Review

Silver sulfadiazine in modern dermatology

Natalia Chalupczak, BS[1][a], Jessica Q. Duong, BS[2], Joseph Jorizzo, MD, PhD[2,3], Steven R. Feldman, MD, PhD[2,3,4,5]

[1] Chicago Medical School, Rosalind Franklin University of Medicine and Science, Chicago, IL, USA, [2] Center for Dermatology Research, Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, NC, USA, [3] Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, NC, USA, [4] Department of Pathology, Wake Forest University School of Medicine, Winston-Salem, NC, USA, [5] Department of Social Sciences & Health Policy, Wake Forest University School of Medicine, Winston-Salem, NC, USA

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Abstract

Silver sulfadiazine, a topical antimicrobial that releases silver ions to disrupt bacterial cell membranes, is primarily used for second- and third-degree burns owing to its broad-spectrum activity against bacteria, fungi, and certain viruses. Beyond burns, silver sulfadiazine can be used off-label for conditions such as diabetic and pressure ulcers, atopic dermatitis, and radiation dermatitis. The literature suggests it may reduce bacterial load, accelerate healing, and address challenges such as multidrug-resistant Staphylococcus aureus. Rare side effects, including localized reactions and systemic toxicity with extensive use, necessitate cautious application, especially in vulnerable populations. Despite these limitations, silver sulfadiazine remains a cornerstone of dermatological wound care. Continued research is needed to optimize its use alongside emerging therapies.

Introduction

Defects in the skin barrier provide entry points for bacterial infection, the second leading cause of death globally.[1] Approximately 180,000 burn-related deaths occur annually, and over 75% of these are a result of infectious complications.[2] Prophylaxis against infection is a critical component of caring for burns and other conditions involving compromised skin. Introduced in 1968, silver sulfadiazine is a sulfa-derived topical antimicrobial with broad-spectrum activity against gram-positive and gram-negative bacteria, as well as some fungi and viruses. Approved by the FDA in 1973 for use in second- and third-degree burns, silver sulfadiazine has become the standard for infection prophylaxis owing to its efficacy, safety, and tolerability. Beyond burns, silver sulfadiazine has been used off-label for dermatologic conditions such as atopic dermatitis and pressure ulcers, where infection is a concern.[3] Its antimicrobial and anti-inflammatory properties, combined with a low risk for adverse reactions, support its suitability for long-term use. This review examines the current applications of silver sulfadiazine, focusing on its efficacy, mechanism of action, and role in managing dermatologic conditions.

Chemical Properties and Mechanism of Action of Silver Sulfadiazine

Silver sulfadiazine, commonly used as a 1% cream or ointment, consists of a silver ion complexed with a sulfadiazine molecule ($AgC_{10}H_9N_4O_2S$), which enhances the stability and solubility of silver in aqueous environments and enables sustained release at the application site.[4] The gradual release of silver ions into the wound disrupts bacterial cell membranes, increases permeability, and binds to bacterial DNA and RNA, inhibiting replication and cell division and ultimately causing cell death.[5,6] It is effective against gram-positive and gram-negative bacteria, notably *Pseudomonas aeruginosa*, which is a common post-burn pathogen, as well as enteric bacteria, *Candida albicans*, and *Staphylococcus aureus*.[7]

Silver ions primarily bind superficially, limiting eschar penetration. Unlike other sulfa drugs, silver sulfadiazine does not inhibit folic acid synthesis.[8] Although silver sulfadiazine acts mainly locally at the site of application, there is pharmacodynamical potential for systemic absorption. No adverse effects were seen in reproduction studies involving animal models; however, systemic absorption can occur with widespread use, although risk of toxicity remains minimal.[9,10]

a Corresponding Author: Natalia Chalupczak, BS, Chicago Medical School, Rosalind Franklin University of Medicine and Science, 3333 N Green Bay Rd, North Chicago, IL 60064, Tel: 847-578-3000, Email: natalia.chalupczak@my.rfums.org

Silver Sulfadiazine in the Treatment of Burns

In dermatologic practice, silver sulfadiazine is primarily used to prevent and treat wound infections in second- and third-degree burns. Burn dressings commonly consist of silver sulfadiazine cream or ointment applied to mesh gauze and are suitable for both inpatient and outpatient care. Its cost-effectiveness and availability establish silver sulfadiazine as the gold standard in burn treatment.[11] *Proteus mirabilis*, a common bacterial pathogen in burns, is highly susceptible to silver sulfadiazine, whereas *Enterococci* species are less sensitive, requiring concentrations greater than 25 µg/mL.[10] Overall, the broad-spectrum antimicrobial properties of silver sulfadiazine make it effective for infection prophylaxis in burns. Compared with controls, patients treated with silver sulfadiazine demonstrate significantly shorter healing time.[12]

