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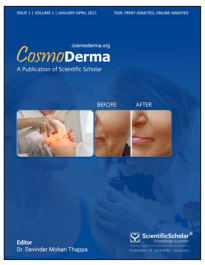

Review Article

Role of topical nadifloxacin as an empirical treatment in patients with skin and soft-tissue infections in India: A review and consensus

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ABSTRACT

Dermatologists often come across cases of skin and soft-tissue infections (SSTIs) which have diverse clinical presentations. Various local, systemic, and environmental risk factors predispose an individual to develop SSTIs. Topical antimicrobial agents are frequently used in superficial uncomplicated SSTIs, whereas systemic therapy is generally reserved for use in severe cases. However, emergence of resistance to these agents is becoming a common problem in clinical practice. This necessitates the use of other classes of antimicrobials for the effective treatment of SSTIs. Nadifloxacin, a potential drug belonging to the fluoroquinolone group, has various advantages such as binding to bacterial DNA gyrase and topoisomerase IV enzymes, inhibition of nor-A efflux pump, survival in acidic pH, anti-MRSA activity, and biofilms penetration. It has also shown least development of resistance since its introduction. Although its topical formulation has shown superior efficacy as an anti-acne agent, there are no specific guidelines for its appropriate use in SSTIs. Hence, a panel of experts was formed, under whose guidance an extensive literature search was performed in MEDLINE, Cochrane Library, and Science Direct databases. Using the modified Delphi technique, the available evidence was reviewed and corresponding recommendations were given for the use of topical Nadifloxacin as an empirical treatment in SSTIs.

Keywords: Biofilms, Delphi technique, Fluoroquinolones, Nadifloxacin, Risk factors, Soft Tissue infections

INTRODUCTION

Skin and soft tissue infections (SSTIs) constitute a group of clinically diverse infections ranging from minor superficial infections, to life-threatening infections like necrotizing fasciitis. Due to their clinically diverse presentation, an accurate assessment is quite challenging.[1-3] As per the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, the total number of patient visits due to SSTIs, increased from 8.6 million in 1997 to 14.2 million in 2005, whereas the incidence increased from 32.1 visits/1000 population in 1997 to 48.1 visits/1000 population in 2005, in the United States.[4] Larru and Gerber (2014) suggested

that an increase in SSSI rates is mainly accredited to the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA).[5]

In India, there are minimal data on the prevalence of SSTIs and only few studies have been done till date[6-8] with one study reporting an incidence rate of 18.21/1000 person years in a tertiary care hospital in South India.[9] Topical Mupirocin and Fusidic acid are widely used in the treatment of SSTIs. However, emergence of resistance against these drugs marks the need for newer antibiotics which have a broad spectrum of activity with lesser chance of the development of antimicrobial resistance in the future.[10-16] One such prospective drug, Nadifloxacin, a fluoroquinolone, has been approved in India as an anti-acne agent and in superficial localized bacterial skin infections,[17] but there are no guidelines available for the appropriate usage of topical Nadifloxacin in SSTIs. Hence, this consensus document was developed to review the available evidence and make recommendations for the use of topical Nadifloxacin as an empirical treatment in SSTIs.

AGENDA FOR THE CONSENSUS

The primary motive of this consensus document is to critically review the prevalence, diagnosis, and standard of care of SSTIs in India and to discuss the role of Nadifloxacin, as a topical antibiotic in the empirical treatment of SSTIs. This consensus will help dermatologists in the management of SSTIs and will in turn improve patient outcomes.

MATERIAL AND METHODS

A panel of nine expert dermatologists and cosmetologists, from different parts of India, with more than 20 years of experience in clinical dermatology was formed. After initial discussion with the experts, literature search was conducted focusing on the SSTIs and the role of topical Nadifloxacin as an empirical treatment in patients with SSTIs in India, based on which, a set of 13 statements were prepared, which were to be discussed in the expert panel meeting.

An extensive literature search was done using the key words provided by the experts – "ABSSTI," "antibiotic resistance," "biofilms," "cSSTI," "levonadifloxacin," "MRSA," "nadifloxacin," "OPC-7251," "SSTI," "topical," and "uSSTI," in MEDLINE, Cochrane Library, and Science Direct databases to identify relevant articles. Full articles published in English and in peer-reviewed and indexed journals were selected.

The panel of experts met in April 2021 in a virtual meeting, during which the modified Delphi method was used to arrive at a consensus.[18] Following presentation of evidence and a thorough discussion among the experts, they were asked to provide their opinion in the form of vote, for each of the 13 statements in an anonymous unbiased manner. A 5-point Likert scale ranging from strongly disagree, disagree, neutral, agree to strongly agree, was used to record the level of agreement or disagreement to the set of statements.

RESULTS

The responses of the panelists were calculated by means of percentages. The responses were considered to have a consensus based on a majority of two-thirds vote (≥66.67%). Only items that had failed to reach a consensus were to be included in the next round. Since during our meeting, a consensus was formed, another round was not needed. The discussion points were compiled and sent to all the panelists for review. The percentages of agreement and the recommendations suggested by them are displayed in [Table 1].

