Unmasking Resistance: effective approaches for bacterial skin infections

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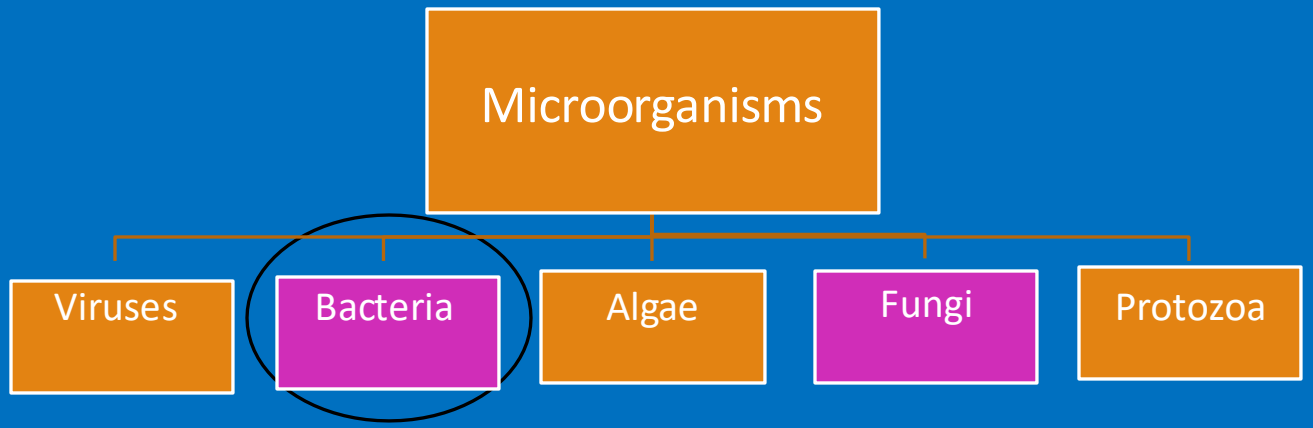
Background

- Microorganisms co-exist inside, on and around our bodies
- Some of these microorganisms are potentially harmful (pathogenic)
- Given the right circumstances, pathogenic microorganisms can penetrate the protective barrier of the skin, replicate and overcome the skin's immune system, leading to infection
- ***Staphylococcus aureus*** is a pathogenic bacteria that most commonly causes bacterial skin infections



Bacterial Skin Infections

- Can range from mild to severe

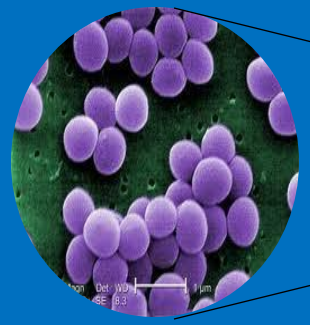
- Typically caused by: (1) *Staphylococcus aureus*
  (2) *Group A Streptococci (Streptococcus pyogenes)*

