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REVIEW

Mupirocin for Skin Infection: Clinical Experience from China

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Abstract: Mupirocin, an antibiotic produced by *Pseudomonas fluorescens*, is mainly used for the topical treatment of various skin and soft tissue infections caused by *Staphylococcus* (including methicillin-resistant *Staphylococcus aureus*) and *Streptococcus* around the world for decades. Nevertheless, the clinical application scope of mupirocin varies in different countries due to differences in their medical policies, prescription types, and drug resistance. According to the experience of Chinese doctors in the past few years, mupirocin presented low drug resistance rates, and could be used as a treatment option for various primary infections and secondary infections, with antibacterial effects in a broad application. In this review, we summarized the experience of mupirocin used in the Chinese population and discussed its clinical value to provide novel insights and inspiration for physicians.

Keywords: experience, mupirocin, skin diseases, infectious

Introduction

Infectious skin diseases are common bacterial infections worldwide, range in severity from benign to life threatening. *Staphylococcus aureus* is the most common pathogen in skin and soft tissue infections (SSTIs).[1] In the past few decades, with increasing prevalence of SSTIs caused by multidrug-resistant *Staphylococcus aureus* (mainly methicillin-resistant *Staphylococcus aureus* [MRSA]), the incidence of community and hospital infections also continued to rise.[1] In the previous development of topical antibiotics for skin infections, mupirocin has emerged as a promising benefit for a large number of SSTIs patients caused by *Staphylococcus aureus* or MRSA, and therefore gained attention.

In 1971, pseudomonas acid, a metabolite was isolated from the culture medium of *Pseudomonas fluorescens* NCIMB 10586, which was later termed mupirocin by the World Health Organization (WHO).[2] Mupirocin has a bactericidal effect through binding to bacterial isoleucine transfer RNA (tRNA) synthetase, preventing the synthesis of proteins containing isoleucine within the cell.[3] Since the 1980s, it has been broadly applied globally. Mupirocin was firstly approved as a prescription drug in the UK in 1985 and now is utilized for skin infections caused by *Staphylococcus* (including MRSA), *Streptococcus*, and *Escherichia coli* (Instructions of Medicines and Healthcare products Regulatory Agency). From 1987, the US Food and Drug Administration (FDA) has successively approved mupirocin ointment, mupirocin calcium cream and mupirocin calcium ointment as prescriptions for indications of impetigo and secondary infections of traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to *Staphylococcus aureus* and *Streptococcus pyogenes*, and the eradication of nasal colonization with MRSA among patients at high risk of infections (FDA Prescribing Information). Mupirocin ointment has also been available and widely used in China since 1993, and in 2008, it was changed from a prescription drug to an over-the-counter drug, which is currently mainly used as a topical antibiotic for skin infections caused by Gram-positive cocci, including primary skin infections, such as impetigo, furunculosis, and folliculitis, as well as secondary skin infections, including eczema with infection, and superficial trauma (not exceeding 10 cm × 10 cm in area) combined with infection.

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However, there may be differences in the medical management policies of mupirocin as a prescription or an over-the-counter drug in various countries. Considering the aforementioned reasons and other influencing factors, the patient populations and experiences in the clinical application of mupirocin may also vary globally. Recently, reports on the use of mupirocin among Chinese patients have shown that this drug has a wide range of applications, from primary skin infections caused by Gram-positive cocci to various secondary skin infections, with low total resistance rates.[4–7] Unlike other countries, some indications for secondary infections have been recommended in Chinese guidelines and consensus, including surgery, burns, catheterization and diabetes-related infections.[8,9] This article, for the first time, was done to summarize the clinical application experience of mupirocin in the Chinese population, discuss the drug's resistance status in China and other countries, and looks forward to its further development potential, aiming to provide some insights and inspiration for the clinical application of mupirocin.

Antibacterial Mechanism of Mupirocin with Broad-Spectrum Antibacterial Activity

The epoxy side chains in the molecular structure of mupirocin resemble those of isoleucine, giving it a high affinity for the binding sites of isoleucine tRNA synthetases (IleRSs). Mupirocin can reversibly and specifically bind to and inhibit IleRSs in bacteria, leading to the depletion of cells carrying isoleucine tRNA, thereby suppressing protein and RNA synthesis in bacteria, and ultimately resulting in bacterial death.[3]