DISCUSSION

Statement 1: Prevalence of SSTIs in India range from 17% to 25%

In India, only few studies have been done in a limited population. As per Abhilash and Varghese (2019), the incidence rate of SSTI in a tertiary care hospital in South India was 18.21/1000.[9] In another study in Northern India, among 6–14-year-old school children, the prevalence of skin infections was 11.4%, among whom 64.4% had pyodermas, 25.4% fungal infections, 9.7% viral infections, and 0.4% had mycobacterial infections.[19] Vasani and Medhekar reported that among superficial bacterial skin infections, furuncle was most common (59.70%), followed by folliculitis (4.4%).[8] Similar findings were reported in other studies which revealed that furunculosis was the most common type of pyoderma (51%), followed by impetigo (21%), folliculitis (19%), sycosis barbae (5%), carbuncle (3%), and ecthyma (1%).[20]

Statement 2: The most common microorganism causing SSTIs is *S. aureus*

Bacteria that colonize the skin can be broadly divided into two groups: Resident flora and transient flora. Resident flora includes *Staphylococcus* spp. such as *Staphylococcus epidermidis*, *Staphylococcus saccharolyticus*, *Staphylococcus saprophyticus*, and *Staphylococcus anginosus*; *Streptococcus spp*. such as *Streptococcus mitis* and *Streptococcus mutans*; and *Propionibacterium granulosum*, *Propionibacterium acnes*, etc. Whereas, the transient flora includes Gram-positive species such as *S. aureus*, *Staphylococcus warneri, Streptococcus pyogenes*, and *Corynebacterium minutissimum*, and Gram-negative species such as *Escherichia coli, Proteus mirabilis,* and *Pseudomonas aeruginosa*.[1] SSTIs are largely

Table 1: Percentage of agreement obtained for statements 1–13 and corresponding expert panel recommendations.

Point of discussion	% Agreement	Expert panel recommendations
Statement 1 Prevalence of SSTIs in India range from 17% to 25%	87.5%	All of the experts agreed that there is a paucity of data regarding the prevalence of SSTIs in India and it varies from region to region. They suggested that more extensive studies are required with precisely defined disease criteria, to identify the burden of disease in India.
Statement 2 The most common microorganism causing SSTIs is *Staphylococcus aureus*	100%	The experts suggested that there is a misuse of topical antibiotics because they are prescribed based on microbiological swab culture report. There is a need to differentiate between a wound that is truly infected and wounds colonized with resident microbial flora. Since a majority of chronic wounds are colonized with at least one bacterial species, the antibiotic prescription should be based even on clinical judgment rather than only microbiological analysis.
Statement 3 MRSA is now becoming a common cause of SSTIs in India with a prevalence ranging from 18-59%	100%	MRSA prevalence has been increasing in India, probably due to the easy availability of over-the-counter drugs and indiscriminate usage amongst the general public (self-medication). Suggestions were made to form a national regulatory agency which prevents the sale of over-the-counter high-end/reserve antibiotics.
Statement 4 Risk factors for SSTIs include presence of systemic co-morbidities, malnutrition, vascular insufficiency, trauma, fungal infections, old age, obesity, drug abuse, poor skin hygiene, etc.	100%	The experts suggested assessment of pre-treatment risk factors before starting the treatment. Improvements in environmental sanitation, creating awareness among the general public about the importance of good nutrition and personal hygiene should also be done.
Statement 5 SSTIs are more common in upper (25.2%) and lower extremities (23.7%)	75%	Some of the experts mentioned that SSTIs of the face are becoming increasingly common nowadays in their clinical practice. They suggested that though the microbiota of the human body is different at different sites of the body, the management of SSTIs largely depends on the morphology and microbiology of the lesions, rather than the site of infection, except in the case of acne vulgaris. As the nasal mucosa acts as a carrier site for many pathogens, intra-nasal triple antibiotic ointment may be needed for nasal decolonization.
Statement 6 In cases where superficial SSTIs are associated with co-morbid conditions, we need to treat them as moderate SSTIs	87.5%	Presence of systemic co-morbidities in patients with SSTIs affects the progression and severity of the disease.
Statement 7 Mild SSTIs are mostly treated by topical antimicrobials, whereas moderate and severe SSTIs requires both systemic and topical antimicrobial agents	100%	Topical agent can be utilized as primary therapy for mild infections or as a supportive therapy to systemic antibiotics for moderate and severe infections.
Statement 8 Mupirocin resistance is increasing in India	75%	Most of the experts admitted that they regularly come across cases of Mupirocin resistance in the clinical setting. Hence it should be preserved as a second line of treatment.
Statement 9 Efficacy of Nadifloxacin is equivalent to Mupirocin and Fusidic acid. Safety is also well established	100%	Experts agreed that Nadifloxacin is efficient is treating SSTIs and suggested that it can be the drug of choice in treating SSTIs occurring in sensitive areas, such as mucosal and perineal regions, where Mupirocin cannot be used. Any reports of skin irritation reported due to Nadifloxacin are mostly due to the other ingredients such as parabens, rather than the Nadifloxacin molecule *per se.*

(Contd...)

