International Journal of Research in Dermatology
Muchhala S et al. Int J Res Dermatol. 2022 Nov;8(6):551-563
http://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20222726

Systematic Review

Management of skin and soft-tissue infections and acne with topical nadifloxacin: a comprehensive review

Snehal Muchhala[1]*, Rashmi Sarkar[2], Koushik Lahiri[3], Rajendra D. Kharkar[4], Rahul Rathod[5]

[1]Medical GG India, [5]Ideation and Clinical Research GG India, Dr. Reddy's Laboratories Limited, Hyderabad, Telangana, India
[2]Department of Dermatology, Lady Hardinge Medical College and Associated SSK Hospital and KSC Hospital, New Delhi, India
[3]Department of Dermatology, Apollo Gleneagles Hospitals, Kolkata, West Bengal, India
[4]Department of Dermatology and Cosmetology, Dr Kharkar Clinic, Suchak Hospital, Malad, Mumbai, Maharashtra, India

Received: 01 July 2022
Revised: 28 July 2022
Accepted: 04 August 2022

***Correspondence:**
Dr. Snehal Muchhala,
E-mail: drssm77@hotmail.com

ABSTRACT

Skin and soft tissue infections (SSTIs) and acne are multi-factorial skin conditions that involve microbial invasion of the skin and underlying soft tissues; though, both have different pathogenesis. Most of these infections are caused by bacteria, affecting all age groups. Early diagnosis and appropriate antimicrobial therapy remain the cornerstone of management of SSTIs and acne. Over the years, an increase in antibiotic resistance has been reported with mupirocin and fusidic acid that makes the management of SSTIs and acne increasingly challenging. Further, these antibiotics are unable to penetrate biofilms and show their action on the microorganisms embedded deep in the polymeric matrix. In this review, we have discussed the current evidence on the efficacy and safety profile of nadifloxacin compared to other currently available antimicrobial agents. An extensive search was performed through PubMed and Medline using relevant key words. This article has highlighted nadifloxacin's broad antimicrobial spectrum, unique dual mechanism of action, distinct characteristics like ability to retain efficacy in acidic pH, low antibiotic resistance and superior action against biofilms. This review concludes that nadifloxacin, could be a potential empirical therapy in the management of SSTIs and acne.

Keywords: Acne vulgaris, SSTI, Nadifloxacin, Antibiotic resistance, Biofilm, Topical

INTRODUCTION

Skin is the first line of defense, which prevents microbes from entering the internal sterile milieu of the host. However, when this barrier is breached by wounds, abrasions, or surgical incisions, bacteria can easily colonize themselves leading to infections.[1] The skin and soft tissue infections (SSTIs) involve loose connective tissue as well as mucous membranes, and is synonymous with skin and skin structure infections (SSSIs) and acute bacterial skin and skin structure infections (ABSSSIs).[2] *Staphylococcus aureus* is the most common organism founds in SSTIs, along with methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pyogenes*, *Enterococci*, other *streptococci* and gram-negative bacteria.[3,4] The SSTIs present clinically diverse presentations which range from minor superficial infections to life-threatening infections such as necrotizing fasciitis. The incidence of SSTIs has rapidly increased from 32.1 to 48.1 visits per 1000 population, accounting for 14.2 million by 2005. According to the literature

available in public domain data, use of antibiotics for the treatment of community acquired MRSA increased from 7% to 28% of visits. There was a 28.9% increase in the US hospital admissions for SSTIs from 675,000 in the year 2000 to 869,800 in 2004. Lee and colleagues assessed trends in SSTIs in the US and reported a 40% increase (2.4 million to 3.3 million) in the overall incidence of SSTIs from 2000 to 2012.[5] The incidence rate of SSTIs was 18.21 per 1000 person-years in the emergency department of a tertiary care hospital in South India in 2018 with uncomplicated bacterial skin infections accounting for 17-25% of the clinical visits.[6,7]

Apart from SSTIs, another skin condition which is frequently encountered is acne vulgaris. It is a multifactorial chronic inflammatory skin disease which manifests clinically as non-inflammatory open or closed comedones and inflammatory papules, pustules, or nodules, affecting up to 80% of adolescents and several adults at some stage.[8] According to the global burden of disease study 2019, acne vulgaris was the 19th leading contributor for disability adjusted life years (DALY) in 2019 (1.6%) showing a 41.5% increase from 1990 to 2019 in the 10–24-year age group.[9]

Nadifloxacin (NF) is a relatively newer antibiotic, belonging to fluoroquinolone group which is effective against aerobic gram-negative, gram-positive, and anaerobic bacteria and has shown promising safety and efficacy profile.[10,11] The use of 1% topical nadifloxacin for the treatment of skin infections such as, impetigo, folliculitis, furunculosis and secondarily infected wounds has been documented in the literature. It is commonly prescribed as a twice daily application for 7-14 days.[11] Furthermore, it has been approved for the treatment of superficial localized and mixed infections of the skin that are associated with inflammation; bacterial skin infections such as contact dermatitis, seborrheic dermatitis and infective eczema; and dermatoses and acne vulgaris with multiple inflammatory lesion. In this article, we have reviewed the current evidence and the role played by nadifloxacin in the management of SSTIs and acne vulgaris.

METHODS

An extensive search of studies published in the last two decades assessing the safety and efficacy of nadifloxacin was performed through PubMed and MEDLINE using the key words: “acne vulgaris”, “ABSSSI”, “antibiotic resistance”, “antimicrobial”, “biofilm”, “MRSA”, “nadifloxacin”, “SSTI”, and “topical”, with the filter’s “humans” and “English language”. The start and end dates for the searches were January 2002 and December 2020, respectively. Proceedings of meetings and case reports were also included. We performed reference mining on all identified articles (n=196) in order to find additional articles that meet the inclusion criteria. Articles published before the start search date provided conceptual content only.

RESULTS

A systematic literature search yielded 196 articles of interest. After removal of duplicates, 138 studies were screened for inclusion. About 104 full text articles were assessed and among them 34 were excluded. Figure 1 represents the PRISMA flow chart of study characteristics. Majority of the included articles compare nadifloxacin to other topical antimicrobials. Most of them described cases in India, with one study each describing cases in Germany and Korea. A few cases were also studied in the paediatric population. Some studies associated clinical manifestation in general with dermatological manifestation.

