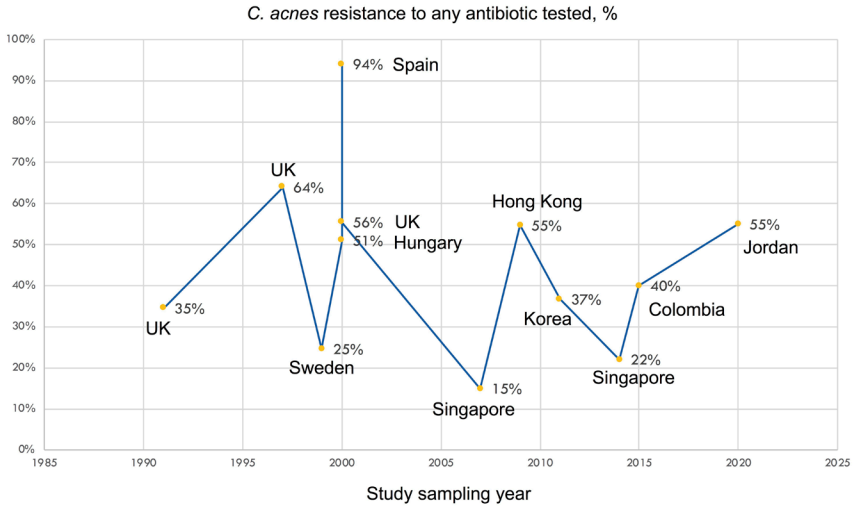

Figure 4. **The frequency of antimicrobial resistance of *C. acnes* to any antibiotic in various countries, and the corresponding study period** (data from studies included in Tables 1 and 2).

viruses. The microbiome refers to the composition of all microbial genes in a community [8]. In the healthy skin microbiota, bacteria are the most abundant kingdom. The relative abundance of bacterial taxa depends on the body location, ie, sebaceous sites are dominated by lipophilic *Propionibacterium* species, while *Staphylococcus* and *Corynebacterium* species are abundant in moist areas, such as the bends of the elbows and the feet [8]. A diversity of the healthy human skin microbiota has been reported, with approximately equal inter-personal and intra-personal variation regarding the bacterial community membership and structure [62].

C. acnes is a commensal (resident) bacterium that forms a fine equilibrium with other microbial species of the skin microbiome. The possible interactions of *C. acnes* with other opportunistic pathogens, including *Staphylococcus* sp, are a field of continuing research. *C. acnes* has been identified in multi-species biofilm communities on the skin and within sebaceous glands [8]. A biofilm is defined by three essential components: the microbial cells, a surface where these cells adhere, and a self-produced extracellular polymeric matrix in which cells are embedded and form larger communities [18]. This biofilm protects bacteria from antibiotic therapy by limiting the penetration of effective antimicrobial concentrations [18]. Bacteria in biofilms may exist in a sessile state (called persister cells), they are able to communicate through "quorum sensing" and they are relatively metabolically inert and protected. In a planktonic state, they are free of the biofilm and capable to induce the expression of new proteins [63]. A recent study showed *in vitro* that the presence of *C. acnes* sterile supernatants reduced the biomass of *S. aureus* cultures and resulted in a defective biofilm maturation with greater susceptibility to antibiotic treatments. In contrast, *C. acnes* supernatant in planktonic *S. aureus* cultures increased antibiotic tolerance [64]. However, different results were shown by Gannesen et al. [65] and Tyner and Patel [66], reporting that *C. acnes* presence within a biofilm increased *S. aureus* biofilm biomass in anaerobic conditions, underscoring the difficulties of microbiological methodology and complex interactions. Furthermore, inter-species competition may exist; an endogenous extracellular nuclease, BmdE, secreted by the skin commensal *Cutibacterium* (*Propionibacterium*) *granulosum* was able to degrade *C. acnes* biofilm both *in vivo* and *in vitro* [67]. In addition, interactions between members of the microbiota prevent colonization by pathogenic bacteria in a process called "colonization resistance" [8]. These findings underscore the importance of avoiding the perturbation of the equilibrium of the skin microbiome caused by antibiotics.