Table 1: *(Continued).*

Point of discussion	% Agreement	Expert panel recommendations
Statement 10 Nadifloxacin MIC is least as compared to other topical antimicrobials	87.5%	Nadifloxacin is superior to many other antimicrobial agents. However, there is need to watch for the development of cross-resistance to other organisms with the use of Nadifloxacin, such as in systemic antibiotic therapy.
Statement 11 Nadifloxacin is beneficial in managing MRSA infections	100%	The bactericidal action of Nadifloxacin against intracellular MRSA offers a major advantage over other antimicrobials in treating SSTIs.
Statement 12 Combination of Nadifloxacin and Adapalene has shown promising results in the management of acne vulgaris	100%	Experts recommend the use of Nadifloxacin in combination in Benzoyl peroxide in order to prevent the further development of antimicrobial resistance.
Statement 13 Nadifloxacin has a unique property of penetrating the biofilm and henceforth less resistance has developed over the years	87.5%	As other mechanisms also exist for the development of resistance, there may be emergence of resistance to Nadifloxacin in the future, if it is not used judiciously. Due to availability of systemic forms of Nadifloxacin, there are higher chances of resistance development.

SSTIs: Skin and soft tissue infections, MRSA: Methicillin-resistant *Staphylococcus aureus*

caused by *Staphylococcus* spp. which form purulent lesions (e.g., abscesses), whereas, lesions caused by *S. pyogenes* are non-purulent (e.g., cellulitis and erysipelas).[5]

Microbiology of pus cultures from SSTI lesions in Indian patients showed that the most common organisms were *S. aureus*, followed by *E. coli*, *Streptococcus* spp., *Pseudomonas* spp. and Coagulase negative staphylococci (CNS).[9,21-26] [Table 2] shows the common isolates from SSTIs across India.

Statement 3: MRSA is now becoming a common cause of SSTIs in India with a prevalence ranging from 7.5% to 59%

Studies across India have reported prevalence of MRSA to be ranging from 7.5% to as high as 90.77% in isolates from SSTIs.[21-23,27-29] MRSA infections are difficult to treat, as some strains produce biofilms.[30] In fact, few studies have found the prevalence of biofilm-producing MRSA to be as high as 78.8%.[31] These wide variations could be attributed to the differences in risk factors, infection control practices, prescription practices of antibiotics and antibiotic stewardship programs.

Statement 4: Risk factors for SSTIs include presence of systemic co-morbidities, malnutrition, vascular insufficiency, trauma, fungal infections, old age, obesity, drug abuse, poor skin hygiene

The presence of systemic comorbidities such as diabetes mellitus, peripheral vascular disease, malnutrition, HIV, and immunosuppression, may increase the risk of developing SSTIs.[1] Local risk factors include anatomical alterations, fungal infections, infected wounds, inflammatory dermatoses, poor skin hygiene, pressure sores, repeated trauma, and vascular. Environmental risk factors include animal/human bite, close contact with infected person, invasive medical procedures, intravenous, or subcutaneous drug abuse.[1,3] In developing countries like India, other aspects such as low socioeconomic status, malnutrition, overcrowding, and poor hygienic conditions, may predispose the individuals for the development of SSTIs.[8,19] Hence, the experts recommended that meticulous assessment of pre-treatment risk factors is essential while treating patients presenting with SSTIs.

Statement 5: SSTIs are more common in upper (25.2%) and lower extremities (23.7%)

SSTIs are found to affect all parts of the body, especially the limbs. Stahlman *et al*. (2017) reported that the upper extremity was most frequently affected (25.2%), especially the arm (50.6%) and finger (40.1%). Lower extremities were affected in 23.7% of the cases.[32] This is in contrast to a study done by Abhilash and Varghese (2019), who reported that lower limb (75.07%) was the most common site, followed by gluteal/perianal/genital regions (8.50%); trunk (7.08%); upper limb (4.82%); and head and neck regions (4.53%).[9] Various other studies reported the most common site to be the lower extremities[20,33] and face.[34]

Statement 6: In cases where superficial SSTIs are associated with co-morbid conditions, we need to treat them as moderate SSTIs

The Infectious Disease Society of America (IDSA) 2014 has classified SSTIs based on the degree of severity into

Table 2: Prevalence of microorganisms causing SSTIs in India.

	Karnataka (Chavan and Thilagavathy, 2020)[21]	Tamil Nadu (Abhilash and Varghese, 2019)[9]	Odisha (Mohanty and Pal 2017)[23]	Rajasthan (Sharma and Gupta, 2016) [26]	Karnataka (Afroz *et al.*, 2015) [25]	New Delhi (Mohanty *et al.*, 2004)[22]
S. *aureus*	75.5%	-	23%	37.5%	Gram positive cocci - 42.59% (*S. aureus* - 82.6%	38.05%
MRSA	17.9% (among *S. aureus*)	5.8%	90.7% (among *S. aureus*)	40.25% (among *S. aureus*)	MRSA - 73.65% among *S. aureus*)	-
MSSA	82.1% (among *S. aureus*)	9.88%	-	59.75% (among *S. aureus)*	Gram neg. bacilli - 57.4%	-
VRSA	-	-	14.8% (among *S.* aureus)	-		-
Staphylococcus epidermidis/CNS	-	4.65%	-	13%	-	5.5%
Streptococcus spp.	-	8.72%	-	2%	-	-
β hemolytic streptococci (Group A)	-	-	-	-	-	0.18%
Streptococcus pneumoniae	-	-	-	-	-	0.03%
Streptococcus pyogenes	14%	-	-	-	-	-
Escherichia coli	5.5%	4.65%	-	17%	17.5% (among gram negative)	17.39%
Klebsiella spp.	5%	1.16%	-	4%	-	6.72%
Pseudomonas spp.	-	4.07% (*Pseudomonas aeruginosa*)	-	12%	21% (among gram negative)	11.82%
Mixed flora	-	38.37%	-	-	-	-

