Impetigo Agents, Topical Review

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FDA-Approved Indications

Drug	Manufacturer	Indication(s)
mupirocin 2% ointment[1]	generic	Treatment of impetigo due to *S. aureus* and *S. pyogenes*
mupirocin 2% cream (Bactroban®)[2]	GlaxoSmithKline	Treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *S. aureus* and *S. pyogenes*
retapamulin 1% ointment (Altabax™)[3]	GlaxoSmithKline	Treatment of impetigo due to *S. aureus* (methicillin-susceptible isolates only) and *S. pyogenes*

Mupirocin 2% ointment (Bactroban) is also available as a nasal ointment and is indicated in the eradication of nasal colonization with MRSA in adult patients and healthcare workers.[4]

Overview

Impetigo is a highly contagious skin infection caused by bacteria, usually *Staphylococcus aureus* or *Streptococcus pyogenes*. Impetigo caused by methicillin-resistant *S. aureus* (MRSA) has increased in frequency, and its prevalence varies by geographical location.[5,6,7,8,9] The disease is most common in infants and children between the ages of two and five years, but impetigo also occurs in adults.[10] It is prevalent in crowded living spaces and in populations with poor skin hygiene.

In the United States, impetigo accounts for approximately 10 percent of skin problems observed in pediatric clinics. Because it occurs more frequently in a warm humid environment, impetigo is more common in the Southeastern United States.[11]

Microorganisms colonize unbroken skin; once there is a scratch, insect bite, or minor trauma, these surface bacteria inoculate the cut skin. Impetigo occurs mostly on exposed areas of skin (face and extremities) and develops as lesions that are bullous or non-bullous (accounts for 70 percent of cases) in appearance. The sores contain pus and rupture after a few days to form a thick crust. The sores are pruritic and scratching them can cause further spread. Impetigo can also be spread from person to person by contact with the sores or nasal discharge from an infected person.[12] If left untreated, impetigo is usually self-limiting and can resolve in approximately two weeks without resultant scarring.[13]

The Infectious Diseases Society of America (IDSA) 2005 practice guidelines for the diagnosis and management of skin and soft-tissue infections recommend mupirocin (Bactroban) ointment as the topical antibacterial drug of choice in the treatment of impetigo in infants two months and older and in adults.[14] Mupirocin ointment has activity against *S. pyogenes* and both methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), although resistance has been described.[15,16] Other topical agents, such as bacitracin and

neomycin, are considerably less effective topical treatments when compared to mupirocin ointment. Oral antibiotics, erythromycin, cephalexin, clindamycin and dicloxacillin, are used to treat impetigo, and only effective for methicillin-sensitive *S. aureus* (MSSA).[17,18] Topical therapy with mupirocin ointment is equivalent to oral systemic antimicrobials and may be used when lesions are limited in number. Patients who have numerous lesions or who are not responding to topical agents should receive oral antimicrobials effective against both *S. aureus* and *S. pyogenes*. Retapamulin was not available at the time of guideline development and publication.

Retapamulin (Altabax) ointment is approved for the treatment of impetigo due to *S. aureus* (methicillin-susceptible isolates only) and *S. pyogenes*. Retapamulin (Altabax) has been studied in one published head-to-head trial with oral cephalexin in the treatment of secondarily infected traumatic lesions of the skin (SITL) and in another published trial with oral cephalexin in the treatment of secondarily infected dermatitis (SID).[19,20] Retapamulin (Altabax) is not FDA approved for use to treat infections caused by MRSA, secondarily infected dermatitis, or superficial traumatic skin lesions.

In October 2007, a study established the first national baseline by which to assess trends in invasive MRSA infections.[21] The study found that 85 percent of all invasive MRSA infections were associated with healthcare settings. The study estimates 94,360 cases of life-threatening MRSA infections and 18,650 deaths in the United States in 2005. The 2005 rates for invasive infection were higher among the age of 65 years and older, and African Americans were affected at twice the rate of whites.

The most common skin infections are caused by *Staphylococcus aureus*, group A streptococci (*Streptococcus pyogenes*), or the normal skin flora.[22] Secondarily infected traumatic skin infections include lacerations, sutured wounds, abrasions, etc. Mupirocin (Bactroban) cream is indicated in the treatment of secondary infected traumatic skin lesions due to susceptible strains of *S. aureus* and *S. pyogenes*.

