Clinical Advances in Antimicrobial Photodynamic Therapy for Staphylococcus aureus–Associated Refractory Skin Wounds and Infections

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Abstract. Staphylococcus aureus is an important infection in chronic skin wounds, where biofilm formation and antibiotic resistance render closure significantly more difficult and create an urgent demand for non-antibiotic options. Antimicrobial photodynamic therapy (aPDT) relies on a photochemical reaction involving a photosensitizer, light of the correct wavelength and molecular oxygen in the tissue, generating reactive oxygen species (ROS) that attack bacterial membranes, nucleic acids and proteins at multiple sites at the same time. This method is active against both planktonic organisms and biofilms, is unlikely to select for resistance, and can also regulate the local inflammatory milieu of the wound so as to favor tissue regeneration, making it an intriguing choice in refractory S. aureus-associated skin wounds. The clinical dilemma faced by S. aureus, the molecular foundation of aPDT, its current clinical use, the available information on efficacy and safety, and the obstacles that still need to be overcome are discussed in this review. We discuss the practical limitations encountered to date, hypoxia within the wound bed, which constrains the photodynamic effect, incomplete penetration of biofilm and the absence of agreed treatment parameters, and consider photosensitizer modification, combination strategies and the prospects for clinical translation, to support the more standardized use of aPDT in refractory infected skin wounds.

Keywords: antimicrobial photodynamic therapy, Staphylococcus aureus, skin wound infection.

1. Introduction

Year by year, the incidence of chronic skin ulcer has risen because of the aging of the world population and the increasing prevalence of obesity, diabetes, and other chronic diseases. Lower-limb ulcers are mostly due to compromised arterial, venous or lymphatic flow which hampers wound healing, putting patients at risk of infection, amputation and even death. S. aureus is a widespread Gram-positive opportunistic bacterium and the major cause of skin and soft tissue infections, postoperative orthopedic infections, and diabetic foot wound infections. A damaged skin barrier allows bacteria to colonize, which further destroys the skin barrier. These factors, coupled with prolonged exposure of the wound and incorrect use of antibiotics, increase the risk of infection [1, 2].

The proliferation of methicillin-resistant S. aureus (MRSA) has exacerbated the clinical issue of infection. Hospital-acquired (HA-MRSA) and community-acquired (CA-MRSA) MRSA can be classified. CA-MRSA is very virulent and is not only transmitted in the community to cause skin and soft tissue infections, but can also be transmitted from host to host via cattle and poultry, creating a complex epidemiological picture. More than 30% of Chinese medical facilities are infected with MRSA, and the death rate of serious illness caused by it is as high as 50%. MRSA is resistant to several types of antibiotics via target modification, development of inactivating enzymes and other mechanisms. Vancomycin and linezolid are effective against MRSA and there are only a few medicines available for therapy. Diabetic foot ulcer (DFU) is a typical intractable wound due to MRSA which is the most prevalent strain in multidrug-resistant infections in such wounds. An ulcer area > 4 cm2, concurrent osteomyelitis, antibiotic overuse and hypoalbuminemia are independent risk factors for MRSA infection in DFU. The blood supply of foot is poor, which is not conducive to the local effect of the medicine, and the wound often takes a long time to heal. Some patients eventually need to be amputated, and the 3-year mortality rate can exceed 50%, which brings a severe disease burden [3, 4, 5, 6, 7].

Biofilm formation is the key mechanism underlying the difficulty of eradicating MRSA infection and the recurrent nature of these wounds. MRSA can colonize damaged tissue and the surfaces of medical devices, secreting polysaccharides, proteins, and extracellular DNA to form extracellular polymeric substances (EPS) and build a dense, three-dimensional biofilm. The biofilm physically blocks antimicrobial agents and immune cells from reaching the bacteria, markedly increasing bacterial resistance; its internal hypoxic and acidic microenvironment, together with the accumulation of metabolic byproducts, further weakens antibiotic efficacy. The biofilm continuously releases planktonic bacteria, causing recurrent wound infection. Because debridement and antibiotic therapy alone struggle to clear the bacteria embedded within the biofilm, such wounds progress to chronic, non-healing states [8, 9].