Mupirocin has broad antibacterial activity against Gram-positive bacteria, including *Staphylococcus* and *Streptococcus*. Of these susceptible bacteria, *Staphylococcus aureus* is the main cause of SSTIs. Once *Staphylococcus aureus* entry into the internal skin layers or blood, it may cause varying degrees of infection, including mild skin infections, as well as serious or life-threatening infections, including meningitis, bacteremia, sepsis, etc., even in cases of antibiotic resistance.[10] Mupirocin is known to inhibit penicillin-sensitive, penicillin-resistant, and methicillin-resistant strains (modal MIC, 0.12 ug/mL), as well as multi-resistant strains, including those harboring resistance to antibiotics, such as penicillin, methicillin, streptomycin, neomycin, erythromycin, fusidic acid, lincomycin, chloramphenicol, and tetracycline.[11] In addition, although mupirocin has relatively weak activity against Gram-negative bacteria, it still exerts antibacterial effects on some of them, including *Haemophilus influenzae* and *Neisseria gonorrhoeae*.[12]

Clinical Applications of Mupirocin

Previous studies have suggested the significant therapeutic effect of mupirocin monotherapy as a topical treatment for patients with primary or secondary skin infections, especially for those caused by *Staphylococcus aureus*. Additionally, Chinese investigators have performed multiple clinical studies on anti-infective combination therapy strategies based on different mechanisms of action (Table 1; Figure 1).

Treatment of Primary Infections

Impetigo

Topical treatment with mupirocin is one of the most effective treatment methods for patients with impetigo, with a high effective rate of 97.09% of mupirocin monotherapy in China,[4] and the effect was reported rapid, with an onset time of approximately 2–3 days.[13] Chinese investigators have also attempted to combine 2% mupirocin ointment with topical chloramphenicol lotion for the treatment of pediatric impetigo, which showed a significantly higher effective rate compared with 1% neomycin ointment (100% vs 70%, $P<0.005$).[14] Most patients could be cured within 5 days, with no recurrence after 1 month of follow-up.[14]

Furunculosis/Folliculitis

Furunculosis is a type of hair follicle infection, where its purulent lesions penetrate subcutaneous tissue through the dermis. Treatment with mupirocin ointment containing highly permeable polyethylene glycol may facilitate drug penetration into the dermis.[39] In China, it was reported that the effective rates of mupirocin ointment for the treatment of patients with folliculitis and furunculosis were as high as 93.9% and 88.46%, respectively.[4] Davido et al attempted to treat recurrent furunculosis patients by using a CMC combination regimen, which included chlorhexidine for skin

Table 1 Evidences for Clinical Applications of Mupirocin (Focusing on the Chinese Experience)

Author (Date)	Participants	Study Design	No. of Patients	Intervention	Efficacy Results
Primary Infections					
Xiao, et al[4] (2003)	Infectious skin diseases	Prospective cohort	700	Mupirocin	Total effective rate (% of cured + improved): All infections 93.86%, impetigo 97.09%, folliculitis 93.9%, furunculosis 88.46%.
Ye, et al[13] (2011)	Infectious skin diseases	RCT	132	Mupirocin vs Erythromycin	Cure rate: 64.4% vs 29.8%, *P*<0.05. The mean time to see the effect of mupirocin was 2~3d.
Huang.[14] (2010)	Pediatric impetigo	Prospective cohort	81	Mupirocin + Chloramphenicol vs Erythromycin	Total effective rate (% of cured + significant effective): 100% vs.70%, *P*<0.005.
Davido, et al[15] (2013)	Recurrent furunculosis	Prospective cohort	36	CMC (Mupirocin + chlorhexidine + clindamycin)	After treatment: Remission rate was 87% at 9 months, with 2 cases of recurrence.
Secondary Infections *Atopic dermatitis/Eczema combined with infections*					
Rist, et al[5] (2002)	Secondary infections include eczema and AD	RCT	159	Mupirocin vs Oral Cephalosporin	Improvement on the Skin Infection Scale (%): 89% vs 82%, *P*=0.29. Responding to bacterial eradication, improvement or colonisation (%): 50% vs 28%, *P*=0.005.
Gong, et al[16] (2006)	Eczema and AD	RCT	327	Mupirocin + Hydrocortisone butyrate vs Hydrocortisone butyrate	Effective rates (% of excellent + good): 79% vs 80% in patients with eczema. 95% vs 89% in patients with AD.
Wu.[17] (2018)	Eczema/AD	RCT	106	Mupirocin + Hydrocortisone butyrate vs Hydrocortisone butyrate	Total effective rate: 92.45% vs 75.47%, *P*<0.05. Time to stop itching: 2.64±0.34 d vs 4.52±1.46 d, *P*<0.05. Time for skin lesions to subside: 6.35±1.75 d vs 8.49±2.03 d, *P*<0.05.
Shi, et al[18] (2022)	Eczema and AD	RCT	150	Mupirocin + Glucocorticoids vs Glucocorticoids	EASI score after 2 weeks of treatment: 8.75±2.48 vs 12.33±3.95, *P*<0.05. Recurrence rate: 2.67% vs.12.00%, *P*<0.05. Dermatology Quality of Life Index score at the end of 2 weeks of treatment vs 1 month after drug withdrawal in the mupirocin group: 6.57±1.06 vs 4.12±1.13, *P*<0.05.
Ji, et al[19] (2018)	Steroid-resistant AD	RCT	82	Mupirocin + Mometasone furoate vs Mometasone furoate	Effective rate (% of cured + significant effective): After 7d of treatment: 18.18% vs 8.70%, *P*<0.05. After 14d of treatment: 62.86% vs 25.00%, *P*<0.05. The recurrence rate after 28 d of treatment: 31.43% vs 35.00%, *P*>0.05.