Alternatives to silver sulfadiazine have been explored. For example, in superficial and partial-thickness burns, aloe vera gel resulted in earlier epithelialization and improved pain relief compared with silver sulfadiazine.[13] Honey-based treatments shortened healing time (mean difference, 5.76 days; 95% CI, –8.14 to –3.39) and rendered a higher proportion of infected wounds sterile (relative rise, 2.59; 95% CI, 1.58 to 2.88) compared with silver sulfadiazine.[14] Despite these findings, silver sulfadiazine continues to be widely used because of its affordability, ease of application, and low risk of adverse effects.

Ulcers

Silver sulfadiazine has been used off-label for the treatment of diabetic ulcers, pressure ulcers, and venous stasis ulcers. In a study of 16 patients with diabetic foot ulcers infected by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, silver sulfadiazine treatment over 30 days led to significant improvement according to the T.I.M.E. criteria (tissue, infection/inflammation, moisture imbalance, and edge of wound) ($P < .002$). It was effective against established biofilms at lower concentrations than typically used (10 mg/mL), highlighting its use as a topical agent for diabetic foot ulcers.[15]

For chronic pressure ulcers, silver sulfadiazine may reduce bacterial counts to fewer than 100,000 organisms per gram of tissue, a threshold critical for healing.[16] In a study of 40 hospitalized patients, 100% of ulcers treated with silver sulfadiazine achieved this bacterial count within 3 weeks, compared with 78.6% of ulcers treated with saline and 63.6% with povidone-iodine. Notably, more than 33% of silver sulfadiazine-treated ulcers reached this level within 3 days, and 50% within 1 week ($P < .01$).[3] Controlling bacterial load is vital for wound closure, as spontaneous healing requires fewer than 100,000 organisms per gram of tissue.[17] Silver sulfadiazine effectively achieves this balance, promoting healing.

Venous stasis ulcers have also been treated with silver sulfadiazine, which is thought to reduce ulcer size by promoting keratinocyte replication and minimizing inflammation.[18] Although prospective, nonrandomized studies have suggested silver sulfadiazine is a safe treatment for venous stasis ulcers, a randomized control trial found no significant difference in healing rates between silver sulfadiazine and placebo at both 4 weeks and 1 year.[19]

Inflammatory Dermatoses

Because of its ability to protect the skin from infectious pathogens and its additional anti-inflammatory and barrier-protecting functions, there may be a role for silver sulfadiazine in the treatment of inflammatory dermatoses in which the skin barrier is compromised.[20] For example, skin injury may occur after radiation therapy, and subsequent colonization by *Staphylococcus aureus* can contribute to radiation dermatitis. In a randomized controlled trial involving 102 women undergoing radiotherapy for breast cancer, 1% silver sulfadiazine cream applied 3 times daily, 3 days per week, for 5 weeks during radiotherapy and 1 week afterward, significantly reduced the severity of radiation dermatitis compared with controls. The intervention group had a lower skin injury score (5.49 ± 1.02 versus 7.21 ± 1.76; $P < .001$), with multivariate analysis confirming an association between silver sulfadiazine and decreased skin injury ($P < .001$).[20]

Atopic dermatitis is characterized by skin barrier defects and a high *Staphylococcus aureus* colonization, affecting up to 90% of patients.[21] Lesional skin in atopic dermatitis harbors higher bacterial densities, which correlate with increased severity.[22] The rise in multidrug-resistant *Staphylococcus aureus* further complicates treatment and may require decolonization protocols, which can be inconvenient for patients.[23] Silver sulfadiazine offers an alternative for infection prophylaxis because of its broad-spectrum coverage to reduce bacterial load, minimal resistance risk, and anti-inflammatory properties that may help soothe atopic dermatitis flares. It may be applied to atopic dermatitis lesions once or twice weekly for infection control.