ANTIMICROBIAL RESISTANCE IN ACNE: CLINICAL PRACTICE CONSIDERATIONS

Earlier reports considered the possible clinical therapeutic failure of oral or topical antibiotics in patients with acne and *C. acnes* strains resistant to the antibiotic used [68-70]. However, in these studies, patients were largely treated with antibiotic monotherapy and this concern has been currently mitigated given that monotherapy with antibiotics is contra-indicated for acne; instead the combination with topical benzoyl peroxide formulations is recommended [20,22]. Benzoyl peroxide shows an-

ti-propionibacterial effects irrespectively of antibiotic susceptibility, may enhance the penetration and the concentration of topical antibiotics in the acne lesions, may act in synergy with topical antibiotics against some resistant strains [71], and may reverse the selectivity of topical clindamycin resistant *C. acnes* strains [72]. Also, oral tetracyclines exhibit anti-inflammatory properties that account, at least in part, for their effectiveness in acne, beyond their bacteriostatic effects [21]. It is recommended to be proactive and take measure to minimize the risk of antimicrobial resistance: limit the use of antibiotics for acne to less than 12 weeks, not use antibiotic monotherapy [22], and favor non-antibiotic pharmacological treatments further discussed below. Moreover, antibiotic failure in acne patients may be due to other causes, apart from antimicrobial resistance, such as low adherence to treatment regimen, high sebum excretion, inadequate duration of treatment or the development of gram-negative folliculitis [73].

Apart from the interactions with other members of the resident skin microbiome and the key roles in the pathophysiology of acne, *C. acnes* subspecies have been implicated in the pathophysiology of other diseases including sarcoidosis, prostate cancer, lumbar disc herniations, postoperative infection following shoulder arthroplasty and other open shoulder procedures, shoulder arthritis, and non-prosthetic spondylodiscitis [74-81]. Recently, changes in the skin microbiome, including *C. acnes,* correlated with cutaneous squamous cell carcinoma compared to actinic keratosis or healthy skin, although a causal relation in skin cancer progression has not been shown [82]. In this context, antimicrobial non-antibiotic pharmacological agents have demonstrated benefit to prevent shoulder infections. A randomized study in 60 patients, a benzoyl peroxide 5%/miconazole nitrate 2% cream was used on the skin of the shoulder for 7 days before surgery, with the aim to reduce the deep *C. acnes* tissue load before elective open shoulder surgery. This intervention significantly reduced the number of intraoperative deep subcutaneous and capsular shoulder samples that were positive for *C. acnes* compared with the control group [83]. Similarly, topical benzyl peroxide significantly decreased the *C. acnes* shoulder burden in two clinical trials [84,85] and in a systematic review [76].

In addition to the risk of developing *C. acnes* resistant strains, the overuse and misuse of antibiotics for acne may lead to emergence of other resistant bacterial pathogens, and thus compromise the effectiveness of antibiotics for other treatment indications [18]. A prospective randomized study investigated microbial alterations on the skin after administration of systemic doxycycline (20 mg or 100 mg), in healthy volunteers, with follow-up for up to 1 year. There was emergence of doxycycline-resistant staphylococci on the skin of all doxycycline-100mg subjects and in two of the four doxycycline-20mg subjects [86]. Another study in four patients with acne reported significant changes in the composition and diversity of skin microbiota after treatment with oral minocycline 100 mg twice daily for 4 weeks. There was a 1.4-fold reduction in the level of *C. acnes*, with recovery after treatment discontinuation. On the other hand, there was a transient 5.6-fold increase in the relative abundance of *Pseudomonas* species and a persistent 1.7-fold increase in the relative abundance of *Streptococcus* species. There was a 4.7-fold decrease in the relative abundance of *Lactobacillus* species, that persisted even 8 weeks after the antibiotic treatment discontinuation [87]. Furthermore, Coagulase-Negative *Staphylococci*, *Staphylococcus aureus* and Group A *Streptococci* can colonize the skin of many individuals as transient skin commensals, but they may also act as potential pathogens. The conversion of the cutaneous staphylococcal flora of acne patients from predominantly antibiotic sensitive to predominantly resistant during long term antibiotic therapy has been documented [88]. Also, the topical application of erythromycin was associated with an overgrowth of erythromycin-resistant coagulase-negative staphylococci. On the other hand, in a prospective study in 263 acne patients under acne treatment, there was significantly lower carriage rate of *S. aureus* in the anterior nares in patients treated with antibiotics compared to those that received non-antibiotic treatments. Resistant *S. aureus* isolates did not differ between the two groups [89].