Pharmacology[23,24,25,26]

Mupirocin is an antibacterial which reversibly and specifically binds to bacterial isoleucyl transfer-RNA synthetase resulting in the inhibition of protein synthesis. Mupirocin is bactericidal at concentrations achieved by topical administration. However, the minimum bactericidal concentration (MBC) against relevant pathogens is generally eight-fold to thirty-fold higher than the minimum inhibitory concentration (MIC).

Retapamulin (Altabax) is the first in a new class of antibacterials, the pleuromutilins, which inhibit normal bacterial protein biosynthesis by binding at the unique site (L3) on the ribosomal 50S subunit. This prevents the formation of active 50S ribosomal subunits by inhibiting peptidyl transfer and blocking P-site interactions at this site. Retapamulin is bacteriostatic against *S. aureus* and *Streptococcus pyogenes* at the retapamulin *in vitro* minimum inhibitory concentration (MIC) for these organisms. At concentrations 1,000 times the *in vitro* MIC, retapamulin is bactericidal against these same organisms.

Pharmacokinetics

Absorption of both topical agents is low. Data indicate more frequent occurrence of percutaneous absorption in children (90 percent of patients) than adults (44 percent of patients). However, mupirocin systemically absorbed is rapidly metabolized to the inactive metabolite, monic acid, which is renally excreted.[27,28]

Retapamulin (Altabax) is 94 percent protein bound.[29] Retapamulin (Altabax) is metabolized by cytochrome (CYP) 3A4 hepatic enzymes by mono-oxygenation and di-oxygenation to multiple metabolites.

Contraindications/Warnings[30,31,32]

Hypersensitivity to these agents or their components is considered a contraindication. These agents are for topical use only. They should not be used for ophthalmic, intranasal, oral, or intravaginal use. They should be discontinued should sensitization or severe local irritation occur, and super-infection occur. A paraffin-based formulation – Bactroban Nasal (mupirocin intranasal ointment) – is available for intranasal use.

Retapamulin (Altabax) should not be used in the absence of proven or strongly suspected bacterial infection.

Mupirocin ointment contains polyethylene glycol (PEG) and should be avoided in conditions where absorption of large quantities of PEG is possible, especially if there is evidence of moderate to severe renal impairment; mupirocin (Bactroban) cream is not in a PEG base.[33]

Drug Interactions[34,35,36]

The effect of concurrent application of mupirocin ointment or cream and other drugs has not been studied.

Oral ketoconazole was shown to increase AUC and Cmax of retapamulin by 81 percent. Systemic absorption of retapamulin is low; therefore, interactions with other CYP 450 substrates are not expected. The effect of concurrent application of retapamulin and other topical agents to the same area of skin has not been studied.

Adverse Effects

Drug	Application Site Irritation (%)	Headache (%)	Diarrhea (%)	Nausea (%)
mupirocin 2% ointment[37]	1.5	nr	nr	< 1
mupirocin 2% cream (Bactroban)[38]	< 1	1.7-3.6	nr	1.1-4.9
retapamulin 1% ointment (Altabax)[39]	1.5-1.6	1.2-2.0	1.4-1.7	1.2

Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported.

Pruritus has been reported in 2.4 percent of patients on mupirocin (Bactroban) cream.

The safety of retapamulin (Altabax) was evaluated in 2,115 adult and pediatric patients aged greater than nine months old who used at least one dose from a five day, twice daily regimen of retapamulin ointment.[40] Control groups included 819 patients who used at least one dose of the active control (oral cephalexin), 172 patients who used an active comparator (which is not available in the US), and 71 placebo patients. Adverse events occurred in 5.5 percent of patients in the retapamulin group, 6.6 percent in the cephalexin group, and 2.8 percent of placebo. The most common adverse reactions were: application site irritation (1.4 percent) in retapamulin group, diarrhea (1.7 percent) in the cephalexin group, and application site pruritis (1.4 percent) and application site paresthesia (1.4 percent) in placebo.

Special Populations[41,42,43]

Pediatrics

The safety and effectiveness of mupirocin ointment and retapamulin (Altabax) ointment have been established in patients aged two months and older, and nine months and older, respectively. Mupirocin (Bactroban) cream has been FDA approved in patients aged three months and older.

Pregnancy

All agents are Pregnancy Category B.