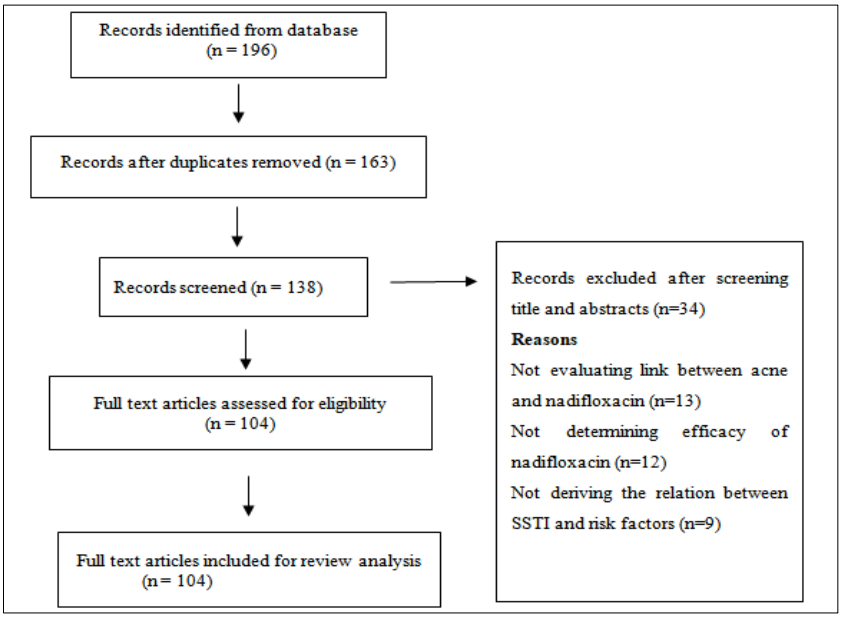

Figure 1: Prisma flow chart of study characteristics.

DISCUSSION

Pathophysiology of SSTIS and acne vulgaris

The etiopathogenesis of SSTIs and acne is multifactorial in nature. Skin serves as an integral part of host defense mechanism and forms an effective barrier against microorganisms. However, there are certain ways by which bacteria can invade the soft tissues. Principally, through a break in the skin continuity and the other being hematogenous spread, which is a rare condition.[1] SSTI's occurring in an otherwise healthy skin are termed as primary SSTI's, whereas microorganisms infecting already damaged skin caused due to trauma or underlying disease factors are considered secondary SSTI's. Though the terminology is different, but the pathogenesis of microorganisms remains same in both the entities.[12] The development of SSTIs occurs in three steps – adherence of bacteria to the host cells, invasion of host tissue with evasion of host defenses and elaboration of toxins.[4] Figure 2a represents the pathophysiology of SSTIs. Bacterial endotoxins and exotoxins activate the T cells, leading to the release of cytokines which cause tissue damage through enzymatic reactions, cellular dysregulation and release of surface proteins M1 and M2.[13] The activated host inflammatory cells phagocytize and destroy foreign material, dead tissue, and dead microbes, leading to SSTIs. The risk factors for the development of SSTIs include diabetes, cuts, bites, drug abuse, excessive skin moisture, inadequate blood supply, immunosuppression, poor hygiene, physical contact, pre-existing skin disease and crowded living conditions.[12,14]

Acne formation starts in the pilosebaceous unit, and it occurs due to interaction of four main factors: excess sebum production, altered follicular keratinization, microbial colonization by *P. acnes* and release of inflammatory mediators into the skin. Figure 2b shows the steps involved in the pathogenesis of acne. The first step involved in the pathogenesis of acne is the microcomedone formation, which is caused due to increased sebum production by the sebaceous glands and follicular corneocytes, and accumulation of keratinocyte debris. Increased sebum production along with the increase proliferation and decrease shedding of intrafollicular keratinocytes causes obstruction of pilosebaceous unit, further leading to formation of a large clinically appreciable open or closed comedones. Microcomedones act as precursors to comedones (open or closed), papules, pustules, and nodules.[15]

The next stage in acne formation is the colonization by *P. acnes* and release of inflammatory mediators leading to the formation of an inflammatory lesion. *P. acnes* release lipases which degrade the triglycerides and proteases and damage the follicular wall and trigger chemotactic factors and inflammatory mediators. Recruitment of CD4 lymphocytes followed by monocytes, neutrophils and pro-inflammatory cytokines such as interleukin (IL) 8 further potentiates the inflammatory process. Furthermore, *P. acnes* influences keratinocyte differentiation and causes release of IL-1 leading to proliferation of keratinocytes and comedone formation.[15]

Excess sebum production due to stimulation of sebaceous glands is believed to be driven by androgens, which usually occurs at the time of puberty. Di-hydrotestosterone (DHT) and testosterone are the endogenous androgens that are found to stimulate the proliferation of sebocytes of the face.[15] Recent data suggests that several other molecular pathways and hormones are also involved in acne formation such as insulin, estrogen, progesterone, corticotropin releasing hormone, adrenocorticotropic hormone, glucocorticoids, melanocorticotropic hormone and lastly growth hormone. Since androgens are considered as major triggers for acne production during puberty, evidence in line suggests the critical role of insulin like growth factor (IGF) 1 in acne formation. Elevated levels of IGF-1 induce androgen synthesis and increase the cutaneous presence of DHT. This leads to decreased expression of fork head box (Fox) 01 transcription factor and increased activation of mechanistic target of rapamycin complex (mTORC)-1 and causes activation of peroxisome proliferator activated receptor- gamma and various other factors. These actions increase the sebum triglycerides and fatty acid desaturation leading to a pro-inflammatory, comedogenic effect along with increased levels of squalene caused due to increased sebum production.[16]

Management of SSTIS

Due to an ever-increasing bacterial resistance, the management of SSTIs is becoming increasingly challenging. It mainly depends on factors such as type of infection, severity, causative microorganisms, and local antibiotic resistance patterns. As per the guidelines of Infectious Diseases Society of America, management of SSTIs broadly consists of surgical drainage and debridement, microbial culture and antibiotic susceptibility testing and antibiotic medication.[17] Early and appropriate antibiotic therapy is one of the best therapeutic strategies for the management of SSTIs.

In general, incision and drainage are indicated for purulent infections and abscesses. It helps in breaking the loculi and perform irrigation of the wound, thereby helping in reducing the bacterial load, and packing prevents the premature closure of wound allowing the abscess to drain.[18]

Systemic antimicrobial therapy is the mainstay in the treatment of SSTIs. They are used as empirical therapy, definitive therapy or as an adjunct therapy along with surgical drainage. Although these are widely used, have some drawbacks, including resistance development, decreased efficacy, poor tissue penetration, and dose modification in patients with comorbidities. However, these limitations do not restrict the use of systemic antimicrobials. Proper knowledge with respect to the

bacterial sensitivity and use as a single or combination therapy helps in achieving the successful clinical outcomes.[14]

Topical antimicrobial therapy for bacterial skin infections allows high concentration targeted drug delivery to the site of infection and have a lower risk of systemic side effects and toxicity. Narayan et al., evaluated a post market study and three randomized trials to determine the efficacy and safety of 1% topical nadifloxacin, used for various skin infections (impetigo, folliculitis and furunculosis) and reported a significant reduction in the symptoms of bacterial infections and concluded that topical nadifloxacin is a new alternative in treating skin infections with minimal adverse effects.[11] Certain limitations exist with topical therapy such as limited evidence for its clinical efficacy, local irritation and allergies, and minimal depth of penetration. Table 1 depicts the different treatments prescribed for various types of SSTIs.