SSTIs: Skin and soft tissue infections, CNS: Coagulase Negative Staphylococci, MRSA: Methicillin-Resistant *Staphylococcus aureus*, MSSA: Methicillin Sensitive *Staphylococcus aureus,* VRSA: Vancomycin Resistant *Staphylococcus aureus*, *S. aureus: Staphylococcus aureus*

three categories. Mild infections are those with superficial involvement. Moderate Class A includes erysipelas, cellulitis, purulent skin and soft infections and traumatic wounds, whereas moderate Class B additionally includes systemically unwell patients. Severe category involves sepsis, life threatening, and necrotizing infections.[35] Patients with systemic co-morbidities need special treatment as such conditions may impact the progression and the course of SSTIs. The presence of fever, hypotension, tachycardia, site of lesion, and altered mental status represent systemic toxicity.[2]

Statement 7: Mild SSTIs are mostly treated by topical antimicrobials, whereas moderate and severe SSTIs require both systemic and topical antimicrobial agents

Topical antimicrobials render several advantages over systemic agents such as availability of high local drug concentration, less systemic absorption and toxicity, reduced risk of development of antibiotic resistance, and higher likelihood of compliance.[36,37] They may also be used to hasten the healing process, minimize the spread of infection and to prevent re-infection.[8] Evidence supports the use of topical antibiotics for infected ischemic wounds and burn wounds which have no vascular supply, in persistent wounds for removal of biofilms and to eradicate multidrug resistant organisms.[38]

Superficial uncomplicated SSTIs (impetigo, localized infected eczemas, and acne vulgaris), staphylococcal nasal carriage and post-operative surgical wounds[39] can be managed with topical antibiotic agents, heat packs or incision and drainage.[1] Whereas, systemic antibiotic therapy is required if the lesions are deep (furunculosis and carbunculosis) or generalized, with involvement of regional lymph nodes, and presence of systemic toxicity.[8,40]

According to the guidelines developed by IDSA, for diabetic foot infections, the use of topical antibiotics is recommended in mildly infected open wounds and superficial SSTIs such as venous stasis ulcers, low-grade pressure ulcers, abrasions, limited surgical wounds, inflammatory skin disorders (e.g., eczema), or limited thermal burns.[35] Thus, experts proposed the use of topical agents either as primary therapy for superficial mild infections or as supportive therapy to systemic antibiotics for moderate or severe infections. [Figure 1] shows the management of SSTIs based on the degree of severity of disease.[8,35,41]

Statement 8: Mupirocin resistance is increasing in India

Mupirocin is regularly prescribed in the prevention and treatment of SSTIs caused by *S. aureus*.[42] In India, Mupirocin alone and in combination with topical corticosteroids is approved for treating atopic and inflammatory dermatitis with secondary bacterial infections.[17] However, there has been emergence of antimicrobial resistance to Mupirocin in many parts of the world due to its increased usage.[15,37,43] Low level Mupirocin resistance results from a point mutation in the native isoleucyl RNA synthetase gene, *IleRS* and high-level Mupirocin resistance is mediated by the *mupA (ileS-2)* gene.[44] Various studies have also reported the increasing Mupirocin resistance in India[10-14] [Table 3].

Fusidic acid is another commonly used topical agent for skin infections. In India, Fusidic acid is approved as eye drops for treating bacterial infections but there is no regulatory approval in the public domain for its usage in treating skin infections. Although its combination with corticosteroids is approved in treating dermatoses with secondary infection; and in acute and chronic infected eczematous dermatitis.[17] Increase in antimicrobial resistance of Fusidic acid has also been noted due to its increased utilization ranging from 0.4% to 57%.[37] In India, Nagarajan *et al*. (2012) isolated *S. aureus* strains from skin infections and found that 3.7% of total isolates were Fusidic acid resistant *S. aureus* and harbored the *fusC* gene.[28]

Nadifloxacin is a broad-spectrum antibiotic, which has been approved in India as an anti-acne agent and in treating superficial localized bacterial skin infections. A combination of Nadifloxacin and corticosteroids is approved in bacterial infections of the skin including contact dermatitis, seborrheic dermatitis, infective eczema, and mixed infections of the skin.[17] Studies on Nadifloxacin have shown no increase in resistance to *P. acnes*, Methicillin Sensitive *S. aureus* (MSSA), MRSA, and *S. epidermidis*.[45-49] This is due to its unique dual

Table 3: Studies showing prevalence of Mupirocin resistance against *S. aureus* isolates in India.