Another concern is whether antibiotic resistant staphylococci colonizing the skin of antibiotic treated acne patients may transfer to and colonize untreated close contacts. A study in 41 family contacts of acne patients who had received sequential anti-acne antibiotics over a minimum period of 2 years, showed increased skin carriage of resistant coagulase-negative staphylococci compared to controls. High rates of resistance were shown independently for tetracycline, erythromycin, clindamycin, fusidic acid, chloramphenicol, trimethoprim, and kanamycin, even though the family contacts had not themselves received any antibiotic in the preceding 2 years [90]. Also, the multicenter study of Ross et al. reported that apart from patients and close contacts, 67% of participating dermatologists were also colonized on the face with resistant propionibacteria, including all those who specialized in treating acne. In contrast, none of the 27 physicians working in other outpatient departments carried resistant propionibacterial strains [46].

An important implication of the use of antibiotics for acne is the possible effect on the risk of infections beyond the skin. A UK retrospective cohort study by Margolis et al. assessed the effect of oral or topical antibiotic acne treatment (tetracyclines, erythromycin, or clindamycin) on upper respiratory or urinary tract infections. Among

118,496 individuals with acne, the risk of developing an upper respiratory tract infection developing within the first year, was two times greater in acne patients receiving antibiotic treatment compared to those not receiving antibiotic treatment [91]. Another UK study in 358 students with acne reported a significantly increased risk of pharyngitis in students taking an oral antibiotic compared to those that did not, however, there were only 36 patients that were treated with an oral antibiotic during the study period [92]. However, a systematic review on the association between treatment with antibiotics for acne and infection beyond the skin, reported the lack of high-quality evidence, with only two relevant studies [93]. In the study of Levy et al. there was a 3-fold increase in asymptomatic colonization of the oropharynx by *Streptococcus pyogenes* in acne patients treated with anti-acne antibiotics. Eighty-five percent of these strains were resistant to tetracyclines [94].

Last but not least, there are some preliminary reports indicating that antibiotics used for acne may have effects on the gut microbiome [95,96]. In *in vitro* models of the human colon, minocycline and doxycycline exposure resulted in a more significant and persistent impact on the gut microbiota composition and diversity, compared to sarecycline [96]. In turn, the gut microbiome has had increasingly recognized implications in human non-infectious diseases, including skin cancer and allergic and inflammatory skin diseases [97-99]. Nevertheless, the direct association of antibiotics used for acne with diseases via the alterations of the gut microbiome has not been studied.

THE SPOTLIGHT ON NON-ANTIBIOTIC PHARMACOLOGICAL TREATMENTS FOR ACNE PATIENTS

In light of the increasing risk of antimicrobial resistance, raising concerns over the use of antibiotics for acne, the selection of non-antibiotic therapies may offer significant advantages.