The increasing prevalence of mupirocin-resistant *Staphylococcus aureus* in atopic dermatitis patients underscores the potential importance of silver sulfadiazine. In a study of pediatric dermatology patients, 31.3% of *Staphylococcus aureus* isolates were mupirocin resistant. Resistance was associated with prior mupirocin use, methicillin resistance, and atopic dermatitis.[24]

Fungal Infections

Fungal infections in burn wounds contribute significantly to burn-associated morbidity and mortality. Silver sulfadiazine is effective against *Aspergillus, Fusarium,* and yeasts, with particular efficacy against *Candida albicans*.[25]

An experimental study involving 32 Sprague-Dawley rats assessed the efficacy of different silver-based dressings on full-thickness burns contaminated with *Candida albicans*. The study compared topical silver sulfadiazine, a nanofiber dressing containing nanosilver, a nanofiber dressing containing silver sulfadiazine, and a control

group. Although the topical silver sulfadiazine and nanosilver-containing nanofiber dressing did not yield significantly different results from the control group, the silver sulfadiazine–containing nanofiber dressing significantly reduced *Candida albicans* growth in the burn eschar compared with the control group ($P < .01$) and was the most effective treatment tested.[26] Although these findings were derived from an animal model, they suggest potential clinical applications for silver sulfadiazine in treating fungal infections, warranting further research on its use and alternative routes of administration.

Aplasia Cutis Congenita

Aplasia cutis congenita associated with *fetus papyraceus*, a rare type V subtype, is characterized by stellate lesions symmetrically distributed over the trunk and proximal extremities. This form occurs when the fetal demise of 1 twin in the early second trimester leads to temporary hypotension, poor perfusion, and subsequent skin necrosis in the surviving twin.[27]

Case reports suggest that silver sulfadiazine may be useful for treating aplasia cutis congenita. In 1 case, a child with type V aplasia cutis congenita achieved complete healing after 4 weeks of treatment with petrolatum-impregnated gauze and topical silver sulfadiazine applied twice daily, with no significant contractures or complications at 6-month and 1-year follow-up visits.[28] In another case, a preterm male with type V aplasia cutis congenita presented with trunk and scalp lesions that were treated with 1% silver sulfadiazine and petrolatum gauze, resulting in complete healing within 2 weeks. By 8 weeks, the scalp defect had resolved and the trunk lesions were fully epithelialized, leaving secondary indurated scars.[29]

Viral Infections

Silver ions possess antimicrobial properties, including antiviral effects. They inactivate viral particles by binding to viral nucleic acids and proteins, disrupting replication.[30] Silver sulfadiazine has demonstrated efficacy against *Herpesvirus hominis* and *Varicella zoster* in both in vitro and clinical studies.[31,32] In vitro, silver sulfadiazine inactivated *Varicella zoster* virus, reducing viral infectivity. Clinically, patients with herpes zoster treated with 1% silver sulfadiazine cream experienced notable symptom relief, including vesicle drying, decreased erythema and edema, and reduced pain and burning within 1 to 3 days.[32]

Advantages of Silver Sulfadiazine in Dermatological Treatments

Silver sulfadiazine is effective in preventing wound infections, facilitating healing, and is generally well tolerated, with rare adverse effects. Resistance to silver sulfadiazine is uncommon, and when it occurs, it does not lead to cross-resistance with other antibiotic classes, making it suitable for both short- and long-term use.[33] The topical formulation allows for easy self-application in outpatient settings, enhancing patient adherence owing to comfort and minimal need for frequent dressing changes. Improved adherence promotes more effective treatment and better outcomes in wound healing and infection prevention.[34]

Limitations and Side Effects

Although silver sulfadiazine is generally safe, adverse reactions can occur with chronic use or in specific patient populations. Common side effects include localized skin reactions such as burning, pruritus, and rash. Silver sulfadiazine releases silver in concentrations as high as 3000 ppm (1% cream), which can rarely cause local toxicity.[35,36] Systemic absorption is low when applied to limited areas, but extensive use requires caution, particularly for large burns.[10] Cutaneous hypersensitivity, typically manifesting as a maculopapular rash, occurs in approximately 5% of patients (**Table 1**).[37]

Propylene glycol in silver sulfadiazine can cause adverse reactions, including dermatologic (itching, rash), hematologic (hemolytic anemia, leukopenia, agranulocytosis, aplastic anemia, thrombocytopenia), hepatitis, local pain and burning, interstitial nephritis, and serum hyperosmolality.[39] Thompson et al[42] reported leukopenia (white blood count, ≤ 5000/mm^3) in 40 of 84 patients (47.5%) treated with silver sulfadiazine and in 13 of 30 patients (43.3%) treated with silver nitrate. No significant difference was observed, suggesting leukopenia may result from burn injury rather than silver sulfadiazine.