(*Continued*)

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Table 1 (Continued).

Author (Date)	Participants	Study Design	No. of Patients	Intervention	Efficacy Results
Trauma/surgical incision/burn wounds and other related infections					
Luo, et al[20] (2015)	Traumatic wound	RCT	60	Mupirocin combined with Comfeel ulcer strap vs Vaseline dressing	Wound healing time: 9.8±3.2 d vs 12.8±4.4 d, *P*<0.05. Mupirocin group had significantly better local scarring than the control group (*P*=0.029).
Yang, et al[21] (2017)	Severe trauma	RCT	86	Intranasal mupirocin + Chlorhexidine baths vs Routine treatment	Bacterial clearance: 81.4% vs 44.2%, *P*=0.044. Incidence of nosocomial infections: 14.0% vs 37.2%, *P*=0.026.
Ruffolo et al[22] (2021)	SSIs in superficial cutaneous surgeries	Systematic Review	37 studies	Intranasal mupirocin	Decolonization of carriers of *Staphylococcus aureus* with mupirocin is warranted for all superficial cutaneous procedures.
Wang, et al[23] (2021)	SSIs in cardiothoracic surgery	Meta-analysis	34589	Mupirocin vs Conventional bacteriostatic therapy	Mupirocin group significantly reduced the risk of all SSIs (RR=0.54; 95% CI: 0.40–0.75) and the risk of *Staphylococcus aureus*-SSIs (RR=0.44; 95% CI: 0.32–0.61)
Jiang, et al[24] (2020)	SSIs	Meta-analysis	5487	Mupirocin dressings vs Vitamin E dressings vs Other drug dressings	Three types of dressings all significantly reduced the overall SSI rate: Mupirocin group: OR=1.076, 95% CI: 1.014–1.142. Vitamin E group: OR=1.129, 95% CI: 1.016–1.255. Dialkylcarbamoyl-chloride: OR=1.047, 95% CI: 1.012–1.083. Surface Under the Cumulative Ranking curve: Mupirocin dressings vs vitamin E: 0.31 vs.0.37.
Zhang, et al[25] (2010)	Incision infection after abdominal surgery	RCT	42	Mupirocin + Vaseline gauze vs Iodoform gauze	Mean treatment time for postoperative incision infection: 4.7±2.6 d vs 10.2±3.7 d, *P*<0.01. Mean healing time of postoperative incision infection: 12.4±2.1 d vs 25.3±2.7 d, *P*<0.01.
Sun, et al[6] (2017)	Postoperative of condyloma acuminatum treated with CO_2 Laser Surgery	RCT	76	Beifuxin (Recombinant Bovine Basic Fibroblast Growth Factor Gel) + mupirocin vs Mupirocin monotherapy	Total effective rate: 95.5% vs 81.3%, *P*<0.05. Mean effective treatment time: 6.17±1.21 d vs 7.92±1.20 d, *P*<0.01.
Zhang, et al[26] (2015)	Small-to-medium-sized burn with *Staphylococcus aureus* infections	Historical controlled cohort study	64	Mupirocin vs Silver Sulfadiazine	Clinical effective rate after 5–10 d of treatment: 90.6% vs 37.5%, *P*<0.05. Bacterial clearance rate: 93.8% vs 28.1%, *P*<0.05.
Chen, et al[27] (2017)	Second-degree burn	Historical controlled cohort study	600	Mupirocin + Recombinant human epidermal growth factor vs Moist exposed burn ointment	Time to complete wound healing: 13.79±2.46 d vs 22.73±4.92 d, *P*<0.05. Incidence of scarring after wound healing: 19.67% vs 39.00%, *P*<0.05.
Wang, et al[28] (2019)	Burn	Historical controlled cohort study	60	Mupirocin + Recombinant human fibroblast growth factor vs Povidone iodine ointment	Total effective rate: 96.7% vs.76.7%, *P*<0.05. Mean wound healing time: 15.62±3.01 d vs.24.05±7.16 d, *P*<0.01.
Miao, et al[29] (2020)	Second-degree burn	RCT	76	Mupirocin + Recombinant bovine basic fibroblast growth factor vs Regular burns cream	Time to complete wound healing: 12.68±1.35 d vs.23.84±5.13 d, *P*<0.05. Incidence of scarring after wound healing: 13.16% vs.39.47%, *P*<0.05.