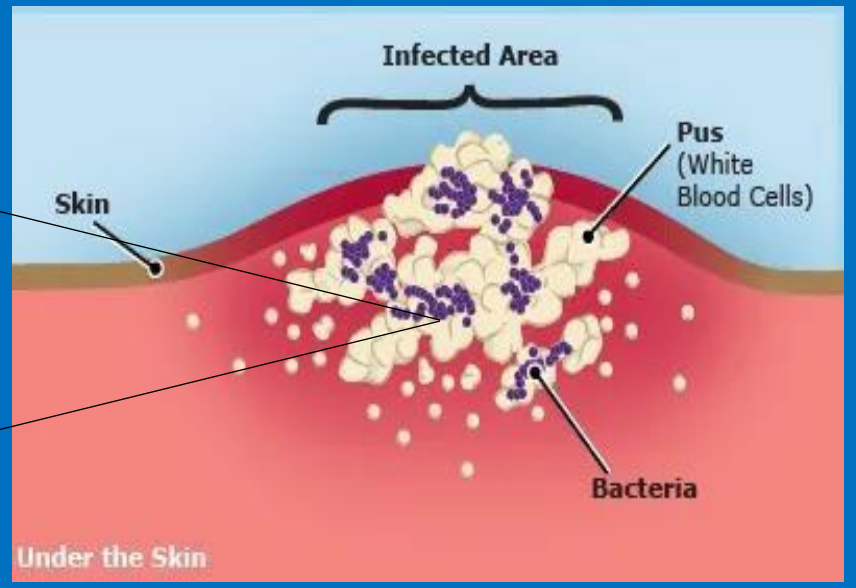
Staphylococcus aureus

- Gram+ve bacteria (coagulase+ve)
- Found normally on the skin and in the nasal passages (normal flora)
- Given the right circumstances, it invades the skin's barrier and causes infection
- Primary or secondary skin infections
- Patients with atopic dermatitis/eczema have a higher count of *Staph aureus* on their skin
- Most often spread through contact with:

  - pus
  - skin to skin of infected individuals
  - personal items (towel, washcloth, etc.)

- Can produce toxins resulting in more serious skin conditions (SSSS or TSS)





Group A Streptococci (Streptococcus pyogenes)

- Gam+ve; beta-haemolytic
- Commonly found in the throat & skin
- Skin infections (impetigo, cellulitis, erysipelas and rarely, necrotizing fasciitis)
- Primary pyodermas and lymphangitis
- Hypersensitivity responses (rheumatic fever, glomerulonephritis)
- Produce toxins (scarlet fever or toxic erythema)
- **Rx** : - oral or IVI antibiotics are essential in these patients
  - topical therapy (mupirocin) only effective for impetigo

Types of Bacterial Skin Infections

- **Impetigo**
- **Ecthyma**
- **Folliculitis** (Bockhart's Impetigo)
- **Furuncles** (Boils)
- **Carbuncles**
- **Erysipelas** (infection of upper skin layers)
- **Cellulitis** (infection of deeper skin layers)

Impetigo

Impetigo contagiosa:

- Common and highly contagious skin infection among children
- Usually caused by *S. aureus* and occasionally by *S. pyogenes*
- Mainly affects infants and children
- Impetigo usually present as red sores & sometimes blisters (**Bullous Impetigo**) on the face, especially around a child's nose and mouth, and on hands and feet
- The sores (vesicles) burst and dry out to form thin honey-coloured crusts
- **Rx: Mupirocin cream +/- oral antibiotics**

Non-bullous Impetigo vs Bullous Impetigo

Ecthyma

Ecthyma (“veldsores”)

- Deep infection of the skin that resembles impetigo
- Lower legs most frequently affected
- Usually oval or round lesions(1-3cm in diameter)
- Begins as a pustule overlying an inflamed area of skin (redness) that deepens into an ulceration with an overlying crust
- The crust of ecthyma lesions is grey-yellow and is thicker and harder than the crust of impetigo
- Somewhat common in patients with poor hygiene, malnutrition, and minor skin injuries such as excoriated insect bites
- **Rx : Mupirocin cream + oral antibiotics**

Ecthyma vs Ecthyma Gangrenosum

Folliculitis

Folliculitis (Bockhart's impetigo)

- Superficial infection of the hair follicles
- Staphylococcal or streptococcal
- Commonly affected areas: beard, posterior neck, occipital scalp, legs and axillae(armpits)
- Presents as clusters of small red bumps or pustules that develop around hair follicles
- Symptoms include itchy, burning, painful and tender skin lesions
- **Rx : Mupirocin cream +/- oral antibiotics**

Furunculosis

Furuncles (Boils)