Author	Year	Microorganism	Percentage of resistant strains
Gadepalli *et al*.[10]	2007	*S. aureus*	1% (L), 5% (H)
Jayakumar *et al*.[11]	2013	*S. aureus*	3.3–1.32% (L), 1.98% (H)
		MRSA	2.2% (H)
Chaturvedi *et al*.[13]	2014	MRSA	46.7% (L), 53.3% (H)
Rudresh *et al*.[12]	2015	*S. aureus*	17% (L), 8.2% (H)
Agarwal *et al*.[14]	2015	MRSA	25% (L), 75% (H)

H: High level resistance, L: Low level resistance. *S. aureus: Staphylococcus aureus,* MRSA: Methicillin-Resistant *Staphylococcus aureus*

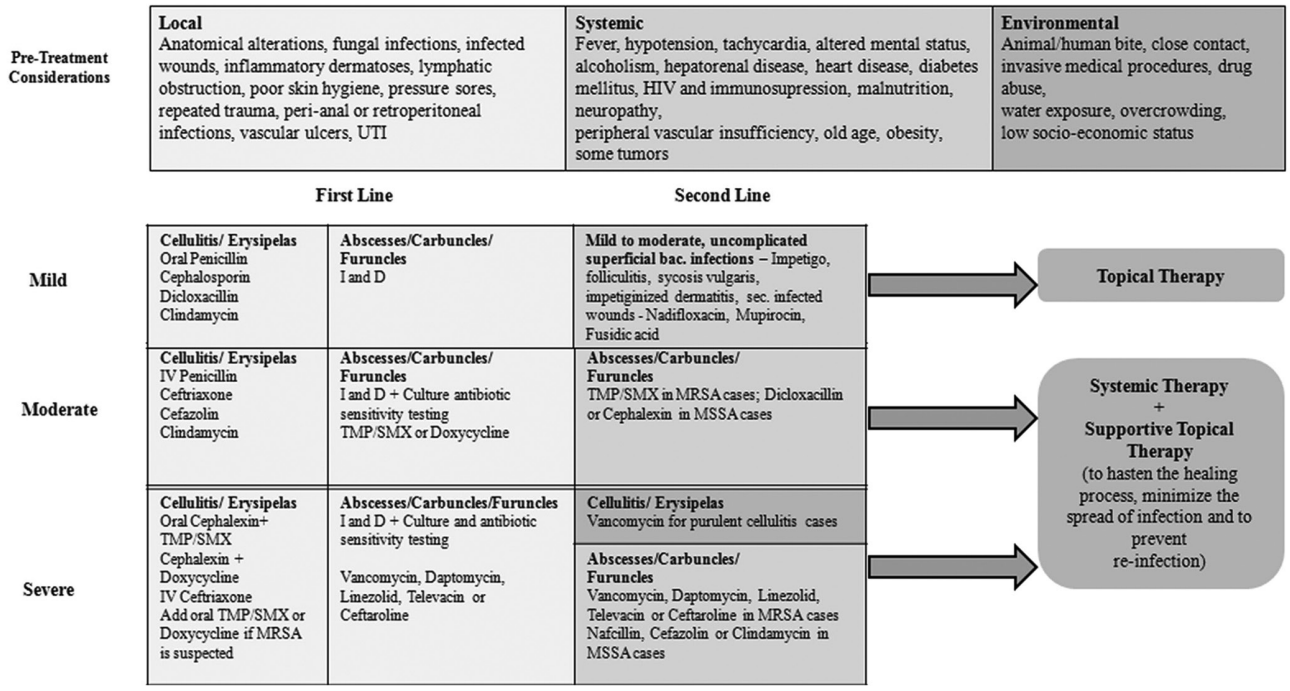

Figure 1: Management of SSTIs based on the degree of severity of disease. I and D: Incision and Drainage, MRSA: Methicillin resistant *Staphylococcus aureus*, MSSA: Methicillin sensitive *Staphylococcus aureus*, TMP/SMX: Trimethoprim/Sulfamethoxazole, UTI: Urinary tract infections.

Table 4: Studies showing the efficacy of topical nadifloxacin in (a) SSTIs and (b) acne vulgaris.