Management of acne vulgaris

A better understanding of the pathogenesis of acne led to the development of newer drugs and various combinations of already existing drugs. Topical agents such as benzoyl peroxide, antimicrobials, and retinoids are widely prescribed in the treatment of mild to moderate acne vulgaris. However, with retinoid topical preparations, certain undesirable effects are reported such as irritation on the application site, erythema, dryness, and peeling.[19] Antimicrobial such as 1% nadifloxacin has been shown too effective in acne treatment. Shah et al in his open label, phase 3 trial reported that 98.3% patients has shown significant reduction in inflammatory and non-inflammatory lesion counts with 75% approaching to a normal healthy skin score by the end of 8 weeks. Mild to moderate adverse events were reported, of which application site dryness was common.[20]

Systemic therapy is indicated in patients with moderate to severe acne, inflammatory lesions, and in those who are non-responsive to topical therapy. Tetracycline, doxycycline, minocycline, and erythromycin are commonly used oral antimicrobials in acne management. Oral antibiotics reduce the load of *P. acnes* in the follicle and inhibit the production of inflammatory cytokines. Results with oral antibiotics are achieved in 6 to 8 weeks. However, certain limitations exist such as tetracyclines cannot be prescribed in pregnant patients and children below age of 9 years. Moreover, with doxycycline use, phototoxicity is an issue. In general development of bacterial resistance to topical or systemic antimicrobial is of great concern.[21]

Intralesional steroids known for their anti-inflammatory action effectively reduce the inflammation in acne lesions. While being effective, they are also associated with undesirable effects such as skin atrophy, hypopigmentation etc. However, risk of side effects depends on the intralesional depth, volume, and concentration of the steroid injection. Additionally, comedone extraction, cryoslush therapy, cryotherapy, electro cauterization, and optical treatments are some of the physical treatment options.[19,21,22] Table 2 shows the topical and systemic drugs for the management of acne vulgaris.

Nadifloxacin: topical antibiotic for managing skin infections

Structure and licensing status

Nadifloxacin is a broad-spectrum antibiotic with a benzoquinoline skeleton with fluorine at the sixth position and N-hydroxypiperidine at the eighth position.[7] It is chemically known as 7-fluoro-8-(4-hydroxypiperidin-1-yl)-12-methyl-4-oxo-1-azatricyclo [7.3.1.0^{5},^{13}]trideca.

2,5,7,9(13)-tetraene-3-carboxylic acid, the L-alanine ester prodrug of levonadifloxacin (LNF) (WCK 2349) and its L-arginine salt (WCK 771) are approved in India for the treatment of ABSSSI, diabetic foot infections (DFI) and concurrent bacteraemia.[23] In 2014, the US FDA granted a status of "qualified infectious disease product (QIDP)" to LNF for the treatment of MRSA infections.[24] Currently, nadifloxacin is being used for the treatment of mild to moderate acne in Japan and other European countries.[25]

Spectrum of activity

Nadifloxacin and its isoforms have a broad spectrum of activity. They are effective against gram positive and negative aerobes, gram positive and negative anaerobes and atypical bacteria.[10,23] Figure 3 represents the spectrum of activity of nadifloxacin.

Mechanism of action

DNA gyrase and topoisomerase IV are two bacterial enzymes which produce double-stranded breaks in the bacterial chromosome during DNA replication. Most of the other quinolones have either affinity towards topoisomerase IV (e.g. ciprofloxacin, levofloxacin) or have dual targets for both enzymes (e.g. clinafloxacin and nadifloxacin) in gram positive bacteria.[10,23] Nadifloxacin has a unique dual mechanism of action. It not only targets the bacterial enzymes interfering with DNA replication but also inhibits nor-A efflux pump. Figure 4 represents the mechanism of action of nadifloxacin and biofilm formation. Nor-A efflux pump is used by bacteria (such as *S. aureus*) to pump out drugs leading to drug resistance. The R component of nadifloxacin acts as a powerful efflux inhibitor. Therefore, nadifloxacin is not influenced by an over expression of the nor-A efflux pump on the bacterial cell membrane which reduces the chances of development of resistance. Another mechanism, through which nadifloxacin acts, is through its ability to exist even in acidic pH. Other quinolones like ciprofloxacin and moxifloxacin get deteriorated at the same pH.[26] This is advantageous as most of the bacterial infections show an

acidic pH at the site of infection. Nadifloxacin is also able to survive in the acidic environment of phagocytic cells and keratinocytes, thus showing its action on intracellular MRSA.[25] The anti-inflammatory action of LNF is said to be because of inhibition of pro-inflammatory cytokines such as TNF-α, IL-6, IL-8 and IL-1β. The drug is also capable of killing microorganisms embedded deep in polymeric matrix of biofilms.[23,25,27]

Emergence of antimicrobial resistance (AMR): a matter of concern

The most established antibiotics that are used in treating MRSA and MSSA are mupirocin, and fusidic acid. Data from various geographical studies suggest a sharp rise in the antimicrobial resistance for both fusidic acid and mupirocin.[28]

Resistance to mupirocin, both high- and low-level, reduces the effectiveness of decolonizing strategies for *S. aureus* or MRSA. Low level mupirocin resistance (LLMR) at minimum inhibitory concentration (MIC) of 8-256 mg/l results from a point mutation in the native IleRS, and high-level mupirocin resistance (HLMR) at MIC ≥512 mg/l is mediated by the mupA (ileS-2) gene. Though LLMR isolates may initially be eradicated as effectively as susceptible isolates, but re-colonization appears to be more usual. Increased use of mupirocin has been associated with emergence of resistance.[29] As per the meta-analysis study by Poovelikunnel et al, mupirocin resistance, as high as 81% has been reported. A strong association between previous mupirocin exposure and both LLMR and HLMR has been reported. The presence of the qacA and/or qacB gene, among MRSA isolates is associated with failed decolonization, ranging from 65% to 91%.[30]

Compared to mupirocin and fusidic acid, the antimicrobial resistance of nadifloxacin is found to be low. Though marketed since 1993, nadifloxacin has not shown significant antimicrobial resistance. From 1995 to 2007, nadifloxacin at MIC 1.56 to 2 µg/ml, is found to be effective against staphylococcus and MRSA strains. With passage of time (2007-2011), the MIC of nadifloxacin remained at MIC 2 µg/Ml.[31] A Japanese study analyzed the trend of resistance of topical nadifloxacin compared to other antimicrobials; levofloxacin, clindamycin and gentamicin against *P. acnes* and *Staphylococcus* species. The strains were isolated from patients diagnosed with dermatological infections for three periods, i.e., 1996, 2000 and 2005. The MIC90 values of nadifloxacin for the four test organisms isolated in 2005 were 0.05 µg/ml; MSSA, 1.56 µg/ml; MRSA, 0.78 µg/ml; *S. epidermidis* and 0.20 µg/ml; *P. acnes*, respectively. The MIC50 values of clindamycin and gentamicin for MRSA were >100 and 25 µg/ml, respectively. The MIC50 value of gentamicin for *P. acnes* was 12.5 µg/ml, but nadifloxacin was potently active against these organisms compared to these two antibiotics and the MIC50 values of nadifloxacin were 0.05 µg/ml for MRSA and 0.20 µg/ml for *P. acnes.*[32]

Role of biofilm in developing antimicrobial resistance and its dispersal by nadifloxacin