Catheter-related infections					
Tacconelli, et al[30] (2003)	Haemodialysis or peritoneal dialysis	Meta-analysis	2445	Mupirocin vs Placebo/no treatment	Mupirocin significantly reduced the infection risk compared to placebo: All patients undergoing dialysis: reduced by 68% (95% CI: 57%-76%). Hemodialysis patients: reduced by 80% (95% CI: 65%-89%). Peritoneal Dialysis patients: reduced by 63% (95% CI: 50%-73%).
Luo, et al[31] (2020)	Diabetic Nephropathy Hemodialysis	RCT	200	Mupirocin + An'erdian skin disinfectant (iodine + chlorhexidine acetate + alcohol) vs An'erdian skin disinfectant	Catheter-related infections rate: 5% vs.16%, $P<0.05$.
Diabetic foot					
Yan, et al[7] (2014)	Diabetic foot ulcers	RCT	66	Mupirocin + infrared irradiation vs povidone-iodine	Total effective rate: 90.91% vs 72.73%, $P<0.01$.
Shan, et al[32] (2021)	Diabetic foot in the elderly	Retrospective cohort study	64	Prostadil + Cilostazol + Mupirocin vs Prostadil	Total effective rate: 90.00% vs 64.52%, $P<0.05$.
Other clinical applications					
Bai.[33] (2019)	Stroke with grade II pressure ulcers	RCT	80	Mupirocin Wound disinfectant spray + Routine treatment vs Routine treatment	Total effective rate (% of effective + significant + cured): 97.5% vs.82.5%, $P<0.05$. Wound healing time: 14.43±2.15 d vs.29.87±4.76 d, $P<0.05$.
Yang.[34] (2013)	Diabetes with pressure ulcers	RCT	63	Mupirocin + Topical norfloxacin vs Topical insulin	Total effective rate (% of cured + significant + improved): 100% vs.83.9%, $P<0.05$.
Li, et al[35] (2005)	Neonate red buttocks	RCT	60	Mupirocin + Nystatin vs Chlortetracycline	Effective rate: 100% vs.66.7%, $P<0.05$.
Zhang.[36] (2004)	Neonatal staphylococcal scalded skin syndrome	RCT	38	Mupirocin + Intravenous azithromycin vs Intravenous penicillin or erythromycin	Cured rate: 75.0% vs.44.4%, $P<0.05$.
Khorvash, et al[37] (2013)	Moderate to severe acne	RCT	105	Mupirocin + Standard treatment vs Standard treatment vs Rifampicin + Standard treatment	All three groups significantly improved acne lesions compared to baseline (All $P<0.001$): Week 6 Global Acne Grading System (GAGS) scores: 12.2±7.3 vs 10.2±6 vs 15.7±6.1. Week 12 GAGS scores: 6.3±5.5 vs 4.6±5.9 vs 9.3±5.5.
Ma, et al[38] (2022)	Fungal infections of the external auditory canal	RCT	92	Mupirocin + trimethoprim econazole vs Trimethoprim econazole	Total effective rate: 95.65% vs.82.60%, $P<0.05$. All cured patients were followed up for 3 months, with no recurrence in the treatment group and 6 cases of recurrence in the control group.

Abbreviations: RCT, Randomised controlled trial; AD, atopic dermatitis; SSIs, surgical site infections; RR, relative risk; OR, odds ratio; 95% CI, 95% confidence interval.