Author (year)	Type of study	Method	Results
(a) Skin and soft tissue infections			
Haustein *et al*. (1997)[54] (Impetigo, Secondarily inf. wounds, Folliculitis, Sycosis vulgaris, Impetiginized dermatitis)	Open, phase II pilot study (*n*=101)	• NF 1%	• Significant reduction in the degree of erythema, exudation, swelling, pain, pruritus, erosion, crusts and scaling • Global assessment of therapeutic effect by Physicians - "very good/good" - 92% cases Eradication of • *S. aureus* - 83% • β-hemolytic streptococci - 100%, • CNS - 68%
Nenoff *et al*. (2004)[53] (Folliculitis, Sycosis vulgaris, Impetigo contagiosa, Impetiginized dermatitis, Sec. infected wounds)	*In vitro* study	• NF • Ofloxacin • Oxacillin • Flucloxacillin • Cefotiam • Erythromycin • Clindamycin • Gentamicin	• NF - Highly active against aerobic and anaerobic bacteria isolated from patients with infected skin disease
Narayanan *et al*. (2014)[55] (Mild to moderate bacterial skin infections)	Open, multi-centric RCTs (*n*=272) Open, multi-centric RCTs (*n*=49) Open, multi-centric RCTs (*n*=49) Post marketing surveillance study (*n*=329)	• 1% NF (*n*=92) • 2% Mupirocin (*n*=90) • 1% Framycetin (*n*=90) • 1% NF (*n*=22) • 2% Fusidic acid (*n*=16) • 1% NF (*n*=24) • 2% Fusidic acid (*n*=19) • 1% NF	Clinical cure rates, reduction in clinical signs/symptoms severity • Day 3 - NF-70.7%, Mupi-72.2%, FR-46.6% • Day 7 - NF-97.8%, Mupi-97.8%, FR-0.8% • Day 14 - NF-92%, Mupi-90, FR-0.9% • Day 3 - NF-77%, FA-19% • Day 7 - NF-95%, FA-81% • Day 3 - NF-42%, FA-21% • Day 7 - NF-83%, FA-63% Global Assessment of treatment ratings by patients and physicians • Study 1: NF - 47.8%, 46.7%, Mupi - 12.2%, 11.1%, FR - 7.8%, 10% • Study 2: NF - 100%, 100%, FA - 37.5%, 25% • Study 3: NF - 45.8%, 45.8%, FA 15.8%, 20.5% • Study 4 - NF • Excellent - 67.2%, 72.6%, Good - 11.9%, 14%, Fair - 20.1%, 12.8%, Poor - 0.9%, 0.6%
Vasani and Medhekar (2015)[8] (Uncomplicated superficial bacterial skin infections)	RCT in out-patient department (*n*=90)	• 1% NF (*n*=30) • 2% Mupirocin (*n*=30) • 2% Fusidic acid (*n*=30)	Grading of lesions at day 4, 8 and 14 • NF was found to be as efficacious as Mupirocin and Fusidic acid, though fusidic acid cream showed faster reduction of the scores at day 4. • No side effects in any of the groups
Janbandhu *et al*. (2020)[6] (<12 years age children with SSTI)	Open label, randomized, comparative study (*n*=60)	• 1% Nadifloxacin (*n*=30) • 1% Mupirocin (*n*=30)	Clinical cure rate at day 15 (*P*=0.313) • NF - 100% • Mupirocin - 96.7%
(b) Acne vulgaris			
Plewig *et al*. (2006)[62] (Mild to Moderate acne)	Double-blind, multinational, phase III study (*n*=474) Duration: 12 weeks	• NF 1% • Erythromycin 2%	• 66.7% reduction in no. of lesions in NF group compared to 64.7% in erythromycin group. • CNS reduction was found only in the NF group. • *P. acnes* reduction was seen in both groups. • There was higher resistance of *P. acnes* and CNS against erythromycin compared to NF

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Table 4: Studies showing the efficacy of topical nadifloxacin in (a) SSTIs and (b) acne vulgaris.

Author (year)	Type of study	Method	Results
Schöfer *et al*. (2009)[63] (Acne grade I, II)	Non-interventional trial in 105 dermatological practices (*n*=555) Mean Duration: 50.8 days	• NF Monotherapy - 68.5% • NF+other topical agents - 27% • NF+systemic medication - 10.3%	Efficacy Rating - "very good/good" • NF monotherapy - 82.1% • NF+other topical therapy - 77.5% • NF+systemic therapy - 82.4% Tolerance Rating - "very good/good" for combination of NF with • Tr/iso-Tr - 74.9% • Adapalene - 90.9% • Azelaic acid - 78.6% • BPO - 85.6%
Tunca *et al*. (2010)[64] (Mild to Moderate acne)	Randomized (*n*=86) Duration: 12 weeks	• NF 1% • Erythromycin 4%	• Significant reduction in lesion counts and Acne Severity Index scores at week 4 to week 12 • Both were equally effective and safe
Choudhury *et al*. (2011)[65] (Mild to Moderate acne)	Post-marketing, randomized study (*n*=84) Duration: 8 weeks	• 1% NF+2.5% BPO (*n*=43) • 1% CLIN+2.5% BPO (*n*=41)	• Both groups were equally efficacious in terms of Total, inflammatory and non-inflammatory lesion counts, Cardiff Acne Disability Index and Investigator Global Assessment scores
Jung *et al*. (2011)[50] (Mild to Moderate acne)	Randomized, prospective, split-face study (*n*=37) Duration: 8 weeks	• 1% NF on one half of face • Vehicle cream on other half of face	• At 8 weeks there was 70% reduction in NF applied half of face compared to 13.5% increase in inflammatory acne lesions in vehicle treated half of face. • Non-inflammatory acne lesions showed 48.1% reduction with NF compared to 10.1% reduction with vehicle cream • Histopathological examinations at 8 weeks showed decreased inflammation and interleukin-8 expression in NF treated half of face.
Kobayashi *et al*. (2011)[66] (Moderate to Severe acne)	Multicentric, randomized, comparative study (*n*=50) Duration: 8 weeks	• Adapalene+NF • Adapalene monotherapy	• Combined therapy showed higher reduction in inflammatory lesions at 2 weeks (*P*=0.047) and at 8 weeks (*P*=0.011)
Takigawa *et al*. (2013)[67] (Moderate to Severe acne)	Multicentric, randomized study (*n*=184) Duration: 12 weeks	• Adapalene 0.1% gel+NF 1% cream (*n*=84) • Adapalene gel alone (*n*=100)	• Combined therapy showed greater decrease in inflammatory lesions at 4 weeks and thereafter (*P*=0.0056) • Physicians and patients favored combined therapy (p=0.02496, *P*=0.00268 resp.)
Shah (2014)[68] (Mild to Moderate acne)	Open-labeled, phase 3, non-randomized, multicentric study (*n*=119) Duration: 8 weeks	• 1% NF+0.1% adapalene gel	• 98.3% showed significant reduction in non-inflammatory, inflammatory and total lesion counts • At 8 weeks - 75% had global assessment scores approaching to normal healthy skin score
Deshmukh *et al*. (2018)[69] (Mild to Moderate acne)	Randomized, comparative study (*n*=80) Duration: 12 weeks	• 1% NF+0.025% Tr (*n*=40) • 1% CLIN+0.025% Tr (*n*=40)	• At 12 weeks there was significant reduction in inflammatory, non-inflammatory and total lesion count in NF+Tr group (*P*<0.05). • At 12 weeks, the percentage improvement in Evaluator's Global Severity Scale rating was 17.94% in NF+Tr group compared to 12.5% in CLIN+Tr group.

