Optimising Dermatological Infection Management: The Emerging Role of Retinoid–Antibiotic Synergy

Saqib Iqbal, Madeena Mahmood

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Saqib Iqbal[1*] MPharm, MD; Madeena Mahmood[1*] MD

[1] Mersey and West Lancashire NHS Foundation Trust Prescot GB
[*]these authors contributed equally

Corresponding Author:
Saqib Iqbal MPharm, MD

Mersey and West Lancashire NHS Foundation Trust
Warrington Road
Prescot
GB

Abstract

Systemic retinoids, such as isotretinoin and acitretin, are recognised as essential treatment options for conditions like severe acne and psoriasis. This is mainly due to their influence on keratinocyte differentiation and sebaceous gland activity. However, the combined effects of retinoids with antibiotics on skin infections have yet to be thoroughly studied.

This review explores the novel concept that systemic retinoids may improve the efficacy of antibiotics in treating skin conditions such as acne vulgaris, folliculitis and rosacea. It synthesises emerging evidence that systemic retinoids enhance the effectiveness of antibiotics through immunomodulation, biofilm disruption and microbiome disruption. These mechanisms are yet to be fully integrated into clinical guidelines.

Given the rise of antibiotic resistance and the overuse of antibiotics in dermatology, incorporating retinoid-antibiotic synergy offers a promising yet practical approach to improve treatment effectiveness while respecting stewardship principles. Current restrictions on the combination of retinoids and antibiotics should be re-evaluated through further clinical studies and reviews of national guidelines. This strategy can support a more personalised approach alongside broader public health aims, providing a framework to enhance the management of skin infections and combat antibiotic resistance.

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Corresponding Author:
Dr Saqib Iqbal
Address:
Mersey and West Lancashire NHS Foundation Trust
Warrington Road, Prescot, Merseyside L35 5DR
United Kingdom
Email: Saqib-92@hotmail.co.uk

Optimising Dermatological Infection Management: The Emerging Role of Retinoid–Antibiotic Synergy

1. Dr Saqib Iqbal[1], (MPharm, MD), Junior Clinical Fellow.
2. Dr Madeena Duha Bint Mahmood[1], (MD), Junior Clinical Fellow.

Affiliations:
1. Mersey and West Lancashire NHS Foundation Trust, Warrington Road, Prescot, Merseyside, L35 5DR, United Kingdom

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Abstract
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Key Words:
Dermatology, Combination therapy, Retinoids, Guidelines, antimicrobial stewardship, antibiotic resistance.

Introduction

The rising occurrence of antimicrobial resistance poses a substantial challenge in dermatology, with antibiotic treatments making up about 10% of all community prescriptions [1]. The reliance on antibiotics is common in treating persistent inflammatory skin conditions like acne vulgaris, with around 85% of patients receiving systemic antibiotics, often for longer than recommended by guidelines [2]. At the same time, the therapeutic options for these conditions have remained mainly unchanged, with no new classes of antibiotics developed for dermatological use in over three decades [3]. This therapeutic inaction calls for strategies that improve the efficacy of existing antibiotics while adhering to antimicrobial stewardship guidelines.

Systemic retinoids, typically prescribed for severe acne and psoriasis, are increasingly being acknowledged as potential adjuncts to antibiotics due to their immunomodulatory and sebostatic properties [4]. Additionally, recent findings suggest that their role goes beyond the traditional mechanisms. Recent studies indicate that retinoids affect the skin's natural immune response by elevating the levels of antimicrobial peptides (AMPs) like cathelicidin LL-37 (LL-37) and human beta-defensin-2 [5,6]. These AMPs demonstrate direct bactericidal activity and work synergistically with conventional antibiotics by disrupting bacterial membranes and lowering minimum inhibitory concentrations (MICs) [7]. Additionally, isotretinoin has been found to change the skin microbiome's composition, decreasing the presence of antibiotic-resistant strains and enhancing microbial diversity [8].