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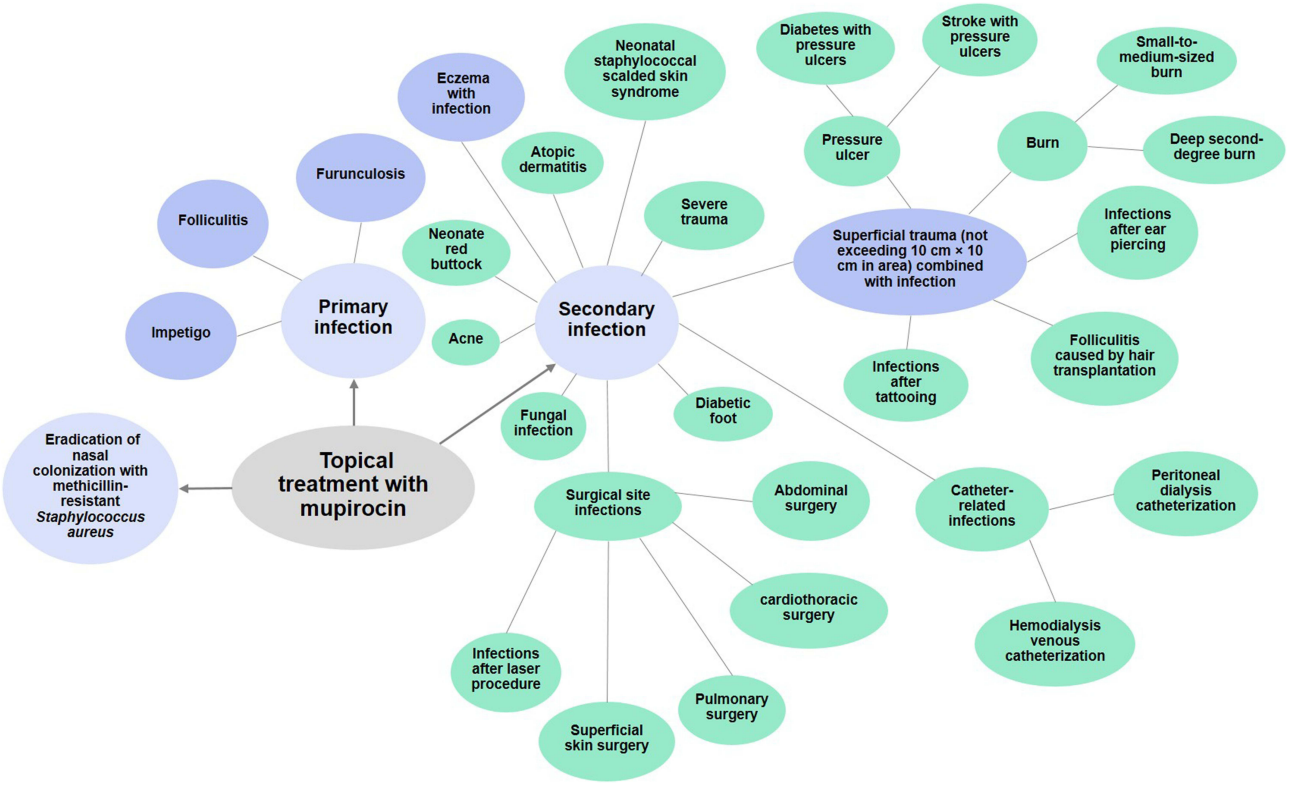

Figure 1 Blue circles represent well known indications for mupirocin. Green circles represent other applications of mupirocin mentioned in this article.

disinfection, mupirocin nasal ointment and systemic antibiotic clindamycin, and achieved significant therapeutic effect (cure rate of 87%).[15]

Treatment and Prevention of Secondary Infections

Atopic Dermatitis/Eczema Combined with Infection

The incidence of *Staphylococcus aureus* colonization in moderate to severe atopic dermatitis (AD) patients is relatively elevated, with approximately 70%.[40] Therefore, anti-infective treatment is necessary. Mupirocin monotherapy has been shown a significant efficacy in the treatment of secondary infections such as eczema and AD. The clinical efficacy of topical 2% mupirocin ointment was similar with oral cephalosporin (89% vs 82%, P=0.29), while the success rate for bacterial infection was higher (50% vs 28%, P=0.005).[5] For the patients' perspective, 65.5% of individuals preferred mupirocin monotherapy, which might be related to the topical treatment's ability to prevent certain systemic side effects.[5]

Combination of mupirocin based on steroid drugs could be used for moderate to severe AD patients concurrent bacterial infections.[16–18] At the end of 28-day treatment period, the efficacy rates, as assessed by researchers, were 79% and 80% for patients with eczema in the mupirocin and steroid combination and steroid monotherapy control groups, respectively. For AD patients, the corresponding rates were 95% and 89%. Meanwhile, compared with pre-treatment, Eczema Area and Severity Index (EASI) scores in both eczema and AD patients in the combination and control groups were significantly reduced (both P<0.01).[16] Furthermore, in patients with moderate to severe eczema, the efficacy was shown significantly better in the mupirocin combined regimen group than control group (hydrocortisone butyrate only) on day 7, while there were no significant differences between groups on day 14 and 28.[16] This suggested that the benefits of early use of the combined regimen were better than in patients administered steroids monotherapy, in moderate to severe cases.[16] It has been found that the total effective rate in patients with eczema/AD patients who administered mupirocin ointment combined with hydrocortisone butyrate ointment was 92.45%, higher than in cases treated with hydrocortisone butyrate alone (75.47%, P<0.05), with the effect of relieving itching and resolving skin lesions (both P<0.05).[17] It has also been found that the combination therapy of mupirocin ointment and budesonide cream could