Although rare, Stevens-Johnson syndrome (SJS) has been reported and is potentially linked to the sulfonamide component.[38,43] Application near mucosal or ocular areas may increase absorption. Sulfonamide therapies should be avoided in pregnant women near term, premature infants, and newborns under 2 months to prevent kernicterus, though no cases from silver sulfadiazine have been reported.[40] In patients with glucose-6-phosphate dehydrogenase deficiency, silver sulfadiazine may induce hemolysis; monitoring for anemia and elevated bilirubin is recommended (**Table 1**).[41] The impact of silver sulfadiazine on re-epithelialization is debated. Some studies indicate delayed healing, while others show accelerated healing and improved neovascularization in animal models, suggesting effects may depend on wound type and depth.[44,45]

Discussion

Silver sulfadiazine remains the gold standard for topical treatment of burns, particularly second- and third-degree burns. Despite its widespread use and demonstrated advantages, it is important to consider alternatives therapies, routes of administration, contraindications, and the overall benefits of silver sulfadiazine.

Table 1. *Safety Issues and Adverse Effects Associated With Silver Sulfadiazine Use in Dermatological Practice.*

Safety Issue	Description	Reference
Local skin reactions	Burning, pruritus, and rash.	Warriner et al, 2005[35]
Local toxicity	High initial silver release causing local toxicity in rare cases.	Warriner et al, 2005[35]
Stevens-Johnson syndrome	Rare, associated with sulfadiazine component.	Wright, et al, 2010[38]
Systemic absorption	Risk increases with large body surface areas and extent of tissue damage.	Warriner et al, 2005[35]
Propylene glycol toxicity	Side effects include dermatologic (itching, rash); hematologic (hemolytic anemia, leukopenia, agranulocytosis, aplastic anemia, thrombocytopenia); hepatic (hepatitis); renal (interstitial nephritis, serum hyperosmolality); and local pain and burning.	Willis et al, 2013[39]
Kernicterus risk	Avoid use in pregnant women at term, premature infants, and newborns owing to the association between sulfonamides and kernicterus.	Thyagarajan et al, 2014[40]
Hemolysis in G6PD deficiency	Increased risk; monitor for anemia and elevated bilirubin.	Eldad et al, 1991[41]
Pseudoeschar formation	Reaction between silver sulfadiazine cream and wound exudate; not harmful but may impede wound assessment.	Oaks et al, 2023[8]
Cutaneous hypersensitivity	Develops in approximately 5% of patients.	Maghsoudi et al, 2017[37]

Alternatives to Silver Sulfadiazine and Comparisons

Mupirocin, gentian violet, nanocrystalline silver, mafenide acetate, and iodine-based products are viable alternatives to silver sulfadiazine. Mupirocin is effective against gram-positive cocci, particularly for treating methicillin-resistant *Staphylococcus aureus* (MRSA), and can be safely applied to mucosal and ocular areas.[46] Gentian violet, a traditional antiseptic dye, possesses antibacterial, antifungal, antiviral, antiparasitic, anti-angiogenic, and wound-healing properties. In MRSA-colonized burn lesions, it reduced pain, febrile episodes, and bacterial growth more effectively than silver sulfadiazine; however, its application can be messy and may require assistance.[47]

Nanocrystalline silver dressings offer advanced antimicrobial properties, improving wound outcomes in diabetic foot ulcers, venous stasis ulcers, and pressure ulcers, and partial-thickness burns. They have been shown to reduce hospitalization, pain, and infection rates compared with silver sulfadiazine.[48-51] Mafenide acetate, a topical sulfonamide similar to silver sulfadiazine but with deeper tissue penetration and no antifungal activity, is effective against resistant organisms such as *Pseudomonas aeruginosa*, making it suitable for invasive burn infections.[52]

Iodine-based products, such as povidone-iodine, continue to be used for their broad antimicrobial activity.[53] The literature is mixed on the effectiveness of silver sulfadiazine versus iodine-based therapies. One prospective randomized study of 40 hospitalized patients compared the effectiveness of silver sulfadiazine cream, povidone-iodine solution, and physiologic saline in preparing pressure ulcers for closure. For successful closure of an ulcer, the bacterial count should be 100,000 or less per gram of tissue in a granulating wound. In this study, 100% of the ulcers treated with silver sulfadiazine cream had bacterial counts reduced to 100,000 or less organisms per gram of tissue within the 3-week test period, compared with 78.6% in the saline group and 63.6% in the povidone-iodine solution group. The ulcers treated with silver sulfadiazine also responded more quickly.[3] However, in another trial, liposomal povidone-iodine hydrogel provided faster healing and more cosmetically favorable results for burns injuries compared to silver sulfadiazine.[54] Both therapies appear to have comparable effectiveness in treating ulcers and burns, making iodine-based products an acceptable alternative to silver sulfadiazine.[55]