Antimicrobial photodynamic therapy (aPDT) is a novel non-antibiotic antibacterial approach. It relies on a photochemical reaction among a photosensitizer, excitation light of a specific wavelength, and molecular oxygen to generate ROS, which oxidatively damage bacterial cell membranes, proteins, and nucleic acids to inactivate pathogens. Unlike the single-target action of antibiotics, aPDT delivers ROS-mediated, multi-target, non-specific killing, so bacteria are unlikely to acquire resistance through mutation. The technique offers a broad antibacterial spectrum and is spatiotemporally controllable: ROS are generated only in the illuminated area, causing minimal damage to normal tissue and providing good biosafety. aPDT can degrade the EPS of biofilms and eradicate MRSA biofilms, achieving clearance rates of up to 90% under optimized conditions; it can also act synergistically with antibiotics by altering bacterial membrane permeability to enhance drug-mediated killing. Beyond its direct bacteriostatic and bactericidal effects, aPDT can modulate the inflammatory microenvironment of the wound and promote fibroblast proliferation and the formation of blood vessels and granulation tissue, thereby combining bactericidal and wound-healing functions. Animal models have likewise confirmed that it can ameliorate MRSA skin infection and accelerate wound healing [10, 11, 12, 13, 14, 15].

In summary, by exploiting multidrug-resistance mechanisms and biofilm-mediated immune evasion, MRSA can drive refractory skin wound infections such as diabetic foot ulcers, chronic lower-limb ulcers, and postoperative incisions. Conventional antibiotic therapy faces limited drug options, difficulty penetrating the biofilm barrier, restricted local efficacy, and a tendency toward recurrence, and there is an urgent clinical need for a novel local anti-infective intervention that is safe, effective, and unlikely to induce resistance. With its broad-spectrum antibacterial activity, biofilm-clearing capacity, low resistance risk, and synergy with antibiotics, aPDT offers a highly promising therapeutic strategy for MRSA-associated refractory wound infections. Accordingly, this review systematically summarizes the basic research and clinical progress of aPDT for S. aureus–associated refractory skin wound infections, with the aim of informing the development of treatment strategies and the clinical translation of therapies for drug-resistant wound infections.

2. Core Mechanisms of Antimicrobial Photodynamic Therapy

aPDT is a novel non-antibiotic anti-infective approach whose antibacterial action depends on three core elements: a photosensitizer, excitation light of a specific wavelength, and molecular oxygen present locally in the wound. It offers a new therapeutic strategy for chronic, refractory MRSA skin wound infections. During treatment, the photosensitizer selectively accumulates on the surface of and within MRSA cells, laying the foundation for the photochemical reaction. Upon irradiation with a matched light source, the ground-state photosensitizer absorbs light energy and is excited to the singlet state, then converts through intersystem crossing to the more stable and reactive triplet state. The triplet-state photosensitizer can undergo two types of photochemical reaction with oxygen in the wound: type I reactions produce reactive radicals such as superoxide anions and hydroxyl radicals through electron transfer, whereas type II reactions generate highly toxic singlet oxygen through energy transfer; together they yield large amounts of ROS. Through their potent, non-specific oxidative action, high concentrations of ROS damage MRSA on multiple levels: disrupting the cell

wall and membrane so that intracellular contents leak out, oxidatively inactivating key metabolic enzymes, and inflicting irreversible damage on bacterial DNA, ultimately killing the pathogen.