Regarding topical non-antibiotic treatments, approved topicals recommended for acne, include benzoyl peroxide (BPO), retinoids, azelaic acid, and clascoterone [22,100]. BPO is a topical treatment that clinically improves acne, does not induce bacterial resistance and shows a well-established antibacterial non-antibiotic action. In addition, BPO has been shown to reduce antibiotic-resistant *C. acnes* strains. BPO 5% gel treatment in acne patients, significantly reduced the surface and follicular *C. acnes* after 2 days of treatment, suggesting usefulness of short-course treatment to reduce the carriage of antibiotic-resistant *C. acnes* [101]. BPO had a bactericidal effect *in vitro* against both antibiotic-resistant and antibiotic-susceptible *C. acnes*. The minimum contact time needed *in vitro* was 60 min, 15 min, and 30 sec, with concentrations of 1.25%, 2.5%, and 5% respectively. The median MIC of BPO did not significantly differ between antibiotic-resistant and non-resistant *C. acnes* [102]. It has been recommended to consider a course of topical BPO, of at least 5 to 7 days, between antibiotic courses with the aim to reduce the emergence of cutaneous resistant strains [100]. Given that the combination of BPO with topical antibiotics may reduce antibiotic-resistant *C. acnes* strains [103,104], BPO has also been formulated in commercially available fixed-dose topical BPO-antibiotic combination treatments for acne that have largely replaced topical antibiotic monotherapy for acne [22]. Clascoterone was more recently FDA-approved in 2020, as a topical androgen receptor inhibitor for acne in patients 12 years and older [105]. A recent multicenter phase 2B randomized double-blind, vehicle-controlled trial showed the effectiveness and safety of a new class topical treatment with a selective peroxisome proliferator-activated receptor-γ (PPARγ) modulator (NAC-GED 5% gel) for moderate-to-severe facial acne vulgaris [106]. Topical probiotics with "healthy-skin" associated *C. acnes* phylotypes represent an ongoing area of research regarding their potential therapeutic benefit on the modulation and restoration of the cutaneous diversity of *C. acnes* phylotypes [107]. A pilot study assessed the topical application of *C. acnes* strains to the skin of 14 patients with acne for 5 weeks. A shift in the composition of the skin microbiome to the mixed strains present in the topical formulation was observed. Also, there was a significant reduction in non-inflamed lesions (comedones) and no change in the inflamed acne lesions [108].

On the other hand, there is a limited range of approved systemic non-antibiotic pharmacological treatments, consisting mainly of isotretinoin and combined oral contraceptives (COC) (varying approval status of COC formulations for acne across countries), highlighting the need of studies on new non-antibiotic treatments for moderate and severe acne [109-111]. Of note, COCs that are approved for the treatment of acne, are indicated for use only in women who also desire contraception [20]. COCs for acne, may be used in women with hyperandrogenism (eg, polycystic ovary syndrome, hirsutism) and in women without these findings [20]. A consideration of the risk-to-benefit profile and potential contra-indications is important [20,110].

Regarding oral probiotics (ie, live microorganisms with a potential to correct dysbiosis), there are a limited number of studies investigating their effects in patients with acne and their potential usefulness has not been established [107,112-114].

CONCLUSIONS AND OUTLOOK

Worldwide efforts have struggled to describe the resistant patterns in *C. acnes* and other bacteria isolated from acne patients. Epidemiological data on antimicrobial resistance in acne mainly refer to the increasing emergence of *C. acnes* resistant strains due to antibiotic treatment for acne. Overall, there are higher rates of clindamycin and erythromycin resistance and lower rates of doxycycline resistance of *C. acnes*, while there are more limited reports on resistance to azithromycin.

Apart from its key roles in the pathophysiology of acne, *C. acnes* is part of complex interactions with other members of the skin microbiome and *C. acnes* subspecies have been implicated in the pathophysiology of other diseases, beyond the skin. In addition to the risk of developing *C. acnes* resistant strains, the overuse of antibiotics for acne may lead to the emergence of other resistant bacterial pathogens, and thus compromise the effectiveness of antibiotics for other treatment indications. In addition, the possible effects of oral antibiotics used for acne on the gut microbiota and associated diseases, merit further investigation.

The call to reduce the risk of antimicrobial resistance and safeguard public health has fueled the initiative for antibiotic stewardship. Studies on the prescribing behavior of acne treatments among dermatologists and non-dermatologists have shown that a considerable part of courses with a systemic antibiotic were longer than 6 months, that there are physicians not expressing concerns for the risk of antimicrobial resistance, and that prescribing trends of systemic antibiotics in the US have not changed over a decade. These findings underscore the need to further raise awareness on the risk of antimicrobial resistance in health providers treating patients with acne.

The concern over antimicrobial resistance has shaped the current international guidelines for the treatment of acne, recommending limiting antibiotic use and select non-antibiotic treatments, when possible. In clinical practice, moving further away from antibiotic treatments in acne can be based on the future availability of additional non-antibiotic treatments with evidence-based efficacy and safety for patients with acne.

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