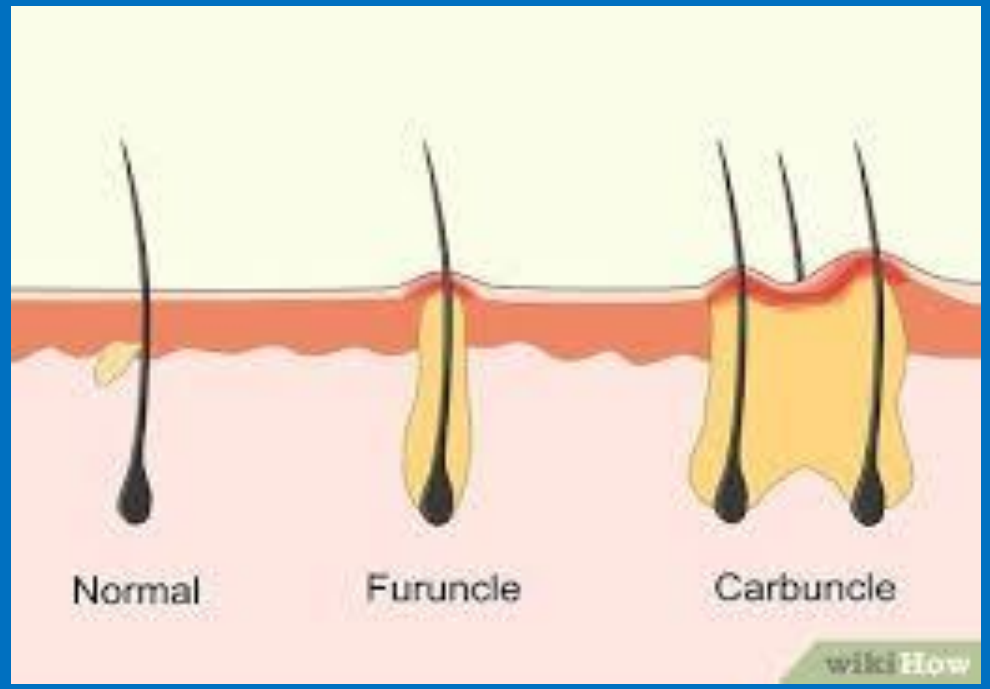
- Commonly known as boils or abscesses
- Deeper infections of the hair follicle, usually starts as folliculitis
- Start as red, painful, tender lumps
- These fill with pus, grow, then rupture and drain
- Maybe chronic or recurrent; single or multiple lesions
- **<u>Rx</u> : Mupirocin cream with oral antibiotics**

Carbuncle

Carbuncle:

- Deep bacterial infection of several adjacent hair follicles
- Painful, tender, hard lump with pronounced surrounding inflammation
- Lesions up to 4-10cm in diameter
- Pus discharging from multiple follicular orifices
- Yellow slough forms leaving a necrotic depression
- Lesions heal with scarring
- Maybe associated with rigors & chills & high fever
- Common in diabetics, malnutrition
- **Rx : Mupirocin cream + oral antibiotics**

Carbuncle



Erysipelas

- Superficial infection of the dermis
- Caused by group A haemolytic streptococci
- Enter skin through minor skin abrasions
- Legs and face commonly affected
- Skin is hot, tender, erythematous with a well-demarcated border
- Sometimes vesicles may occur
- **Rx** : - topical therapy not indicated

  - systemic penicillin is the treatment of choice

Erysipelas

Cellulitis

- Infection of the deeper dermis & subcutaneous tissue
- Caused by Group A streptococci & Gram -ve organisms
- Complication of a wound or ulcer and lymphoedema
- Most commonly on the legs
- Erythema, swelling & tenderness with a poorly-defined edge
- Patients are systemically unwell with high fever
- **Rx** : - topical antibiotics can be used at the site of entry
  but not indicated for the management of cellulitis
  - systemic antibiotics is the treatment of choice

Cellulitis

Secondary Skin Infections

- **When the skin's protective barrier layer is damaged, it allows for easy entry of bacteria**
- **Once entered, the bacteria can replicate and overcome the skin's immune system, leading to a secondary bacterial infection**