Biofilms are surface attached multicellular communities composed of microbial cells embedded in an extracellular polymeric matrix.[33] Biofilms develop in three stages: initial attachment, wherein, an individual planktonic cell reversibly associates with a surface, and if the cell does not dissociate, it binds irreversibly to the surface; biofilm maturation, that occurs through cell division and production of the extracellular polymeric matrix; and biofilm dispersal.[34] Bacterial cells existing as biofilms can be 10–1000 times more resistant to antibiotics (Figure 5). *P. acnes,* which is frequently a causative organism for acne, is capable of forming biofilms which in turn decreases antimicrobial susceptibility. Moreover, the prolonged use of systemic antibiotic therapy results in the development of antimicrobial resistance.[33] For SSTIs, the causative microorganism in majority of cases is *S. aureus* and *S. epidermidis.* Biofilm dispersal coupled with effective antibiotic therapy could be the suitable treatment approach to treat persistent *S. aureus* infections.[34] The superiority of nadifloxacin among other antibiotics, for tackling high bacterial load makes it a suitable choice in overcoming antimicrobial resistance by killing biofilm-embedded microorganisms in acne and SSTI infections. This highly potent activity is accounted to the substitution of fluoro group at C-6 of nadifloxacin, that prevents bacterial cell multiplication (bacteriostatic at low concentrations) and cell death (bactericidal at higher concentrations) by improving its ability to bind the DNA gyrase complex (2- to 17-fold) and cell penetration (1- to 70-fold) as compared to quinolones with no substitution.[11]

Comparison of nadifloxacin with other topical antimicrobials

A study conducted to compare the effectiveness of nadifloxacin, erythromycin, clindamycin and tetracycline against *P. acnes* and CNS isolates from inflammatory lesions reported that no *P. acnes* isolates were found to be resistant to the antibiotics tested and the antibiotic resistance status among CNS isolates was 28%, 36%, 23% and 0% for tetracycline, erythromycin, clindamycin and nadifloxacin respectively. For nadifloxacin, the susceptibility of *P. acnes* and CNS isolates was shown at ≤1 µg/ml MIC level and the resistance was shown at MIC level ≥4 µg/ml. The study concluded that susceptibility of *P. acnes* and CNS isolates to nadifloxacin, makes it more effective in the treatment of acne than other antimicrobial agents.[35]

In yet another study of 90 patients, comparing topical mupirocin (2%) and fusidic acid (2%) with nadifloxacin (1%), in patients of uncomplicated bacterial infections; no statistical difference was noted in the efficacy. In addition, the study showed that nadifloxacin acts like tetracyclines in treating acne. It worked as an antioxidant by reducing the number of superoxide radical anions and hydroxyl radicals generated by neutrophils.[7]

In an open, multi-centric, and randomized comparative analysis, twice daily application of 1% nadifloxacin with 2% mupirocin and 1% framycetin, in 272 subjects, reported a significant reduction in the mean scores for bacterial infection symptoms was found in the nadifloxacin group compared to mupirocin, framycetin and fusidic acid groups at the end of 14 days. Both physicians and patients rated nadifloxacin as "excellent" on a 4-point scale.[11] In comparison of *in vitro* activity of nadifloxacin (OPC-7251) with those of ofloxacin, oxacillin, flucloxacillin, cefotiam, erythromycin, clindamycin, and gentamicin against 144-gram positive bacteria, nadifloxacin was found to be highly active against aerobic and anaerobic bacteria isolated from patients with bacterial skin infections. The MIC of nadifloxacin was 0.1 µg/ml for *S. aureus*, 0.78 µg/ml for *Streptococcus spp.* and CNS; and 0.39 µg/ml for *Propionibacterium* spp.[36] Table 3 shows the MIC values of nadifloxacin compared to other antimicrobials for common pathogens involved in SSTIs and acne vulgaris.[31] Table 4 represents the efficacy and safety of nadifloxacin in comparison to other antimicrobials.[7,11,31]

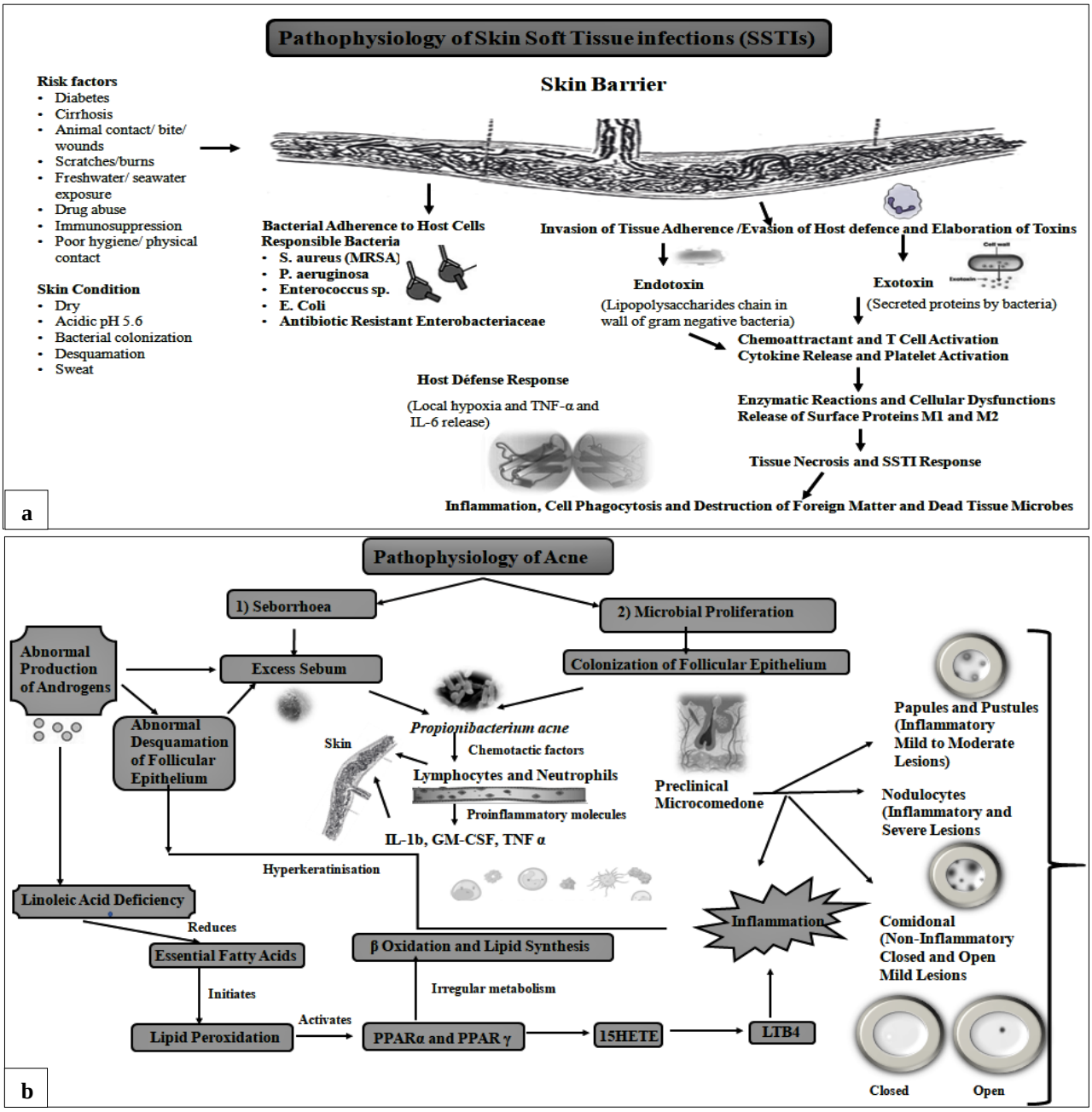

Figure 2: (a) Pathophysiology of SSTIs, and (b) pathophysiology of *Acne vulgaris.*

IL=Interleukin, MRSA=methicillin resistant *Streptococcus aureus*, SSTI=skin and soft tissue infection, TNF=tumor necrosis factor; GM-CSF=granulocyte macrophage-colony stimulating factor, HETE=5-hydroxyeicosatetraenoic acid, IL=interleukin, LT=leukotriene, PPAR=peroxisome proliferator activated receptors, TNF=tumor necrosis factor.