SSTIs: Skin and soft tissue infections, BPO: Benzoyl peroxide, CLIN: Clindamycin, CNS: Coagulase negative Staphylococcus, FA: Fusidic acid, FR: Framycetin, Mupi: Mupirocin, NF: Nadifloxacin, RCT: Randomized controlled trial, Tr: Tretinoin, *P. acnes*: *Propionibacterium acnes*, *S. aureus*: *Staphylococcus aureus*

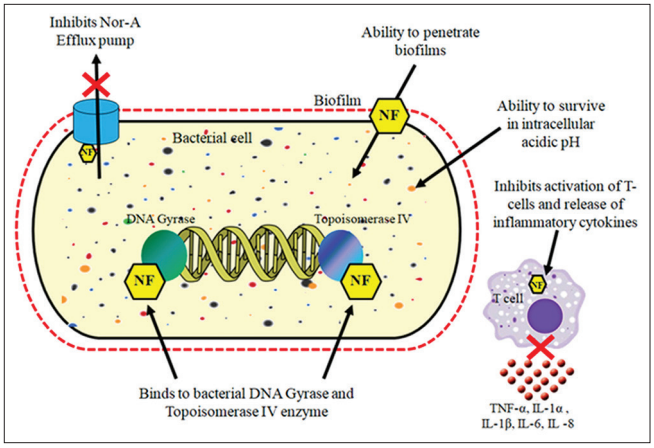

Figure 2: Mechanism of action of Nadifloxacin. NF: Nadifloxacin, IL: Interleukin, TNF: Tumor necrosis factor.

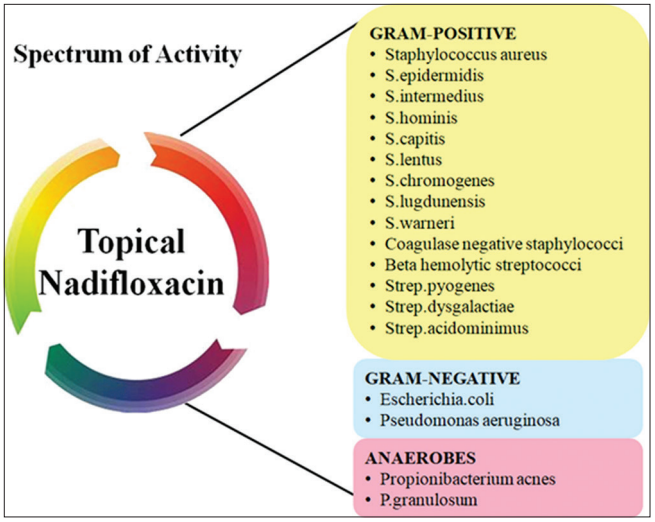

Figure 3: Spectrum of activity of Topical Nadifloxacin.

mechanism of action. Figure 2 shows the mechanism of action of Nadifloxacin.[50-52]

Statement 9: Efficacy of Nadifloxacin is equivalent to Mupirocin and Fusidic acid. Safety is also well established

Although there are meager studies comparing the efficacy of Nadifloxacin with other antimicrobials such as Mupirocin and Fusidic acid, they have shown promising results [6,8,53-55] [Table 4a]. It was equally efficacious and as safe as Mupirocin and Fusidic acid in the treatment of SSTI in the Indian population. Few of the experts suggested that topical Nadifloxacin could be used as an effective, low-cost option in treating bacterial nail infections.

Safety of Nadifloxacin is also well documented. Muto *et al.* (1990) reported that the peak plasma concentration was only 1.6 ng/ml, 8 h after percutaneous application of 10 g of Nadifloxacin 1% cream, in healthy volunteers, indicating extremely low systemic absorption.[56] There have been no reports on the occurrence of allergic contact dermatitis to Nadifloxacin. Only one case report of contact dermatitis was reported in a patient who used lysozyme chloride ointment, 1% Nadifloxacin cream, 1% sulfadiazine silver cream, and 0.25% tretinoin tocoferil ointment, for the treatment of livido reticularis. He was diagnosed with allergic contact dermatitis due to methylparaben and propylparaben present in lysozyme chloride ointment and not due to Nadifloxacin cream.[57]

Statement 10: Nadifloxacin MIC is least as compared to other topical antimicrobials