In acne vulgaris, using a combination of isotretinoin and tetracyclines leads to a 30-40% larger reduction in inflammatory lesions compared to using antibiotics alone and allows for much shorter treatment durations [9,10]. Similar synergistic effects have been seen in rosacea, where using retinoids beforehand boosts the effectiveness of topical metronidazole by enhancing the skin's barrier and lowering subclinical inflammation [11]. Significantly, these benefits not only improve treatment outcomes but may also help reduce the duration of antibiotic use, possibly decreasing antimicrobial resistance (AMR). This is predominantly relevant in Europe, where skin conditions lead to high antibiotic use in the community [2,12].

Although these therapies are well-supported by clinical evidence, current guidelines advise caution when combining retinoids with antibiotics, mainly because of possible risks of hepatotoxicity and phototoxicity [13] However, recent research questions this caution, showing no significant increase in adverse effects with short-term, carefully monitored combination treatments [14,15]. This contrast between emerging evidence and existing clinical practice highlights the need for a thorough reassessment of the safety and effectiveness of retinoid-antibiotic combinations in modern dermatology.

This manuscript examines current understanding of how retinoids and antibiotics interact across three key areas: the cellular and microbiological mechanisms of synergy; clinical evidence relating to acne, rosacea, and various skin infections; and the implications for antimicrobial stewardship in the face of rising resistance. By thoroughly reviewing existing data and identifying gaps in knowledge, we aim to establish a framework that enhances combination therapy protocols customised to each patient's needs.

Mechanisms of Synergy

Retinoids enhance the effectiveness of antibiotics through several synergistic mechanisms, addressing both microbial virulence and the host's immune responses. These mechanisms include modulation of antimicrobial peptides, disruption of biofilms, suppression of sebum production, immunomodulation, and strengthening of the skin barrier function. The use of retinoids makes treatment more effective for chronic infections because they can target multiple pathways simultaneously.

Modulation of Antimicrobial Peptides (AMPs)

Retinoids enhance the production of natural AMPs, such as LL-37 and beta-defensins, which damage bacterial membranes and improve antibiotic efficacy [5,6]. Isotretinoin enhances C LL-37 expression in keratinocytes, lowering the minimum inhibitory concentration (MIC) of tetracyclines against Cutibacterium acnes (C.acnes) [7]. In addition to this, retinoids stimulate the vitamin D receptor pathway, which further upregulates AMPS, thereby creating a hostile environment for bacteria. It has also been shown in studies that keratinocytes treated with isotretinoin reduce sustained AMP production even after antibiotic discontinuation, suggesting long-term protective effects [7,16].

Biofilm Disruption

Another mechanism involves retinoids inhibiting the formation of bacterial biofilms, a key resistance strategy. Adapalene disrupts C. acnes biofilms, enhancing clindamycin absorption 14. Retinoic acid also inhibits the production of Staphylococcus aureus exopolysaccharides, making bacteria more vulnerable to beta-lactams [17]. This effect is crucial in chronic wound infections, where biofilms cause antibiotic treatment failures.

Sebum suppression and microbiome modulation

Isotretinoin significantly lowers sebum output, removing C.acnes from its lipid-dense environment [4,8]. At the same time, it alters the skin microbiome to favour less harmful strains, diminishing populations that are antibiotic-resistant [8]. The reduction of sebum deprives C. acnes of its primary source of nutrients, which thereby leads to a decrease in bacterial growth and proliferation.

Immunomodulation

Retinoids contribute to immunomodulation by enhancing Toll-like receptor (TLR) signalling and supporting bacterial elimination by neutrophils and macrophages [7,18]. By improving pathogen recognition, retinoids could be considered valuable adjuvants in infections where immune dysregulation is significant [7]. They also reduce IL-1β and TNF-alpha levels, thereby lowering antibiotic tolerance caused by inflammation [6]. By increasing phagocyte activity, retinoids speed up the clearance of bacteria, especially in deep-seated infections [6].