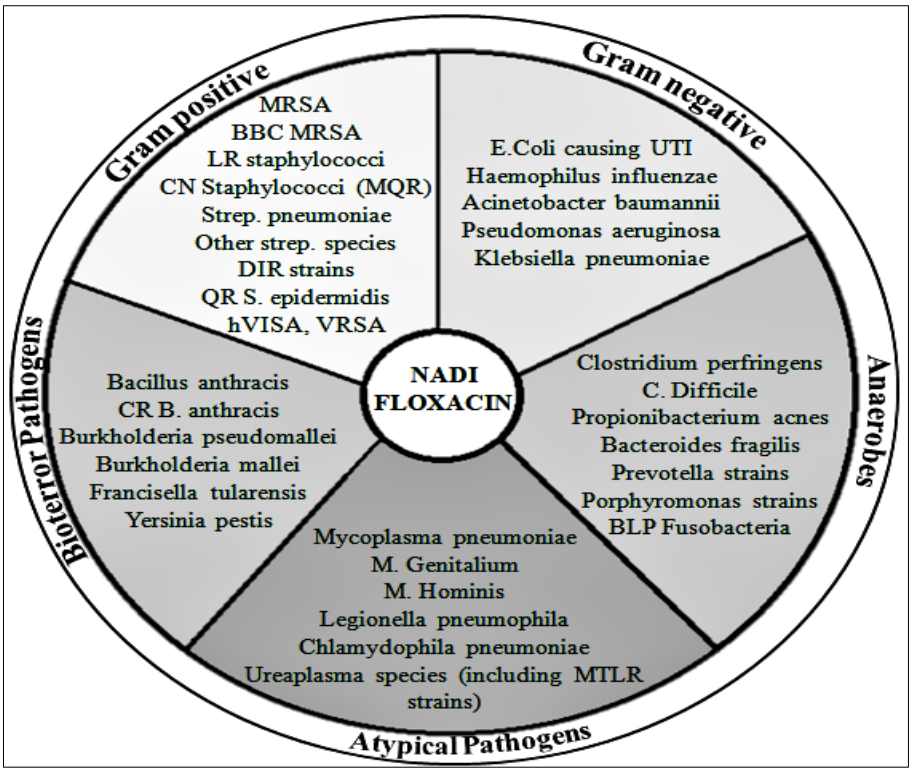

Figure 3: Spectrum of activity of nadifloxacin.

BC=Bengal Bay clone, BLP=β lactamase producing, CR=ciprofloxacin resistant, CN=coagulase-negative, DIR=daptomycin-intermediate/resistant, MQR=methicillin and/or quinolone resistant, MRSA=methicillin resistant *S. aureus*, MTLR=macrolide, tetracycline, and levofloxacin resistant strains, LR=linezolid resistant, QR=quinolone resistant, UTI=urinary tract infections, hVISA=hetero-vancomycin intermediate *S. aureus*, VRSA=vancomycin-resistant *S. aureus.*

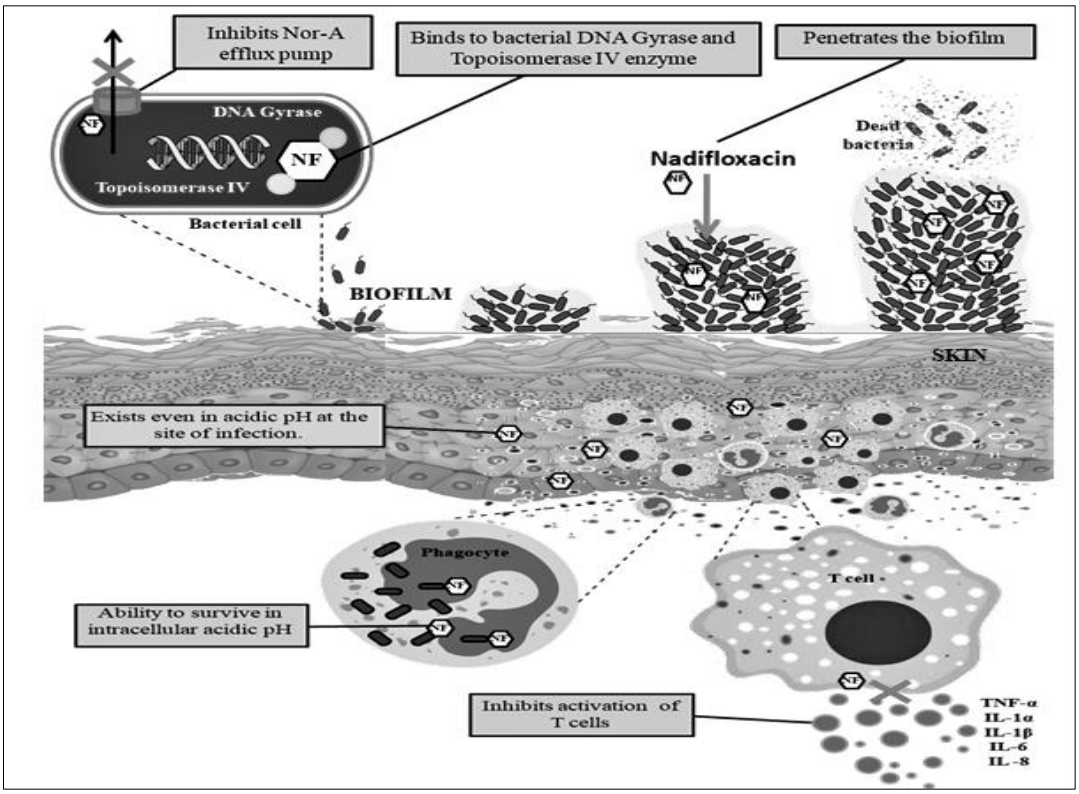

Figure 4: Mechanism of action of nadifloxacin and biofilm formation.

NF=Nadifloxacin, IL=interleukin, TNF=tumor necrosis factor.

Table 1: Current management of skin soft tissue infections (SSTIs).