  - Infected dermatoses e.g. infected eczema

  - Infected traumatic lesions e.g. abrasions, insect bites, minor wounds and burns

- **<u>Rx</u> : Mupirocin cream or ointment +/- oral antibiotics**

Prophylaxis

- Mupirocin cream may be used to prevent infection of abrasions, small cuts and wounds

MUPIROCIN: Broad Range of Antibacterial Activity

- ***Effective Against Gram-Positive Bacteria:***

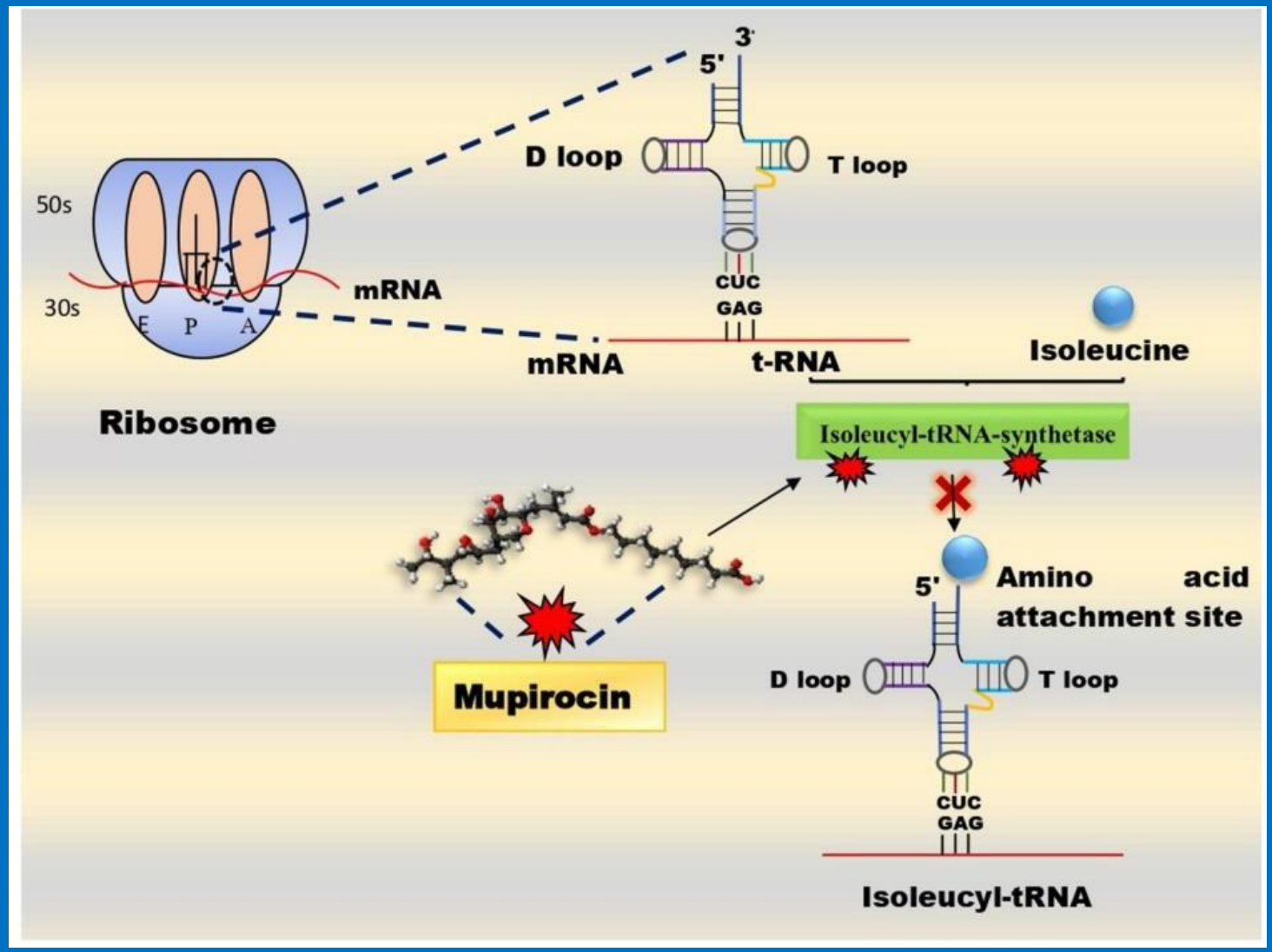
  - Staphylococcus aureus (including MRSA)
  - Staphylococcus epidermidis
  - Streptococcus pyogenes
  - Staphylococcus saprophyticus
  - ß-hemolytic streptococci