reduce recurrence rate in eczema/AD patients within 3 months after discontinuation to 2.67%, significantly lower than that in the budesonide monotherapy group (12.00%, $P<0.05$).[18] Besides, for certain cases of steroid-resistant AD patients, Ji et al demonstrated that effective rates of the mupirocin and mometasone furoate combination regimen were 18.18% and 62.86% after 7 and 14 days, respectively (the control group were 8.70% and 25.00%, both $P<0.05$).[19]

Trauma/Surgical Incision/Burn Wounds and Other Related Infections

Trauma, especially open trauma, can promote infections by bacteria such as *Staphylococcus aureus* or MRSA,[41] so antibiotics are needed for treatment and prevention. Chinese investigators have explored various types of traumatic infections and found that in patients with open wounds (3 cm×3.5 cm-10 cm×13 cm), mupirocin ointment combined with hydrocolloid dressings might bring pain relief during dressing changes, improved the comfort of patients, decreased wound healing time and frequency of dressing changes, and reduced scar formation.[20] In addition, mupirocin could also be used as a preventive tool to reduce the risk of hospital-acquired infections in patients with severe trauma.[21]

Multiple meta-analysis or systematic review have demonstrated that mupirocin was effective in preventing infection risk in superficial skin surgery, pulmonary surgery, and cardiothoracic surgery, and reducing the incidence of surgical site infections (SSIs).[22–24] In China, the application of mupirocin ointment in patients who had undergone abdominal surgery and superficial skin surgery to prevent wound infection has also been reported, and the combination of mupirocin was thought to be effective in wound healing because the healing time was shortened.[6,25] For example, mupirocin ointment could be applied after routine debridement with vaseline gauze used to cover the wound surface in patients who had undergone abdominal surgery, with the shorter average treatment (4.7±2.6 days) and average healing (12.4±2.1 days) times for postoperative incision infection than filled with iodoform gauze only (both $P<0.01$).[25] In patients with condyloma acuminatum who have administered CO_2 laser procedure, may also at risk of postoperative wound infections.[6] Mupirocin combined with recombinant bovine basic fibroblast growth factor topical gel was found to have significantly efficacy in wound healing in the above patients, with total effective rate of 95.5%, and healing time was shortened (average effective time for the treatment of 6.17±1.21 days).[6]

Burn patients are also highly susceptible to infection with *Staphylococcus aureus*, which is an important cause of delayed wound healing. In China, mupirocin ointment can be used for anti-infective and healing-promoting treatments of small-to-medium-sized burn, with significantly improved bacterial clearance rate (93.8% vs 28.1%, $P<0.05$) and clinical effective rate (90.6% vs 37.5%, $P<0.05$), compared with the control group administered topical 2% sulfadiazine silver.[26] For larger or more severe burn wounds, it was possible to consider adding mupirocin to conventional burn drugs such as recombinant human epidermal growth factor, recombinant human fibroblast growth factor, and recombinant bovine basic fibroblast growth factor, which could significantly reduce healing time for burn wounds (12.68–15.62 days), improve the effective rate (up to 96.7%), and reduce the incidence of scar formation post-healing (13.16%-19.67%), especially for deep second-degree burn with significant therapeutic effects.[27–29]

In summary, mupirocin not only exhibits strong antibacterial activity against various Gram-positive cocci associated with skin infections but also plays a promotive role in wound healing. It has been discovered that topical application of mupirocin might satisfy the wet healing environment, stimulate the proliferation of human keratinocytes, and promote the production of growth factors for wound healing, thereby promoting re-epithelialization and reducing scar formation.[42] This may be one of the reasons for its pro-healing effects, but more research is needed to verify it.