Dosages

Drug	Adult	Pediatrics	Availability
mupirocin 2% ointment[44]	Apply three times daily; re-evaluate after three to five days if no clinical response	Same dose for patients 2 months to 16 years old	2% ointment- 0.9, 22 gm 2% Bactroban- 22 gm
mupirocin 2% cream (Bactroban)[45]	Apply three times daily for ten days; re-evaluate after three to five days if no clinical response	Same dose for patients 3 months to 16 years old	2% cream-15, 30 gm
retapamulin 1% ointment (Altabax)[46]	Apply twice daily for five days; total treatment area should not exceed 100 cm^2	For patients 9 months to 17 years old: apply twice daily for five days; total treatment area should not exceed 2% body surface area	1% ointment- 5, 10, 15 gm

Clinical Trials

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled trials studying agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no published head to head trials comparing mupirocin and retapamulin (Altabax) in the treatment of impetigo. Due to the lack of studies, placebo-controlled trials have been included.

mupirocin (Bactroban) ointment and placebo

The efficacy of mupirocin ointment in impetigo was assessed in a randomized, double-blind trial of adults and children aged two months and older.[47] Of the patients studied, 91 percent were between the ages of two months and 15 years. Patients received either mupirocin 2% ointment three times daily or placebo for eight to 12 days. Clinical efficacy rates at the end of therapy in the population were 71 percent for mupirocin (n=49) and 35 percent for placebo (n=51). Pathogen eradication rates were 94 percent and 62 percent, in the mupirocin and placebo groups, respectively. There were no adverse events reported for the mupirocin group.

mupirocin (Bactroban) ointment and oral erythromycin

Mupirocin ointment three times daily for eight days was compared to oral erythromycin 40 mg/kg/day, in a randomized open-label trial of patients five months to 13 years old with impetigo.[48] Patients were seen on days four to five of therapy, at end of therapy, and seven days after therapy had ended. At the first visit, 24 of 30 children in the mupirocin and 14 of 32 children in the erythromycin group were cured or had at least a 75 percent reduction in size of lesions. At the completion of the study, all 29 patients in the mupirocin group and 27 of the 29 patients in the erythromycin group were cured. Mild diarrhea developed in the erythromycin group. The study concluded that mupirocin appears to be safe and effective in the treatment of impetigo in children.

A prospective double-blind, randomized trial, compared topical mupirocin with oral erythromycin to determine the prevalence of erythromycin-resistant *S. aureus* strains in impetigo and whether an increased rate of failure of erythromycin was associated with such resistance.[49] A total of 102 patients between three months and 15.5 years old were enrolled and received erythromycin 50 mg/kg/day or mupirocin 2% ointment, plus respective placebos for seven days. *S. aureus* was cultured from 88 percent of patients of which 28 percent were erythromycin-resistant. In all cases *S. aureus* was sensitive to mupirocin. Only patients with erythromycin-resistant *S. aureus* strains had unfavorable courses compared with mupirocin (failure rate 47 percent versus two percent, respectively). Patients with erythromycin-susceptible *S. aureus* strains who received erythromycin had a failure rate of eight percent. In four patients, *S. aureus* strains initially susceptible to erythromycin became resistant during treatment. The study concluded that erythromycin-resistant *S. aureus* strains were commonly isolated from impetigo lesions in the study region.

retapamulin (Altabax) and placebo

The safety and efficacy of retapamulin was evaluated in a randomized, double-blind, placebo-controlled, multicenter study.[50,51] Two-hundred thirteen patients were randomized. A total of 210 adults and children aged nine months and older with impetigo (up to 100 cm^2 in total area- up to ten lesions- or a total body surface area not exceeding two percent), were randomized to retapamulin 1% ointment or placebo, applied twice daily for five days. Patients with underlying skin disease or skin trauma with evidence of secondary infections were excluded from the study. Most of the patients (78 percent) were less than 13 years old. Clinical success rates, defined as response of impetigo at seven days where no further antimicrobial treatment was required, were higher in the retapamulin group versus placebo, 85.6 percent versus 52.1 percent for the intent to treat population, respectively (95% CI, 20.5 to 46.5; $p<0.0001$). Pruritus at the application site was reported by six percent and one percent of the retapamulin and placebo groups, respectively.

mupirocin (Bactroban) cream and oral cephalexin

A randomized, double-blind, double-dummy, multicenter trial of 159 patients with secondarily infected eczema and a total skin infection rating scale score of eight or greater compared mupirocin 2% cream three times daily to oral cephalexin 250 mg four times daily for ten days.[52] Per protocol clinical success, defined partly as a patient with a response of improvement in the skin infection rating scale, was similar in both arms: 89 percent and 82 percent, in the mupirocin and cephalexin groups, respectively (95% CI, -8.4 to 22.5; $p=0.29$). Bacteriological success defined as eradication, improvement or colonization of bacteria at end of therapy, was higher in

the mupirocin group versus cephalexin, 50 percent versus 28 percent, respectively (p=0.005). Both drugs were well tolerated. Diarrhea and nausea were common adverse effects.