- ***Effective Against Gram-Negative Bacteria:***

  - N. gonorrhoea

MUPIROCIN: Mechanism of Action

- **Origin:** Mupirocin is derived through the fermentation process of Pseudomonas fluorescens, a Gram-ve bacterium.
- **Mechanism of Action:** It inhibits bacterial protein synthesis, specifically targeting isoleucyl-tRNA synthetase occurring in ribosomes, which is crucial for bacterial survival and proliferation.
- **Bactericidal Properties:** When applied topically, Mupirocin exhibits bactericidal effects, effectively eliminating bacteria at the site of application.



MUPIROCIN: Ideal Topical Antibiotic

MUPIROCIN: A Dermatologically Potent Antibiotic

- **Good Dermal Penetration:** Mupirocin demonstrates the capability to penetrate into the dermis, the second layer of the skin, ensuring targeted action at the infection site.
- **Potent Bactericidal Action:** Exhibits potent bactericidal properties, effectively eradicating bacteria upon application.
- **Limited Systemic Penetration:** Characterized by limited systemic penetration, ensuring low absorption into the bloodstream and localized action.
- **Great Safety Profile:** Mupirocin is notable for having minimal interactions and side effects, enhancing its safety in topical applications.

MUPIROCIN: Ideal Topical Antibiotic

➢ Broad-Spectrum and Targeted Antibacterial Activity:

- **Broad-Spectrum Efficacy:** Demonstrates broad-spectrum antibacterial activity, making it versatile in managing various bacterial infections.
- **Targeted Action:** Particularly directed against key pathogens such as Staphylococcus aureus and Streptococcus pyogenes.

➢ Low Resistance Rates and Unique Mechanism of Action (MOA):

- **Low Resistance Rates:** Mupirocin maintains low bacterial resistance rates, ensuring its efficacy over prolonged use.
- **Unique MOA:** Owing to its distinctive mechanism of action, Mupirocin does not exhibit cross-resistance with other antibiotics, preserving its effectiveness against a range of bacterial strains.

Supiroban Cream: Product Overview

- **Schedule:** 2
- **Classification:** Topical Antibiotics
- **Active Ingredient:** Mupirocin Calcium 20mg/g
- **Formulation:** Cream
- **Pack sizes:** 15g and 30g

Dosage and Directions for Use

- For topical use only
- Apply a small quantity to cover the affected area
- Treated area may be covered by a dressing
- **Adults, Children and Elderly:**
  - 2-3 times a day
  - For up to 10 days, depending on the response
  - safe in patients with kidney or liver impairment
- **Do not mix with other preparations** as there is a risk of dilution, resulting in a reduction in the antibacterial activity and potential loss of stability of the mupirocin in the cream
- Not suitable for use in the eyes

Indications

- **SUPIROBAN CREAM® is indicated for the topical treatment of primary and secondary bacterial skin infections caused by *Staphylococcus aureus* and other susceptible organisms**

➢ **Primary skin infections:**

- Impetigo, folliculitis, furunculosis and ecthyma

➢ **Secondary skin infections:**

- Infected dermatoses e.g. infected eczema

- Infected traumatic lesions e.g. abrasions, insect bites, minor wounds and burns