Availability and Cost Considerations

Silver sulfadiazine is widely available in healthcare settings and considered cost-effective for burn treatment, with an average cost of $75 for a 400 mg jar.[56] It is often covered by insurance but can also be purchased out-of-pocket at relatively low prices in United States pharmacies. For comparison, topical mupirocin cream averages $33 for 15 g.[57]

Administration and Formulation of Silver Sulfadiazine

Silver sulfadiazine is available as a topical cream, allowing for ease of use and independent application, which may improve adherence. However, its use on large body surface areas may not be ideal, prompting the need for systemic antibiotics or alternative topical agents with different mechanisms or side-effect profiles.

Contraindications for Silver Sulfadiazine Use

Silver sulfadiazine is contraindicated in patients with hypersensitivity to silver, propylene glycol, or any component of the formulation. Caution is advised for patients with significant hepatic impairment, as minimal systemic absorption of silver ions could have heightened effects.[58,59] Burn patients with renal impairment are at risk for silver accumulation, potentially leading to neurologic complications.[60] Routine laboratory monitoring for silver sulfadiazine use is generally unnecessary.

Safety in Sulfa-Allergic Patients

The safety of silver sulfadiazine in sulfa-allergic patients, particularly those at risk for Stevens-Johnson syndrome or toxic epidermal necrolysis, is an important consideration. It remains unclear whether patients with sulfonamide allergies are at risk for cross-reaction to silver sulfadiazine. Most product labeling advises that patients with known silver sulfadiazine reactions should avoid use.[61,62]

One cohort study suggested that silver sulfadiazine–containing central venous catheters (CVCs) and pulmonary artery catheters (PACs) could contribute to perioperative allergic reactions. Among 4 patients with a sulfa allergy who had CVCs containing silver sulfadiazine, all experienced possible non–IgE-mediated anaphylaxis. The study assessed allergic reactions in 2937 patients with pre-existing chlorhexidine, sulfonamide, and/or latex allergies who had CVCs or PACs containing these substances. Of all perioperative anaphylaxis cases, 13% occurred in patients with reported sulfa and latex allergies at the time of insertion. Overall, the incidence of anaphylaxis potentially attributed to CVCs or PACs containing silver sulfadiazine was low (4 of 2335 patients) in those with reported allergies low.[63] Larger prospective studies are needed to establish definitive safety profiles in high-risk groups.

Clinical Recommendations

Silver sulfadiazine remains a first-line treatment for second- and third-degree burn wounds, particularly when infection prevention is a priority. For superficial burns, alternatives such as aloe vera or honey may promote quicker healing, likely as a result of increased epithelialization; however, silver sulfadiazine is still recommended whenever infection risk is significant.[64] It should be applied in a thick layer and covered with an appropriate dressing; it can be safely used in both inpatient and outpatient settings. Caution is advised when applying silver sulfadiazine over large areas to avoid toxicity from increased absorption.

In diabetic foot ulcers and pressure ulcers, silver sulfadiazine effectively reduces bacterial load and supports healing and is recommended for ulcers with high infection risk or colonization by resistant bacteria.[15] Debridement and pressure offloading may optimize results. For venous stasis ulcers, alternative treatments may be preferred, as silver sulfadiazine does not consistently improve healing rates.[65]

For atopic dermatitis with recurrent *Staphylococcus aureus* infections, especially in cases of mupirocin resistance, silver sulfadiazine offers an effective alternative with anti-inflammatory benefits. It can be applied intermittently during flares on infected or impetiginized areas.[66] Patient education regarding proper application is essential to maximize benefits and avoid overuse. Physicians should monitor for side effects, particularly in patients with extensive burns or hematological conditions such as glucose-6-phosphate dehydrogenase deficiency.[41] Careful monitoring for systemic absorption or adverse reactions is recommended in these cases.

Conclusion

Although alternatives to silver sulfadiazine exist, its broad-spectrum antimicrobial properties, accessibility, and cost-effectiveness maintain its relevance as a topical agent in dermatological practice, especially in burn care. Careful patient selection, awareness of contraindications, and monitoring for potential adverse reactions are essential. Future research should continue to explore the efficacy of silver sulfadiazine, particularly in comparison with emerging therapies for the treatment and prophylaxis of dermatologic conditions.

Potential conflicts of interest

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