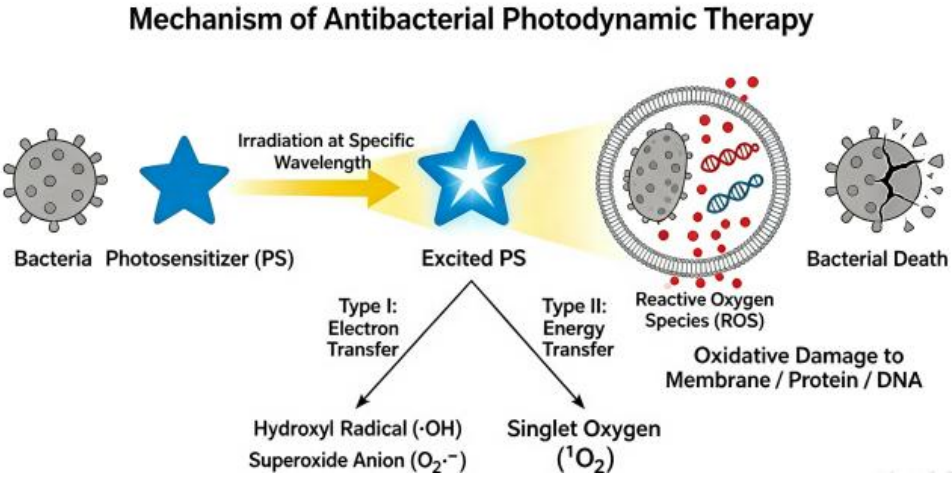


Figure 1. Mechanism of Antibacterial Photodynamic Therapy

Figure 1 aPDT is a non-antibiotic antibacterial strategy. The photosensitizer accumulates at the site of bacteria and has no intrinsic antibacterial activity; upon irradiation at a specific wavelength, it is converted to an excited state. Two reaction pathways then follow: the type I pathway generates hydroxyl radicals and superoxide anions through electron transfer, whereas the type II pathway produces singlet oxygen through energy transfer. Both products are reactive oxygen species which oxidatively damage bacterial cell membrane, protein and DNA, alter the normal bacterial structure and physiological function and finally cause bacterial lysis and death. The method is also efficient toward medication resistant diseases, as it is unlikely to generate bacterial resistance.

Unlike the single-target bacteriostatic mode of conventional antibiotics, aPDT kills bacteria through multi-target oxidative damage mediated by ROS. This effectively prevents bacteria from developing resistance through gene mutation, drug efflux, or the synthesis of inactivating enzymes, thereby avoiding the emergence of resistant strains at the mechanistic level. aPDT is also highly effective in terms of spatiotemporal control, where the photochemical process occurs only at the area of illumination with negligible effects on surrounding healthy tissues and normal flora, making it very safe. In addition, attaching the photosensitizer to medical dressing substrates like hydrogels and nanofibers may prevent aggregation quenching and ensure that a working concentration is maintained; the use of such substrates will also allow hemostasis, moisture retention, granulation tissue formation, and scarring prevention.

In regard to biofilm infection by MRSA, aPDT undoubtedly has distinct strengths compared to normal antibiotics. This is because the MRSA biofilm creates a protective EPS wall out of polysaccharides, protein, and extracellular DNA, which not only hinders the entry of antibiotics into the biofilm but also reduces the effectiveness of antibiotics due to the internal hypoxic and acidic environment of the biofilm. ROS produced through the process of aPDT are capable of oxidizing each element that constitutes the EPS and breaking down the three-dimensional structure of the biofilm, making it possible to destroy the resilient bacteria that have been residing inside. Scientific studies have proven that when a photosensitizer system is optimized, aPDT can result in a bacterial kill rate of 99.4% in case of planktonic MRSA and more than 90% clearance of the biofilm.

aPDT alone and in combination with conventional antibiotics has been exploited as a synergistic antibacterial system to overcome the limitations of each modality alone, providing an effective combination therapy for the treatment of chronic wound infections due to multidrug resistant bacteria. These two phenomena complement each other in both directions: ROS formation due to aPDT can oxidize the outer membrane of bacteria and make it more permeable for antibiotics which will enter the cell, resulting in improved efficiency of the therapy; and on the other hand, membrane-disrupting antibiotics like polymyxins can disrupt the outer bacterial membrane, making the uptake of the

photosensitizer easier and, therefore, increasing ROS formation under light. In the event of MRSA infection covered by biofilm, aPDT can first break down the biofilm barrier, which helps antibiotics diffuse into the deeper layers of the biofilm for complete removal of the residual germs, and successfully reduces the recurrence incidence of wound infection.