Catheter-Related Infections

Topical antibiotic therapy may decrease the risk of dialysis exit-site infection (ESI) and peritonitis in patients. A meta-analysis demonstrated that among patients undergoing dialysis who received treatment of mupirocin, the incidence of *Staphylococcus aureus* infection was reduced by 68%, specifically, infection risk in hemodialysis patients was reduced by 80%, while infection risk in peritoneal dialysis patients was reduced by 63%.[30] In Chinese clinical experience, the anti-infective efficacy of mupirocin in dialysis patients generally corroborates foreign reports. During hemodialysis venous (including internal jugular, femoral, subclavian, central and other veins) catheterization, the incidence of catheter-related infections were significantly reduced in patients who treated by 2% mupirocin ointment combined with routine treatment, with the prolonged indwelling time.[31]

Diabetic Foot

The infection rate of diabetic foot is high, and the most involved bacteria are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. There is a lack of current reports on the treatment of diabetic foot with mupirocin in other countries, while in China, clinicians have applied mupirocin based regimens for diabetic foot, and have achieved significant efficacy.[7,32] Topical mupirocin ointment plus infrared irradiation in the treatment of diabetic foot ulcers was discovered a significantly better total effective rate of 90.91% than the control group of iodophor dressing change (72.73%, $P<0.01$).[7] The triple therapy regimen of mupirocin, alprostadil and cilostazol was reported significantly improved the total effective rate in treating elderly cases with diabetic foot, when compared with alprostadil monotherapy (90.00% vs 64.52%, $P<0.05$).[32] These findings suggested a significant therapeutic effect of mupirocin based regimens on diabetic foot, which could improve the healing of ulcer surface or reduce treatment time.

Other Clinical Applications

Chinese investigators have also extended previous findings by conducting multiple clinical studies assessing the application of mupirocin in other diseases/states, including stroke patients with grade II pressure ulcers,[33] diabetes patients with pressure ulcers,[34] neonate red buttocks,[35] neonatal staphylococcal scalded skin syndrome,[36] and acne or fungal infections,[37,38] with the total effective rate of 95%~100%. These results suggested treatment regimens containing mupirocin have broad clinical application potential. In recent years, clinicians have also applied this drug to post-care following medical cosmetic procedures such as infections after ear piercing, folliculitis after hair transplant, infections after tattooing and post-laser treatment. And further clinical trials are warranted to provide sufficient evidence to support these notions.

Safety of Mupirocin

Mupirocin is a topical antibiotic with limited systemic absorption and elevated permeability only on the surface of traumatic skin. Topical application of this drug generally has no adverse reactions. Currently, most reported cases have mild local side effects, with rare systemic toxicity or abnormal laboratory examination indexes. In addition, the excipient of mupirocin ointment is polyethylene glycol, and high doses of polyethylene glycol may cause kidney damage, so mupirocin should be avoided in conditions where absorption of large quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment.

Role of Mupirocin in Guidelines

Mupirocin is used in multiple countries around the world to treat SSTIs, especially primary infections. It is highly recommended as a drug for impetigo in clinical guidelines in many countries, eg, the United States,[43] Italy,[44] and South Korea.[45] The experience of mupirocin in impetigo treatment and the prevention of MRSA infection in China is basically consistent with those reported in other countries, moreover, earlier supporting its recommendation in Chinese clinical practice,[8,46,47] usually as the preferred topical antibiotic. Other countries have insufficient evidence for mupirocin in the field of secondary infections, while Chinese guidelines and consensus recommend mupirocin in many clinical application indications, including surgery, burns, catheterization and diabetes-related infections,[8,9] confirming its clinical efficacy.

Mupirocin Resistance in China and Other Countries

Long-term and large-area topical application of mupirocin may promote drug resistance, which is unlikely with short-term use. Mupirocin effectively reduces the risk of MRSA colonization and cross-transmission, while drug resistance decreases its effectiveness against *Staphylococcus aureus*/MRSA colonization, limiting treatment options for MRSA infected patients.

The mechanisms of mupirocin resistance include: (1) due to a point mutation in the *ileS* gene, which encodes isoleucyl-tRNA synthetase, amino acid substitutions such as V588F, V631F, G593V, R816C, H67Q, and F563L in IleRSs are combined, leading to a Val-to-Phe change at the mupirocin binding site, which in turn induces low-level mupirocin resistance, ie, chromosomal-encoded mupirocin resistance; (2) high-level mupirocin resistance is plasmid-encoded

mupirocin resistance: 1) can be mediated by acquisition of plasmid-mediated *mupA* or *ileS2* gene, which encode an IleRSs variant not sensitive to mupirocin; 2) due to the the *mupB* gene, with a 65% similar sequence to *mupA*.[3] Despite the presence of resistance, mupirocin's unique mechanism of action makes it relatively less likely to exhibit cross-resistance with other antibiotics. It has been demonstrated in vitro that this drug has lower resistance rate to multi-resistance compared to many other antibiotics, *Staphylococcus aureus* (including MRSA) has a higher sensitivity to antibiotics,[48] which may explain the lowest MIC value of mupirocin.[49] Furthermore, there is currently no evidence of cross-resistance between mupirocin and many other antibiotics, such as erythromycin, ciprofloxacin, and fusidic acid.