Nature of infection	First line of treatment	Empirical treatment	Definitive treatment*
Abscesses, carbuncles or furuncles			
Simple infections	I and D		
Moderate non-purulent infections	I and D + culture and antibiotic sensitivity testing	TMP/SMX or DOXY topical NF**	TMP/SMX in MRSA cases dicloxacillin or cephalexin in MSSA cases
Severe non-purulent infections	I and D + culture and antibiotic sensitivity testing	VAN, daptomycin, LZD, televacin or ceftaroline	VAN, daptomycin, LZD, televacin or ceftaroline in MRSA cases nafcillin, cefazolin or CLN in MSSA cases
Recurrent abscesses	I and D	Removal of local cause decolonization with intranasal mupirocin, CHX washes, decontamination of sheets, towels and clothes	
Cellulitis/erysipelas			
Mid infections	Oral PCN VK, cephalosporin, dicloxacillin or CLIN	Topical NF**	
Moderate infections	IV PCN, ceftriaxone, cefazolin or CLIN		
Complicated infections	Oral cephalexin+ TPM/SMX cephalexin + DOXY	IV ceftriaxone, add oral TMP/SMX or DOXY if MRSA is suspected	VAN for purulent cellulitis cases
Recurrent cellulitis	Treat predisposing factors	Prophylactic PCN or erythromycin, if pre-disposing factors persist and more than 3-4 episodes occur per year	
Abscess + cellulitis	I and D + culture and antibiotic sensitivity testing	-TMP/SMX -DOXY	
Necrotizing skin infections			
Severe infections	Surgical exploration and debridement	VAN + PIP/TAZ or carbapenems	*S. pyogenes*– PCN+CLN; *S. aureus* – CLN; *Clostridial* spp.– PCN+CLN; *Vibrio vulnificus* – DOXY+ ceftazidime, *Aeromonas hydrophila* - DOXY+ ciprofloxacin; polymicrobial infections – VAN+PIP/TAZ
Resistant strains			
MRSA infections			CLN, daptomycin, LZD, teicoplanin, VAN
MRSA resistant to VAN			LZD, tedizolid, daptomycin, ceftaroline

*Definitive treatment is started based on culture and antibiotic sensitivity testing report; **NF is effective in treating uncomplicated superficial bacterial infections.[12] CHX=Chlorhexidine, CLN=clindamycin, DOXY=doxycycline, I and D=incision and drainage, LZD=linezolid, PCN=penicillin, PIP/TAZ=piperacillin/tazobactam, TMP/SMX=trimethoprim/sulphamethoxazole, VAN=vancomycin

Table 2: Current management of acne vulgaris.

Drug	Concentration/dose (%)	Mechanism of action	Advantages	Limitations
Topical therapy				
Retinoids				
Tretinoin	0.025 to 0.1	Regulation of hyper proliferation of follicular epithelial cells, reduce the	Limited solubility results in a slow and sustained release	Skin irritation, erythema, peeling, pain, lipophilic and photolabile

Continued.

Drug	Concentration/dose (%)	Mechanism of action	Advantages	Limitations
Adapalene	0.1 to 0.3	release of pro-inflammatory cytokines[19]	Best tolerability among topical retinoids	Dry skin, peeling and erythema
Tazarotene	0.05 to 0.1		Low systemic exposure	Contraindicated during pregnancy
Trifarotene	50 µg/g		Low systemic exposure, no drug-drug interaction with oral contraceptives[22]	
Antimicrobials				
Benzoyl peroxide	2.5 to 10.0	Bactericidal agent - kills *P. acnes* by releasing oxygen within the follicle	Prevents the resistance of *P. acnes* to antibiotic therapy, economical	Stronger preparations are irritating to the skin, potent bleaching agent[19]
Erythro-mycin	1-4	Binds to 50s ribosomal subunit of bacteria and disrupts protein synthesis		Resistance can develop against erythromycin
Clindamy-cin	1-4	Binds to 50s ribosomal subunit of bacteria and disrupts protein synthesis by interfering with transpeptidation reaction		Bacterial resistance may develop
Dapsone	5-7.5	Inhibits bacterial synthesis of dihydrofolic acid thereby inhibits nucleic acid synthesis	No risk for bacterial resistance	
Azelaic acid	10, 15, 20	Inhibition of bacterial protein synthesis	Decreases hyperpigmentation caused by acne, does not induce resistance in *P. acnes*	Transient burning, tingling sensation, mild erythema, pruritus
Systemic therapy				
Antibiotics				
Tetracy-cline	250–500 mg twice daily	Inhibits protein synthesis by preventing the attachment of amino acetyl-tRNA to the ribosomal acceptor (A) site	Inexpensive	Contraindicated in pregnant women or in children below nine years of age; chelated by antacids and milk; to be taken on empty stomach
Minocy-cline	50–200 mg daily	Binds to the bacterial 30S ribosomal subunit and inhibit protein synthesis	Can be taken with food	Contraindicated in pregnant women or in children below 9 years of age; adverse reactions: dizziness, pigment changes, hepatitis, lupus-like reactions
Doxycy-cline	100–200 mg daily	Binds to the bacterial 30S ribosomal subunit and inhibit protein synthesis	Can be taken with food; acceptable for use in patients with renal failure	Contraindicated in pregnant women and children <9 years of age; AE: GI upset, photo toxicity
Erythro-mycin	500 mg twice daily	Binds to the bacterial 50S ribosomal subunit and inhibits protein synthesis	Safe in pregnant women and children	May develop resistance to *P. acnes;* AE: GI upset
Trimethop rim/ sulfametho xazole	80/400 mg or 160/800 mg four times a day	Sulfamethoxazole inhibits formation of dihydrofolic acid from para-aminobenzoic (PABA),	Useful in patients resistant to other antibiotics	Contraindicated in patients with impaired liver and kidney function; AE: rash, Stevens–Johnson syndrome

Continued.

Drug	Concentration/dose (%)	Mechanism of action	Advantages	Limitations
		trimethoprim inhibits dihydrofolate reductase		
Hormonal therapy				
Oral contraceptives (estrogen+ progestin)	Varying formulations	Reduces conversion of testosterone to dihydrotestosterone thereby decreasing sebum production[21]	Reduced risk of colon, uterine, and ovarian cancer	3-6 months course is usually required, breakthrough bleeding, is often associated with missed pills, nausea, breast tenderness, slightly increased risk of breast cancer in women
Spironolac-tone	50–200 mg/day	Inhibition of the androgen receptor on sebocytes, Reduces synthesis of androgen precursors in the adrenal glands		Recurrence when it is discontinued, slow onset of action, menstrual irregularities, breast tenderness, dizziness, nausea, headache, polyuria, fatigue, hyperkalemia in patients with renal insufficiency or severe heart failure[21]
Isotretin-oin		Reduces follicular Keratinization and sebum production, decreases *P. acnes* colonization, anti-inflammatory	Recommended for severe nodular acne	Relapse following discontinuation of treatment, mucocutaneous dryness Teratogenicity, hypertriglyceridemia, pancreatitis, hepatoxicity, blood dyscrasias, hyperostosis, premature epiphyseal closure, erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis[19,21]

Table 3: Comparison of MIC values of various antimicrobials with nadifloxacin.