➢ **Prophylaxis:**

- Mupirocin may be used to avoid bacterial contamination of small wounds, incisions and other clean lesions, and also to prevent infection of abrasions, small cuts and wounds

Resistance to Topical Antibiotics

- Antimicrobial resistance is an increasingly serious problem in the public sector
- Mupirocin and fusidic acid are common topical antibiotics used to treat bacterial skin infections
- Resistance patterns in SA:

1. **S. aureus**: - high levels of MRSA (up to 70%)

   - fusidic acid resistance (50-64% of MRSA isolates)

2. **S. pyogenes**: - low levels of resistance to penicillin & macrolides

Resistance to Topical Antibiotics

➢ **MUPIROCIN RESISTANCE**:

- low to moderate resistance rates of mupirocin reported worldwide (1-40%)
- mostly in MRSA strains:- high levels of resistance (1.4%-14% of MRSA isolates)
  - low levels of resistance (10.3%-40.6% of MRSA isolates)
- high-level resistance is more concerning and increasing in some regions
- due to overuse & misuse for minor skin infections

➢ **FUSIDIC ACID RESISTANCE**:

- resistance rates vary widely (1-70%) depending on region & bacterial species
- often associated with prolonged or repeated use

RESISTANCE: Comparison & Regional Variation

➢ **SA study (2017-2018) found**:

- Mupirocin resistance: 14.1% in MRSA isolates
- Fusidic acid resistance: 34.5% in S. Aureus isolates

➢ **UK study (2019) reported**:

- Mupirocin resistance: 23.4% in MRSA isolates
- Fusidic acid resistance: 44.7% in S.Aureus isolates

➢ **Mupirocin resistance study at Tygerburg Hospital,CT, SA (2020)**:

- 12% of S.Aureus isolates were resistant to mupirocin & 44% were methicillin resistant
- High rates of low-level mupirocin resistance (10.3%-40.6% of MRSA isolates)
- Low rates of high-level resistance (1.4%-14% of MRSA isolates)

Resistant Mitigation Strategies

- Use antibiotics only when necessary
- Choose the right antibiotic for the specific infection (susceptibility testing - NB!)
- Use the correct dosage & duration
- Monitor for resistance & adjust treatment accordingly
- Avoid using on large surface areas & for prolonged periods
- Cyclically rotate antibiotics
- Combination therapy with oral antibiotics has been proposed
- Implement infection control measures (hand hygiene, proper wound care)

Mupirocin Cream

Supiroban™ Cream is the First Market Generic of Mupirocin Cream

Mupirocin Cream vs Mupirocin Ointment:

- **Cream formulation ensures better patient acceptability and compliance:**

- Less thick than ointments (higher water than oil content)
- Easier to apply, especially over larger skin surface areas
- Non-greasy
- Does not stain clothing

Supiroban™ Cream vs Bactroban™ Cream

Supiroban™ Cream is the First Market Generic of Bactroban™ Cream

Supiroban™ Cream vs Bactroban™ Cream:

- **Both are Schedule 2**
  - Easy switch at Pharmacy
- **Only Supiroban™ Cream has a 30 g pack size**
  - Ideal for larger skin surfaces such as bed sores and large burn wounds, etc.
- **Supiroban™ Cream is more affordable**
  - 15g is 25% more affordable than Bactroban™ Cream 15g
  - 30g is also 25% more affordable than 2 x Bactroban™ Cream15 g

Supiroban™ Cream vs Fucidin™ Cream:

	[S2] **Supiroban™ Cream**	[S2] **Fusidic Acid Cream**
MOA	Bactericidal Broad spectrum activity against Gram+ and Gram- bacteria	Bacteriostatic Narrow spectrum activity against Gram+ bacteria
Efficacy (bacteriological cure rate)	97%	87%
Resistance rate*	5.2%	12.4%
Pack sizes	15 g and 30 g	15 g
Cost (SEP incl. VAT)	R76,74 and R153,47	R125,14