Nadifloxacin is effective against Gram positive, Gram negative, and anaerobic bacteria, including MRSA and MSSA[53,54] [Figure 3]. When the effectiveness of Nadifloxacin, Erythromycin, Clindamycin, and Tetracycline against *P. acnes* and CNS isolates from inflammatory lesions were compared, the MIC for Nadifloxacin was ≤1 μg/mL and resistance was shown at MIC level ≥4 μg/mL.[58] Compared to Ciprofloxacin, Erythromycin, and Clindamycin, Nadifloxacin demonstrated better activity against *P. acnes* as the MIC50 and MIC90 values were lesser compared to those of other antimicrobials.[45] Biswal *et al.* (2016) demonstrated that the MIC50 and MIC90 values for Nadifloxacin (0.25 and 1μg/mL) were lower than those for Ciprofloxacin (0.5 and 1μg/mL).[59] Nishijima *et al.* (1996) reported that Nadifloxacin did not induce cross-resistance to other fluoroquinolones, but suggested cross-resistance among the fluoroquinolone group as a whole.[48] Hence, there is a need to watch for the development of cross-resistance to other organisms with the use of Nadifloxacin, such as in systemic antibiotic therapy.

Statement 11: Nadifloxacin is beneficial in managing MRSA infections

Several studies have demonstrated the efficacy of Nadifloxacin against MRSA. Nishijima *et al.* compared the *in vitro* susceptibility of MRSA and MSSA isolates from skin infections to other fluoroquinolones from 1991 to 1994. Nadifloxacin exhibited the lowest MIC for both MSSA and MRSA (0.012–1.56 μg/ml). There were also no resistant *S. aureus,* neither MSSA and MRSA, to Nadifloxacin, whereas other fluoroquinolones developed resistance quickly during the study period.[46,48] The effects of Nadifloxacin cream on atopic dermatitis (AD) with MRSA was assessed by Kimata (1999) in 35 young children (<1-syear-old). After 4 weeks, MRSA was eradicated in all patients, and AD was significantly improved in the Nadifloxacin group.[60]

Most of the other antimicrobials do not effectively treat intracellular infections due to poor penetration and reduced

action in intracellular acidic environment. A formulation of polyhexamethylene biguanide and Nadifloxacin could kill intracellular MRSA in keratinocytes, prevent bacterial re-growth, and also helped in the recovery of infected keratinocytes.[51,61] Thus, Nadifloxacin can be used not only against planktonic MRSA, but is also effective against intracellular MRSA.

Statement 12: Combination of Nadifloxacin and Adapalene has shown promising results in the management of acne vulgaris

The efficacy and safety of Nadifloxacin as an anti-acne agent, has already been proved through various *in vitro* and clinical studies[50,62-69] [Table 4b]. Combination of Nadifloxacin and Adapalene was approved in India for the topical treatment of acne vulgaris in 2006.[17] This combination has shown superior efficacy compared to Nadifloxacin used alone.[70] Moreover, it also minimizes the emergence of antibiotic-resistant bacterial strains.[71] Thus, experts suggested that such a combination therapy could be a useful means by which further resistance development towards Nadifloxacin can be avoided along with better clinical efficacy.

Statement 13: Nadifloxacin has a unique property of penetrating the biofilm and henceforth less resistance has developed over the years

Biofilms are the main cause for the persistence of chronic skin infections. Due to their presence, the susceptibility of the microorganisms to antimicrobials and immune defenses is decreased.[72] They need higher drug concentration to be inhibited.[73] Sharma and Gupta (2016) reported that among the *S. aureus* and CNS isolates from pus samples of patients with SSTIs, 32.03% were biofilm producers, MRSA (54.83%) showing higher biofilm production than MR CNS (38.46%).[26] Biofilms may result in dispersal of bacterial cells leading to the spread of infection to secondary sites.[72] Topical agents such as Mupirocin and Fusidic acid were less effective in removing biofilms compared to Povidone iodine;[74] Gentamicin;[75] Ceftarolin, Daptomycin, Fosfomycin, Ofloxacin, Rifampicin, and Vancomycin.[76] A study demonstrated that sub-inhibitory concentrations of Mupirocin promoted biofilm formation of *S. aureus*, in particular the MRSA USA300 clone. However, the antibiofilm effect of Mupirocin was seen at the higher concentrations (near or above MIC).[77] Thus, experts suggested that the correct use of this drug should be done at optimal concentration.

Nadifloxacin effectively penetrate biofilms and displays improved bactericidal activity under low pH biofilm environments.[78] Tellis *et al.* (2019) demonstrated that Levonadifloxacin showed ≥90% bacterial kill rate against biofilm-embedded organisms, while vancomycin and linezolid displayed inconsistent activity. This might be attributed to its lipophilic nature, which aids in permeation of the drug in biofilm polymer matrices.[79]

CONCLUSION

Topical Nadifloxacin has a demonstrated history of efficacy in the treatment of acne vulgaris. Owing to its unique mechanism of binding to both DNA gyrase and topoisomerase IV bacterial enzymes, inhibition of nor-A efflux pump, capacity to survive in acidic pH environment, potent action against MRSA, ability to penetrate biofilms, competent efficacy and safety profile compared to other antimicrobials, and least chances of emergence of resistance, it could be a potential drug in the empirical treatment of mild and superficial SSTIs and as an adjuvant in moderate to severe SSTIs. However, it is recommended that Nadifloxacin be used judiciously to safeguard it from developing antimicrobial resistance.

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Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

Archana Karadkhele, Snehal Muchchala and Rahul Rathod work for Dr. Reddy's Laboratories Limited, Hyderabad, Telangana, India.

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