MIC (mg/ml)	Nadifloxa-cin		Ciproflo-xacin		Ofloxacin		Levofloxa-cin		Clindamy-cin		Erythro-mycin		Gentam-ycin	
Organism	**MIC$_{50}$**	**MIC$_{90}$**	**MIC$_{50}$**	**MIC$_{90}$**	**MIC$_{50}$**	**MIC$_{90}$**	**MIC$_{50}$**	**MIC$_{90}$**	**MIC$_{50}$**	**MIC$_{90}$**	**MIC$_{50}$**	**MIC$_{90}$**	**MIC$_{50}$**	**MIC$_{90}$**
P. acnes	0.06-0.125	0.25-1.0	0.5-1.0	0.5->16	0.78	1.56	0.39	0.78	0.06-0.125	0.125->32	0.06-0.125	0.06->32	6.25	12.5
MSSA	0.015-0.5	0.03-2.0	0.25-0.5	1.0-4.0	0.39	0.78	0.2	0.39	0.06	0.2	0.25-0.5	>100	0.39	100
MRSA	1.0	2.0	>64	>64	50	50	25	25	0.125->32	>32	>32	>32	25	100
S. epidermidis	0.015-0.03	0.5	0.25	16-64	0.39	0.39	0.2	0.2	0.125	>32	128-256	>256	0.1	50
P. aeruginosa	3.13	12.5			0.78	3.13	0.39	3.13	>100	>100	>100	>100	1.56	12.5
S. pyogenes	0.39	0.78			0.78	3.13	0.39	1.56	0.05	0.1	0.025	0.05	0.78	12.5

MIC=Minimum inhibitory concentration, MRSA=methicillin resistant *S. aureus*, MSSA=methicillin sensitive *S. aureus*.

Table 4: Studies showing the efficacy and safety of nadifloxacin.

Author (year)	Type of study	Sample size	Method	Result
Alba et al (2009)[31]	Comparative study	811; clinical isolates of *P. acnes*, MRSA,	Nadifloxacin activity versus ciprofloxacin, erythromycin and clindamycin	Nadifloxacin performed better than the comparator drugs; moreover, study reported that nadifloxacin possesses better activity against strains of *P. acnes* than other test antibiotics as the MIC50 and MIC90 values for

Continued.

Author (year)	Type of study	Sample size	Method	Result
		MSSA and CoNS		nadifloxacin were lesser than those of other antibiotics
Jung et al. (2011)[27]	Prospective, randomized, double blind trial	34	1% nadifloxacin on half of face and vehicle cream on other half of face	70% reduction in inflammatory acne was observed with 1% nadifloxacin and 13.5% increase was noted with vehicle cream; study concluded that 1% nadifloxacin cream is an effective, safe well tolerated treatment for mild to moderate acne
Narayanan et al (2014)[11]	Open, multicentric, RCT and post market analysis	272	1% nadifloxacin versus 2% mupirocin and 1% framycetin	Significant reduction in the mean scores for bacterial infection symptoms was found in the nadifloxacin group compared to mupirocin, framycetin and fusidic acid groups at the end of 14 days. Both physicians and patients rated nadifloxacin as "excellent" on a 4-point scale; no adverse events were reported in clinical studies
Vasani et al (2015)[7]	RCT	90	1% nadifloxacin versus 2% mupirocin versus 2% fusidic acid	Nadifloxacin was found to be equally efficacious as mupirocin and fusidic acid. However, fusidic acid showed faster improvement at the end of first week; no adverse events were reported in any of the groups

Safety of nadifloxacin

Nadifloxacin is safe and well tolerated.[11,20,37] A multi-centric post marketing surveillance study reported only 0.6% of study population with burning and itching, when twice daily application of topical nadifloxacin was used in treating bacterial skin infections. In addition to this, post market no major side effects were recorded.[11] No substantial intolerance reactions were observed with topical nadifloxacin (1%) used in combination with other topical anti-acne agents such as benzoyl peroxide, azelaic acid and isotretinoin, tretinoin, and adapalene.[20,37] Most of the reported adverse events were mild to moderate such as, dry skin exfoliation, skin irritation, pruritus, and burning sensation, which were resolved spontaneously. Kaur et al demonstrated that 2.5% benzoyl peroxide gel plus 1% nadifloxacin cream showed a better safety profile compared to combination of 1% clindamycin with 2.5% benzoyl peroxide or 0.025% tretinoin.[38] Jung et al observed reduced inflammation and IL-8 expression in histopathological examinations of acne lesions in Korean patients after 8 weeks of using 1% nadifloxacin cream compared to vehicle-treated skin.[27] A non-interventional trial conducted in Germany at 105 dermatological centers, studied nadifloxacin as a monotherapy and in combination with other topical agents. A slightly better appraisal (82.1%) was obtained for topical nadifloxacin monotherapy compared to combination therapy (77.5%).[39]

The safety profile of nadifloxacin is also established in pediatric population. An Indian study compared topical nadifloxacin 1% ointment with mupirocin 1% ointment in 60 children less than 12 years of age for SSTI. The drug was found to be equally efficacious and safe compared to mupirocin. In another study, use of topical nadifloxacin cream was found safe for atopic dermatitis caused by MRSA in 18 children.[40]

CONCLUSION

Topical nadifloxacin has demonstrated promising results in the treatment of SSTIs and mild to moderate acne vulgaris. The drug has an established safety and efficacy profile in clinical studies. Its unique dual mechanism of action, ability to survive in acidic pH, low antibiotic resistance and superior action against biofilms makes it a potential empirical therapy for the management of SSTIs and acne.

ACKNOWLEDGEMENTS

Authors would like to thank Knowledge Isotopes Pvt. Ltd. for the medical writing support provided for the manuscript.

Funding: The study was funded by Dr. Reddy's Laboratories
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Sartelli M, Guirao X, Hardcastle TC, Kluger Y, Boermeester MA, Raşa K, et al. 2018 WSES/SIS-E consensus conference: Recommendations for the management of skin and soft-tissue infections. World J Emerg Surg. 2018;13(1):1-24.