3. Current Clinical Applications of Antimicrobial Photodynamic Therapy

It has unique benefits such as non-specific oxidative death, no drug resistance, degradation of bacterial biofilms and bidirectional modulation of wound repair, which can successfully overcome the defects of traditional antibiotics in the treatment of refractory skin wounds. The approach has been extensively examined in chronic wounds produced by S. aureus and MRSA, with mature research frameworks and abundant clinical evidence in the fields of diabetic foot ulcer, pressure injury and burn wounds. A lot of animal and clinical studies have shown that aPDT can substantially decrease the bacterial load of wounds, control infection, inhibit excessive inflammation and stimulate tissue regeneration, providing a novel adjunctive treatment of high clinical translational value for refractory drug resistant wounds [16, 17, 18].

Diabetic foot ulcer is a typical example of refractory wounds associated with MRSA. The prolonged and non-healing nature of these wounds is attributed to hyperglycemia-induced local microcirculatory dysfunction and immunosuppression and persistent MRSA biofilm colonization. In clinical investigations it has been shown that aPDT mediated by photosensitizers such as red light or narrow band red light combined with methylene blue or 5-aminolevulinic acid can successfully clear pathogens, reduce inflammatory exudate and relieve wound pain, and patients have good tolerance. Clinical data indicate that the complete wound healing rate at 3 months after aPDT reaches 50%, significantly higher than the 12% achieved with conventional treatment. Methylene blue–mediated aPDT can rapidly kill bacteria by photoactivating the generation of ROS, and when combined with conventional treatment it effectively reduces wound inflammation, promotes granulation tissue growth, and ameliorates the infected state of the wound. Novel functional carriers such as nano-photosensitizers and microneedle bandages can further strengthen the anti-biofilm, pro-angiogenic, and reparative macrophage-polarizing effects of aPDT, although hyperglycemia-mediated oxidative stress dysregulation still limits its therapeutic effect to some extent.

Pressure injuries are common among bedridden patients: sustained local pressure damages the skin's blood supply and barrier function, predisposing the tissue to secondary infection by S. aureus and multidrug-resistant bacteria. Persistent inflammatory infiltration and biofilm colonization impede wound repair, preventing the normal transition from the inflammatory phase to the proliferative and remodeling phases and ultimately producing chronic, intractable wounds. aPDT can target both wound infection and tissue repair throughout this process. On the one hand, ROS oxidatively degrade the EPS of the biofilm, disrupting the three-dimensional structure of MRSA and clearing dormant resistant bacteria within—thereby addressing the clinical problems of poor biofilm penetration and frequent recurrence associated with conventional antibiotics. On the other hand, aPDT can balance the wound inflammatory response, upregulate repair factors such as TGF-β1 and TGF-β3, and promote orderly collagen deposition and extracellular matrix remodeling, accelerating wound healing and improving repair quality. By optimizing photosensitizer structures and intervention protocols, current research has developed novel technologies such as cationic water-soluble photosensitizers and indocyanine green–mediated photodynamic therapy that maintain potent antibacterial efficacy while reducing skin phototoxicity, providing a reliable experimental basis for the precise treatment of pressure injuries.