*** resistance of 97 clinical *S.aureus* strains to mupirocin and fusidic acid**

Clinical Evidence of Mupirocin Efficacy

The efficacy of Mupirocin has been shown in numerous studies:

1. Bioequivalence of Supiroban to originator (Bactroban) - **Glenmark, India(2010)**
2. Mupirocin 2% cream vs other treatments for Impetigo **(Gisby 2000)**
3. Topical Mupirocin 2% vs Topical Fucidic acid 2% **(Gilbert 1989)**
4. IDSA (Infectious Diseases Society of America) Guidelines for MRSA infections **(Liu 2011)**
5. IDSA (Infectious Diseases Society of America) Guidelines for Skin Infections **(Stevens 2014)**
6. Burn wounds **(Smoot 1992)**

Clinical Evidence of Mupirocin Efficacy

1. Bioequivalence of Supiroban to Originator (Bactroban)

- **Comparative study by Glenmark, India (2010)**

Objective: To demonstrate comparable safety and efficacy (bioequivalence) of Glenmark Pharmaceuticals' Mupirocin 2% (Supiroban) and GSK's Bactroban (Mupirocin 2%)

Design: Double-blind, randomised, placebo-controlled study

Patients: 482 Patients with impetigo (18 months and older)

Methods: Patients applied either Glenmark's Mupirocin or Bactroban or Placebo to affected areas, 3 times a day for 7 days

Clinical Evidence of Mupirocin Efficacy

1. Bioequivalence to Originator (Bactroban)

- **Comparative study by Glenmark, India**

Results: Efficacy

- Clinical cure rates (% patients with reduced signs and symptoms)
- Bacteriological cure rates (% patients with absence of *Staph. aureus* and *Strep. pyogenes*)

- **Glenmark's Mupirocin 2% was bioequivalent to Bactroban on both efficacy endpoints**

Conclusion :

Glenmark Pharmaceuticals' Mupirocin 2% ointment is safe, clinically effective, and bioequivalent to GSK's Bactroban ointment

Clinical Evidence of Mupirocin Efficacy

2. Mupirocin Cream vs other treatments (Gisby et al, 2000)

- Multiple studies were conducted in multiple models of impetigo (mice, hamsters, etc.)
- Different topical and oral treatments were compared
- To determine **efficacy**, bacterial numbers were calculated (*Staph. aureus* and *Strep. pyogenes*)
- **Compliance** was also considered

Gisby J, Bryant J. Efficacy of a New Cream Formulation of Mupirocin: Comparison with Oral and Topical Agents in Experimental Skin Infections. *Antimicrobial agents and Chemotherapy*. 2000:255–260

Clinical Evidence of Mupirocin Cream Efficacy

2. Mupirocin Cream vs other treatments (Gisby et al, 2000)

Results: Efficacy

- Mupirocin Cream was **more effective** than Mupirocin Ointment in 2/8 studies
- Mupirocin Cream was **as effective** as Mupirocin Ointment in 6/8 studies

Results: Tolerability of Topical Formulations

- Safety profiles of topical treatments are good, but tolerability of ointment formulations not ideal
- Ointments are thick, making it difficult to apply
- Ointments are greasy and stains clothing
- **Cream formulation will provide better patient acceptance and compliance**

Clinical Evidence of Mupirocin Cream Efficacy

2. Mupirocin Cream vs other treatments (Gisby et al, 2000)

Results: Safety

- Mupirocin has excellent activity against the major skin pathogens while having little effect on normal skin flora which is part of the skin natural defense system
- No cross-resistance with other antibiotics due to its unique MOA
- Lacks the potential to cause photosensitive, irritant reactions and contact sensitization

Gisby J, Bryant J. Efficacy of a New Cream Formulation of Mupirocin: Comparison with Oral and Topical Agents in Experimental Skin Infections. ***Antimicrobial agents and Chemotherapy*****.**
2000:255–260