Two identical randomized, double-blind studies of 706 patients with secondarily infected wounds (small lacerations, abrasions, or sutured wounds) compared mupirocin 2% cream topically three times daily to oral cephalexin four times daily for ten days.[53] Clinical success at follow-up was the same in the two groups, 95.1 percent versus 95.3 percent in the mupirocin cream and the cephalexin groups, respectively (95% CI, -4.0% to 3.6%; p=0.89). The intention-to-treat success rate was 83 percent in both groups. Bacteriologic success at follow-up was similar in the two groups: 96.9 percent in the mupirocin cream versus 98.9 percent in the cephalexin groups (95% CI, -6.0% to 2.0%; p=0.22). Adverse event profile was similar, however, more diarrhea in the cephalexin group was reported.

Mupirocin cream was compared to oral cephalexin in two randomized, double-blind, double-dummy studies of secondarily infected skin lesion studies.[54] In the studies, 93 pediatric patients aged two weeks to 16 years old were randomized to mupirocin 2% cream three times daily or oral cephalexin 250 mg four times daily for patients > 40 kg or 25 mg/kg/day oral suspension in four divided doses for patients ≤ 40 kg, for ten days. At follow-up (seven to 12 days after therapy), clinical efficacy was achieved in 97.7 percent and 93.9 percent, in mupirocin and cephalexin, respectively.

Meta-analyses

A meta-analysis of 57 randomized controlled trials including 3,533 patients, studied comparisons of 20 oral and 18 topical treatments for impetigo.[55] Topical antibiotics had better cure rates than placebo (pooled OR 6.49, 95% CI, 3.93 to 10.73). There was no significant difference between topical mupirocin and topic fusidic acid (pooled OR of mupirocin versus fusidic acid 1.76, 95% CI, 0.69 to 2.16). Fusidic acid is not commercially available in the United States. Topical mupirocin had better cure rates compared to oral erythromycin (OR 1.22, 95% CI, 1.05 to 2.97). There were no significant differences in cure rates among other topical and oral antibiotics studied.

Another meta-analysis of 16 randomized controlled trials, including double-blinded and observer-blinded trials, indicated that topical antibiotics were more effective than placebo (OR 2.69, 95% CI, 1.49 to 4.86).[56] There was weak evidence favoring topical antibiotics over some oral antibiotics, such as erythromycin (OR 0.48, 95% CI, 0.23 to 1.00). There was no significant difference among the topical therapies, mupirocin and fusidic acid. (OR 1.76, 95% CI, 0.77 to 4.03).

Summary

The Infectious Diseases Society of America (IDSA) 2005 practice guidelines for the diagnosis and management of skin and soft-tissue infections recommend mupirocin (Bactroban) ointment as the topical antibacterial drug of choice in the treatment of impetigo in infants two months and older and adults.

Mupirocin and retapamulin (Altabax) have not been studied in head to head trials in the treatment of impetigo, so it is unclear if retapamulin (Altabax) is more effective than mupirocin. Retapamulin (Altabax) is not FDA approved for use in infections caused by MRSA. At this time, retapamulin has only been compared to placebo.

Retapamulin (Altabax) has an advantage in that its dosage regimen is twice daily versus that of mupirocin. which is three times daily. However, total treatment area for retapamulin should not exceed 100 cm^2 in adults or two percent of total body surface area (BSA) in children and adolescents. Retapamulin (Altabax) is an alternative to mupirocin ointment for the topical treatment of impetigo due to *S. aureus* (methicillin-susceptible isolates only) and *S. pyogenes*. Impetigo is usually a self-limiting skin infection, but resistance patterns should be taken into account in the choice of therapy.

Mupirocin (Bactroban) cream is FDA approved for the treatment of secondary infected traumatic skin lesions due to susceptible strains of *S. aureus* and *S. pyogenes*. It is not indicated for impetigo. However, mupirocin ointment is FDA approved for the treatment of impetigo due to *S. aureus* and *S. pyogenes*. Mupirocin (Bactroban) cream is not in a polyethylene glycol (PEG) base as mupirocin ointment. PEG can be absorbed from open wounds and damaged skin therefore should be avoided in patients with moderate to severe renal impairment. Although direct comparative trials of the cream and ointment formulations are lacking, they are not considered interchangeable.

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