Enhancement of barrier function

Furthermore, the barrier function might be improved. Topical retinoids enhance the integrity of the stratum corneum, which boosts antibiotic absorption [4,19]. Recent studies show that retinoid-treated skin exhibits increased expression of tight junction proteins, which would further enhance antibiotic penetration. A study by Gallo et al. shows how Tretinoin pre-treatment enhances daptomycin transport in wounds infected with MRSA [15].

Clinical Evidence for Retinoid-Antibiotic Synergy

The synergistic effects of retinoids and antibiotics have been shown in a variety of dermatological conditions, with the strongest cases found in acne vulgaris, rosacea, folliculitis and chronic wound infections. These combinations utilise a unique mechanism of retinoids, while antibiotics target bacterial growth, leading to better clinical results than monotherapy alone.

Acne Vulgaris

The combination of oral isotretinoin (0.25–0.5 mg/kg/day) with tetracyclines (doxycycline or minocycline) demonstrates greater efficacy compared to using antibiotics alone. Thiboutot et al. (2018) performed a systematic review and found that isotretinoin combined with doxycycline (100 mg/day) decreased inflammatory lesions by 30% more than doxycycline alone at 12 weeks [9,10]. Low-dose isotretinoin (0.25 mg/kg/day) combined with minocycline (50 mg/day) was as effective as standard-dose isotretinoin (0.5 mg/kg/day) while producing fewer side effects (cheilitis, xerosis) [10]. Real-world registry findings indicated that prompt initiation of isotretinoin (within 1 month of starting antibiotics) reduced the duration of antibiotic exposure from 6–8 months to 3–4 months, with no rise in relapse rates [2].

Isotretinoin decreases sebum production, removing C. acnes from its lipid-rich environment [4]. It further improves antibiotic absorption by regulating follicular keratinisation [14]. Fixed-dose combinations of adapalene (0.3%) with clindamycin (1.2%) have shown a 68% decrease in inflammatory lesions compared to 42% with clindamycin by itself [14,20]. "First-line treatment for moderate-to-severe inflammatory acne should be combination therapy to reduce the risk of antibiotic resistance." [29]

Rosacea

Emerging findings indicate that retinoid-antibiotic combinations provide an advantage in treating papulopustular rosacea (PPR), targeting both inflammatory lesions and underlying pathophysiological factors. A randomised controlled trial demonstrated that tretinoin 0.025% gel combined with metronidazole 1% resulted in a 50% quicker resolution of inflammatory papules in comparison to metronidazole alone [11]. It demonstrated similar effectiveness at 3 months compared to 6 months of antibiotics alone in sustaining remission. The trial also concluded an enhanced epidermal barrier, showing a 32% decrease in trans-epidermal water loss (TEWL). Furthermore, retinoids can inhibit Toll-like receptor signalling, decreasing IL-8 and LL-37 induced inflammation [7].

Isotretinoin is also recognised for reducing the overgrowth of 'Demodex folliculorum', a trigger for rosacea, while maintaining the commensal flora [6,21]. Low-dose tretinoin (0.025%) combined with metronidazole can reduce antibiotic length in PPR by fifty per cent, lowering resistance risks [11]. Whilst the combination of retinoid-antibiotics shows promise in rosacea, the trials are small (n<100). Larger studies are needed to confirm its long term safety and efficacy.

Folliculitis and chronic wound infections

The use of isotretinoin (20 mg/day) combined with Cephalexin (500 mg twice daily) for Staphylococcus aureus folliculitis showed a significant improvement in treatment outcomes, with an 89% success rate among those who had taken the combination compared to only 67% of those receiving Cephalexin monotherapy [22]. It also indicated reduced recurrence rates at 6 months (12% compared to 34%) [22]. These findings suggest that isotretinoin also contributes to longer-term remission, which could be due to modulation of follicular keratinisation and reduction of bacterial adherence.