Clinical Evidence of Mupirocin Cream Efficacy

2. Mupirocin Cream vs other treatments (Gisby et al, 2000)

Conclusions of this study:

- Mupirocin cream is at least as effective if not more effective than mupirocin ointment but with better patient compliance
- Mupirocin cream is at least as effective as oral treatments but with better tolerability and lower resistance
- On the grounds of efficacy and improved patient compliance compared to mupirocin ointment and oral therapies, **Mupirocin Cream should have a significant role in the treatment of primary and secondary skin infections**

Gisby J, Bryant J. Efficacy of a New Cream Formulation of Mupirocin: Comparison with Oral and Topical Agents in Experimental Skin Infections. ***Antimicrobial agents and Chemotherapy*****.**
2000:255–260

Clinical Evidence of Mupirocin Efficacy

3. Topical 2% Mupirocin vs Topical 2% Fucidic acid (Gilbert 1989, JAAD 1989)

Objective: To compare the efficacy and safety profile of topical 2% mupirocin vs topical 2% fusidic acid in the treatment of primary and secondary skin infections

Design: Double-blind, randomised study

Patients: 70 Patients with primary and/or secondary bacterial infections of the skin

Methods: Patients applied either Mupirocin or Fusidic acid to affected areas, 3 times a day for 7 days

Gilbert M. Topical 2% mupirocin versus 2% fusidic acid ointment in the treatment of primary and secondary skin infections. J Am Acad Dermatol. 1989 Jun; 20(6): 1083-1087

Clinical Evidence of Mupirocin Efficacy

3. Topical Mupirocin 2% vs Topical Fucidic acid 2% (Gilbert 1989, JAAD 1989)

Results: Efficacy

- Bacteriological cure rate with **Mupirocin 2% = 97%**
- Bacteriological cure rate with Fucidic acid 2% = 87%

Results: Safety

- No side effects were observed
- Topical 2% mupirocin has little or no potential for irritation, systemic side effects, or cross-resistance with other antibiotics

Gilbert M. Topical 2% mupirocin versus 2% fusidic acid ointment in the treatment of primary and secondary skin infections. J Am Acad Dermatol. 1989 Jun; 20(6): 1083-1087

Clinical Evidence of Mupirocin Efficacy

4. IDSA Guidelines for MRSA Infections (Liu, et al. 2011)

➢ **Recommendations for Mupirocin 2% in Children:**

- For minor skin infections such as impetigo
- For secondarily infected skin lesions such as eczema, ulcers, or lacerations
- For mild cases of pustulosis (pus-filled skin bumps) in full-term newborns and young infants

Liu C, Bayer A, *et al*. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus aureus infections in Adults and Children. IDSA Guidelines. *Clinical Infectious Diseases*. 2011:1–38.

Clinical Evidence of Mupirocin Efficacy

5. IDSA Guidelines for Skin Infections (Stevens 2014)

- **Recommendations for Mupirocin 2%: For treatment of impetigo**

  (As effective as oral antimicrobials)

Stevens DL, Bisno AL, *et al*. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. IDSA Guidelines. *Clinical Infectious Diseases*. 2014;59(2):e10–52

Clinical Evidence of Mupirocin Efficacy

6. **Burn wounds :** Smoot E.C. et al. J. Burn Care Rehabil. 1992;13: 198-02

Benefits of Mupirocin Cream

- Mupirocin is the HCP's treatment of choice for bacterial skin infections
- Recommended by the IDSA and FDA Guidelines
- Indicated for treating a wide range of skin infections and as well as prophylaxis
- Unique MOA that contributes to low resistance rates
- As effective as, or superior to, other topical agents commonly used for skin infections
- Safe treatment with no drug interactions and does not cause photosensitive irritation
- Cream formulation for better patient acceptance and compliance
- Only Cream formulation in 30g pack for treating larger areas or longer periods
- 24% more affordable than originator
- Schedule 2