At present, there are inconsistent reports on mupirocin resistance worldwide. A systematic review conducted in 2020 found global resistance rates for *Staphylococcus aureus* and MRSA to mupirocin of 7.6% and 13.8%, respectively.[50] In the past few years, the MRSA-mupirocin resistance rates reported in the United States seemed to be high (22.5%),[51] while South Korea and Argentina reported relatively low values, at 4.4% and 2.3%, respectively.[52,53] Mupirocin has been shown total low resistance in clinical applications in China, with the rate of mupirocin resistance for *Staphylococcus aureus* is about 0.1% to 5.02% (2007–2016),[54–56] and about 0.9% to 10% (2004–2020) for MRSA,[48,56–59] and the overall change in mupirocin resistance rate in China over the years is relatively low.[54]

According to genetic heterogeneity, mupirocin resistance can be divided into two categories: high-level resistance (MuH) and low-level resistance (MuL). Many reports from other countries have found relatively similar incidence rates of MuH and MuL. For example, the proportions of *Staphylococcus aureus*-infected patients with MuH and MuL in Africa ranged from 0.5%-38% and 4%-47%, respectively.[60] The incidence rates of MRSA-MuH and MRSA-MuL in South Korea were 1.8% and 2.6%, respectively.[52] Different from other countries, in China, resistance to mupirocin is usually dominated by MuH, which has several times higher resistance than MuL, with the rates of 6.6% and 0% in 2010,[61] 4.1% and 1.0% in 2020, respectively.[57] These differences in values may be attributed to distinction in diverse prevalence rates, medical policies and treatment adherence for mupirocin in various countries/regions, or related to the patient's genetic heterogeneity.

Conclusion and Future Directions

The advantages of mupirocin lie in its potent inhibitory effect on Gram-positive bacteria while also having a broad-spectrum antimicrobial action. Mupirocin is the most applied topical antibiotic for *Staphylococcus aureus* worldwide, especially MRSA. It is safe and effective in treating SSTIs and may be used for secondary infections caused by *Staphylococcus aureus* or MRSA. Additionally, as a topical preparation, mupirocin is easy to use, and its negligible systemic absorption may reduce the risk of systemic side effects. The main disadvantage of mupirocin, similar to other antibiotics, mupirocin also has resistance, but the total resistance rate in China is low, so mupirocin still plays an important role in infectious skin diseases and more extensive *Staphylococcus aureus* infections. The safety and precautions of this medication have been described earlier, and mupirocin is limited in its use for patients with kidney function impairment.

Over the last several years, clinical experience of this drug in China has provided valuable references and novel ideas, including the control of MRSA infections by combination therapy that may be better than monotherapy, eg, combining antibiotics with different mechanisms of action, antifungal drugs. In recent Phase 4 clinical studies of mupirocin, it is being validated in terms of preventive effects on surgical site infections (NCT05586776 and NCT03962907) and dialysis-related infections (NCT02945722), and also mupirocin is being explored for potential benefits in other skin diseases such as radiation dermatitis (NCT0383828 and NCT05505214).

The clinical application of and drug resistance to mupirocin vary among countries, so it is necessary to perform further epidemiological investigations. In the future, the reduction of mupirocin resistance or enhancement of its bactericidal effect is expected to be achieved by: (1) controlling the biosynthesis and/or structure of this drug via biotechnological approaches to develop novel mupirocin derivatives, and (2) developing new formulations such as mupirocin nanomaterial formulations and mupirocin-silver complexes, etc. (3) developing combination therapy such as combining mupirocin with novel inhibitors targeting *Staphylococcus aureus* (including MRSA) and novel chimeric lysozyme ClyQ. Additionally, developing new therapies targeting mupirocin-resistant bacteria through drug repurposing

strategy is also worth exploring. We look forward to expanding the spectrum of diseases treated with mupirocin, which is expected to benefit more patients clinically.

This article still has some limitations. Firstly, mupirocin was developed and marketed quite some time ago, so the evidence from recent years discussed in this article was relatively insufficient. Secondly, there is heterogeneity in bacterial infection conditions and policies on the use of mupirocin vary across different countries. Therefore, the clinical experience from China provides some reference, but may not be suitable for all patient populations. Clinical physicians still need to formulate individualized plans based on a comprehensive consideration of various factors. We look forward to more updated evidence-based evidence of mupirocin, resistance control strategies, and clinical practical experience in the future, so as to bring benefits to more patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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