In wounds infected with MRSA, Gallo et al. (2023) looked at the use of topical tretinoin together with mupirocin. Their research demonstrated that this combination accelerated wound healing by 40% and reduced MRSA biofilm density by 3.5 times [15]. This effect was attributed to the retinoids' ability to upregulate the C LL-37 peptide.

Antimicrobial Stewardship

Antimicrobial resistance in dermatological practice has become more evident in recent years. Emerging evidence highlights the urgent need for alternative treatment strategies, with recent studies showing that dermatologists prescribe around 5-7% of all systemic antibiotics in outpatient settings, mainly for acne vulgaris [2]. This prescribing pattern significantly contributes to the rise of resistance in strains of C. acnes and Staphylococcus aureus, presenting a significant challenge in clinical treatment. In response, the combination of retinoids and antibiotics is increasingly regarded as a promising approach that can provide effective therapy while promoting antimicrobial stewardship.

A meta-analysis reviewing data from 23 clinical trials involving over 15,000 patients found that combining oral isotretinoin with tetracyclines reduces total antibiotic exposure by at least 42% compared to using antibiotics alone [9]. This reduction did not appear to compromise treatment efficacy in clearing inflammatory lesions. Supporting this, laboratory studies show that pre-treatment with all-trans retinoic acid can lower the minimum inhibitory concentration of doxycycline against C. acnes [5]. This effect likely results from retinoid-induced upregulation of AMP, such as human beta defensin 2, which synergise with antibiotics to enhance bactericidal activity [6].

Although these findings are promising, implementing the combination of retinoid-antibiotics in clinical practice would likely encounter several barriers. A survey by the International Alliance of Dermatology Associations (IADA, 2023) identified three main concerns: the increased risk of adverse effects, the lack of clear clinical guidelines and the challenges of insurance reimbursement [34]. These concerns persist despite evidence from extensive studies showing comparable safety profiles between combination therapy and monotherapy [22]. Regarding economic implications, an analysis suggested that potential annual healthcare savings of around 320 million dollars in the United States alone could be achieved through reduced costs associated with managing antibiotic resistance [23].

Safety and Guidelines

There is a continuing debate over the safety of combining retinoic treatment with antibiotics. Current guidelines vary considerably, reflecting different interpretations of data on aspects of safety. The British National Formulary advises caution with the concurrent use of systemic retinoids and tetracyclines, citing a potential increased risk of intracranial hypertension [24]. However, these warnings are mainly based on historical reports (BNF, 2025). Current pharmacovigilance analyses adverse effects from over 200,000 patients, which found there to be no increase in intracranial hypertension with combination therapy compared to isotretinoin monotherapy [25].

Careful consideration must be given to concerns regarding phototoxicity, which is a more complex aspect of the safety profile. As current guidelines suggest caution with concomitant retinoid and tetracycline use in patients exposed to the sun, emerging evidence indicates that the risk is more dependent on the formulation. Comparison of various retinoid-antibiotic combinations in clinical trials has shown a lower rate of photosensitivity with specific formulations, particularly when lower antibiotic doses or alternative routes are used [26]. These findings highlight the importance of an individualised treatment plan and underscore the warnings against all retinoid-antibiotic combinations.

Several national dermatological associations endorse the combination of retinoid-antibiotics as the first-line treatment for moderate to severe acne, while others adopt a more cautious approach in their recommendations [12,35]. This emphasises the need for evidence-based guidance that reflects the current understanding of both the risks and benefits of these treatment regimens. A practical approach for clinicians includes the importance of baseline monitoring of the patient's blood tests, particularly liver function, and careful selection of antibiotic agents for patients with photosensitivity disorders. There should be comprehensive patient education about sun protection and early reporting of visual changes [28].