2. Nathwani D, Dryden M, Garau J. Early clinical assessment of response to treatment of skin and soft-tissue infections: how can it help clinicians? Perspectives from Europe. Int J Antimicrob Agents. 2016;48(2):127-36.
3. Talan DA, Krishnadasan A, Gorwitz RJ, Fosheim GE, Limbago B, Albrecht V, et al. Comparison of staphylococcus aureus from skin and soft-tissue infections in us emergency Department patients, 2004 and 2008. Clin Infect Dis. 2011;53(2):144-9.
4. Ki V, Rotstein C. Bacterial skin and soft tissue infections in adults: A review of their epidemiology, pathogenesis, diagnosis, treatment and site of care. Can J Infect Dis Med Microbiol. 2008;19(2):173-84.
5. Kaye KS, Petty LA, Shorr AF, Zilberberg MD. Current epidemiology, etiology, and burden of acute skin infections in the United States. Clin Infect Dis. 2019;68(3):S193-9.
6. Abhilash KPP, Varghese S. Profile and outcome of patients presenting with skin and soft-tissue infections to the emergency department. Curr Med Issues. 2019;17(2):30.
7. Vasani, Medhekar SV. Topical 2% mupirocin versus 2% fusidic acid versus 1% nadifloxacin cream in the treatment of superficial bacterial infections of the skin. Indian J Drugs Dermatol. 2015;1(1):16.
8. Titus S, Hodge J. Diagnosis and treatment of acne. Am Fam Physician. 2012;86(8):734-40.
9. Abbafati C, Machado DB, Cislaghi B. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-22.
10. Bhagwat SS, Nandanwar M, Kansagara A, et al. Levonadifloxacin, a novel broad-spectrum anti-MRSA benzoquinolizine quinolone agent: Review of current evidence. Drug Des Devel Ther. 2019;13:4351-65.
11. Narayanan V, Motlekar S, Kadhe G, Bhagat S. Efficacy and Safety of Nadifloxacin for Bacterial Skin Infections: Results from Clinical and Post-Marketing Studies. Dermatol Ther (Heidelb). 2014;4(2):233-48.
12. Silverberg B. A Structured Approach to Skin and Soft Tissue Infections (SSTIs) in an Ambulatory Setting. Clin Pract. 2021;11(1):65-74.
13. Thurlow LR, Joshi GS, Richardson AR. Peroxisome Proliferator-Activated Receptor γ Is Essential for the Resolution of Staphylococcus aureus Skin Infect. Cell Host Microbe. 2018;24(2):261-70.
14. Leong HN, Kurup A, Tan MY, Kwa ALH, Liau KH, Wilcox MH. Management of complicated skin and soft tissue infections with a special focus on the role of newer antibiotics. Infect Drug Resist. 2018;11:1959-74.
15. Gollnick HPM. From new findings in acne pathogenesis to new approaches in treatment. J Eur Acad Dermatol Venereol. 2015;29:1-7.
16. Tan JKL, Stein Gold LF, Alexis AF, Harper JC. Current concepts in acne pathogenesis: Pathways to inflammation. Semin Cutan Med Surg. 2018;37(3 S):S60-2.
17. Stevens D, Bisno A, Chambers H, Dellinger E, Goldstein E, Gorbach S. Stevens DL - 2014.pdf. Clin Infect Dis. 2014;59(2):e10-52.
18. Patankar S. Changing trends in abscess management. Med J Dr DY Patil Univ. 2014;7(6):747.
19. Kraft J, Freiman A. Management of acne. Cmaj. 2011;183(7).
20. Shah BJ, Sumathy TK, Dhurat RS. Efficacy and tolerability of topical fixed combination of nadifloxacin 1% and adapalene 0.1% in the treatment of mild to moderate acne vulgaris in indian patients: A multicenter, open-labelled, prospective study. Indian J Dermatol. 2014;59(4):385-9.
21. Barbieri JS, Spaccarelli N, Margolis DJ, James WD. Approaches to limit systemic antibiotic use in acne: Systemic alternatives, emerging topical therapies, dietary modification, and laser and light-based treatments. J Am Acad Dermatol. 2019;80(2):538-49.
22. Wagner N, Benkali K, Alió Sáenz A, Poncet M, Graeber M. Clinical Pharmacology and Safety of Trifarotene, a First-in-Class RARγ-Selective Topical Retinoid. J Clin Pharmacol. 2020.
23. Bakthavatchalam YD, Rao SV, Isaac B. infections. Indian J Med Microbiol. 2019;37:478-87.
24. Saxena D, Kaul G, Dasgupta A, Chopra S. Levonadifloxacin arginine salt to treat acute bacterial skin and skin structure infection due to S. aureus including MRSA. Drugs of Today. 2020;56(9):583-98.
25. Choudhury S, Chatterjee S, Sarkar DK, Dutta RN. Efficacy and safety of topical nadifloxacin and benzoyl peroxide versus clindamycin and benzoyl peroxide in acne vulgaris: A randomized controlled trial. Indian J Pharmacol. 2011;43(6):628-31.
26. Dubois J, Dubois M. Levonadifloxacin (WCK 771) exerts potent intracellular activity against Staphylococcus aureus in THP-1 monocytes at clinically relevant concentrations. J Med Microbiol. 2019;68(12):1716-22.
27. Jung JY, Kwon HH, Yeom KB, Yoon MY, Suh DH. Clinical and histological evaluation of 1% nadi?oxacin cream in the treatment of acne vulgaris in Korean patients. Int J Dermatol. 2011;50(3):350-7.
28. Peng K-T, Huang T-Y, Chiang Y-C. Comparison of Methicillin-Resistant Staphylococcus aureus Isolates from Cellulitis and from Osteomyelitis in a Taiwan Hospital, 2016–2018. J Clin Med. 2019;8(6):816.
29. Hetem DJ, Bonten M. Clinical relevance of mupirocin resistance in Staphylococcus aureus. J Hosp Infect. 2013;85(4):249-56.
30. Poovelikunnel T, Gethin G, Humphreys H. Mupirocin resistance: Clinical implications and potential alternatives for the eradication of mrsa. J Antimicrob Chemother. 2015;70(10):2681-92.
31. Alba V, Urban E, Angeles Dominguez M. In vitro activity of nadifloxacin against several Gram-

positive bacteria and analysis of the possible evolution of resistance after 2 years of use in Germany. Int J Antimicrob Agents. 2009;33(3):272-5.
32. Matsuzaki K, Omika K, Hasegawa M, Sato Y, Kobayashi I. Antibacterial activity of nadifloxacin against Staphylococcus and Propionibacterium isolated from patients with dermatological infections. Jpn J Antibiot. 2006;59(4):316-20.
33. Coenye T, Brackman G, Rigole P. Eradication of Propionibacterium acnes biofilms by plant extracts and putative identification of icariin, resveratrol and salidroside as active compounds. Phytomed. 2012;19(5):409-12.
34. Lister JL, Horswill AR. Staphylococcus aureus biofilms: Recent developments in biofilm dispersal. Front Cell Infect Microbiol. 2014;4:1-9.
35. Doğan B, Bektöre B, Karabacak E, Özyurt M. Resistance status of antibiotics in Gram-positive bacteria isolated from acne lesions in Istanbul. Turkderm Deri Hast ve Frengi Ars. 2017;51(2):32-6.
36. Nenoff P, Haustein UF, Hittel N. Activity of nadifloxacin (OPC-7251) and seven other antimicrobial agents against aerobic and anaerobic Gram-positive bacteria isolated from bacterial skin infections. Chemotherapy. 2004;50(4):196-201.
37. Wilhelm KP, Wilhelm D, Neumeister C, Zsolt I, Schwantes U. Lack of irritative potential of nadifloxacin 1% when combined with other topical anti-acne agents. Clin Exp Dermatol. 2012;37(2):112-7.
38. Kaur J, Sehgal V, Gupta A, Singh S. A comparative study to evaluate the efficacy and safety of combination topical preparations in acne vulgaris. Int J Appl Basic Med Res. 2015;5(2):106-10.
39. Schöfer H, Göllner A, Kusche W, Schwantes U. Effectiveness and tolerance of topical nadifloxacin in the therapy of acne vulgaris (grade I-II): Results of a non-interventional trial in 555 patients. J Appl Res. 2009;9(3):44-51.
40. Kimata H. Effect of nadifioxacin on atopic dermatitis with methicillin-resistant Staphylococcus aureus in young children. Eur J Pediatr. 1999;158(11):949.

Cite this article as: Muchhala S, Sarkar R, Lahiri K, Kharkar RD, Rathod R. Management of skin and soft-tissue infections and acne with topical nadifloxacin: a comprehensive review. Int J Res Dermatol 2022;8:551-63.