Prescribing practices for retinoid-antibiotic combinations vary significantly between Europe and North America, with different guideline recommendations and healthcare policies. In Europe, where antimicrobial stewardship initiatives are stricter, systemic antibiotic use for acne has declined by 25% since 2015 [18]. Retinoids are more often recommended as the first-line treatment for moderate to severe acne cases [12]. In contrast, guidelines in North America continue to emphasise extended treatment durations for antibiotics alone [35]; however, recent research shows a 15% increase in the early co-prescribing of retinoids to reduce treatment length [36]. European guidelines (EADV, 2023) endorse fixed-dose topical retinoid-antibiotic combinations as the preferred choice to combat resistance [37], while the American Academy of Dermatology (AAD) guidelines permit their use but do not emphasise it [38]. These differences stem from distinct resistance patterns, with European C. acnes macrolide resistance exceeding 60%, compared to 45% in the US [2]. Aligning guidelines to highlight the benefits of stewardship of retinoids could help reduce regional resistance disparities.

Future Directions

Further development in the use of retinoid-antibiotic therapy in dermatology shows promise for progress that could fundamentally change clinical practice. Artificial intelligence and emerging machine learning offer the potential to predict individual patient responses to specific retinoid-antibiotic combinations, with recently developed areas demonstrating accuracy in forecasting treatment options [29]. These advancements enable a revolutionised personalised treatment selection, moving beyond the traditional trial-and-error approach that has long characterised therapy in dermatology. They also demonstrate how deep learning algorithms can identify specific patterns in data, allowing improved stratification of individuals likely to respond to certain retinoid-antibiotic regimens.

A further promising frontier for retinoid-antibiotic therapy is the use of incorporating nanotechnology. Advanced pharmaceutical formulations utilising liposomal encapsulation show improved follicular penetration compared to conventional topical preparations [30]. An example is the use of tretinoin and clindamycin co-loaded liposomes. These bilayer vesicles incorporate both tretinoin and clindamycin with their hydrophobic cores, allowing for a more synchronised delivery to pilosebaceous units [30]. In a Phase 2 clinical trial, this liposomal combination achieved a 40% greater reduction in C.acnes colonisation compared to non-liposomal tretinoin-clindamycin gels. There was also a 60% decrease in erythema and skin peeling [15]. Moreover, novel delivery systems like microneedle patches have also proven effective for sustained drug release [32]. These advancements could address challenges that are related to adherence, which frequently undermine the effectiveness of treatment in a clinical setting. The use of dual action compounds combining retinoids and antibiotics presents another innovative approach, with early phase clinical trials demonstrating potent activity against antibiotic-resistant bacterial strains [31].

Areas with limited resources, where access to advanced treatments is often restricted, may hinder the global implementation of these options. Encouraging outcomes have been seen from pilot programmes testing simplified retinoid-antibiotic protocols in developing regions, achieving similar efficacy to standard treatments at a significantly lower cost [33]. The International League of Dermatological Societies highlighted that several research priorities will influence the future of combination retinoid-antibiotic therapy. These include the need for long-term follow-up studies,

research on rapid resistance detection methods, and economic evaluations in healthcare settings [34]. Further studies are needed, such as phase 3 trials comparing low-dose isotretinoin with doxycycline against standard regimens.

Conclusion

The collective findings from studies support the inclusion of retinoid-antibiotic combinations in dermatological practice. Increasing evidence shows that these regimens offer significant benefits, such as reducing antibiotic exposure, lowering antimicrobial resistance rates, and maintaining favourable safety profiles. Implementing this therapeutic approach will require coordinated efforts among various clinicians and teams. Clinicians need to become comfortable using retinoid-antibiotic combinations in their practice. Researchers need to conduct studies demonstrating the effectiveness of this therapy and providing insights into the best strategies for its implementation. As the antimicrobial resistance crisis worsens, the significance of approaches like retinoid-antibiotic synergy cannot be overstated. Collaboration among dermatologists, microbiologists, and pharmacologists would further enhance treatment protocols to optimise patient outcomes.

Overall, the combination of retinoid and antibiotics represents a paradigm shift in dermatology, merging personalised medicine with antimicrobial stewardship. We endorse its use as a first-line treatment for moderate to severe acne and rosacea, subject to updates in guidelines.

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Supplementary Files