Burns disrupt the skin barrier and cause tissue necrosis and local immunosuppression, predisposing the wound to invasion and colonization by S. aureus and MRSA; biofilm formation further exacerbates the intractability of infection and impedes wound healing. Owing to its multi-target oxidative killing mediated by ROS, aPDT can efficiently clear drug-resistant bacteria across a broad spectrum without inducing resistance, making it well suited to the treatment of complex

infected burn wounds. Animal studies show that aPDT can effectively clear colonizing bacteria from burn wounds, suppress local inflammation, upregulate a range of wound-repair factors, and promote collagen remodeling and wound healing. Low-dose aPDT can activate relevant signaling pathways to promote stem cell proliferation and activation and to regulate matrix synthesis, supporting wound regeneration at the stem cell level; it can also activate neutrophils and enhance local innate immunity to strengthen the anti-infective effect. At present, research on aPDT for burn wounds remains dominated by basic experiments and animal models, clinical treatment parameters have not yet been standardized, and mixed-species biofilms can antagonize the killing effect of ROS—issues that await further optimization in subsequent studies [19, 20, 21].

4. Efficacy and Safety Evaluation of Antimicrobial Photodynamic Therapy

aPDT is a novel, non-invasive photochemical anti-infective technique that can effectively eliminate pathogenic microorganisms and biofilm infections. Indocyanine green, a commonly used photosensitizer, has a strong safety profile and clinical applicability and combines imaging, antitumor, and antibacterial functions. The antibacterial efficacy of aPDT is influenced by multiple factors, including photosensitizer concentration, oxygen content, and irradiation parameters; however, constrained by the biofilm barrier and its internal hypoxic microenvironment, its killing effect on bacteria embedded within the biofilm is relatively weak, which can lead to recurrent infection. aPDT eliminates bacteria via non-specific ROS oxidation and, compared to traditional antibiotics, has broad-spectrum activity, a low probability of resistance development and spatiotemporal control. It is significantly effective against resistant bacteria such as MRSA and is also able to decrease wound inflammation. The photosensitizer can be composited with carriers such as hydrogels and nanofibers to increase its penetration and minimize quenching, thus integrating antibacterial, hemostatic, anti-inflammatory and reparative properties. aPDT is a promising novel therapeutic approach for infections caused by resistant bacteria and for chronic wound healing [22, 23, 24].

Current methods to improve the anti-infective efficacy of aPDT can be divided into three major categories: parameter adjustment, nano-based photosensitizer modification, and combination with antibiotics. The photosensitizer dose, irradiation intensity, duration and wavelength can be adjusted to improve the bactericidal efficacy, while sparing normal tissue. Nano-modification may improve the solubility, targeting and biocompatibility of photosensitizer, increase the accumulation of the drug at lesion site, effectively kill resistant bacteria such as MRSA and lower the systemic toxicity. aPDT with antibiotic therapy is very synergic as it breaks down the biofilm architecture, penetrates deeper into the body for eliminating dormancy, and manages to treat the wound quickly without recurrence. The aPDT method has high safety features as it is spatially and temporally controlled, minimally invasive, non-side responsive, and does not carry any risks of developing resistance. Together with the dressing carriers, it is more applicable to refractory wounds. In conclusion, there is a lot of potential use for aPDT in MRSA wound infections, but there are several barriers that should be addressed. [25, 26, 27]

5. Conclusions and Perspectives

aPDT offers a novel local treatment for refractory skin wound infections caused by S. aureus and drug-resistant MRSA. It can effectively reduce the wound bacterial load, alleviate inflammation, and promote granulation-tissue repair, and it is suitable as an adjunctive treatment for chronic wounds such as diabetic ulcers. At present, however, the clinical efficacy of aPDT remains limited, and its wider adoption faces several bottlenecks. Conventional photosensitizers have inadequate solubility and targeting, and the bactericidal action of aPDT is highly oxygen-dependent; the hypoxia of the wound and biofilm and the extracellular matrix barrier weaken the therapeutic effect and can lead to recurrent infection. Moreover, aPDT lacks standardized treatment parameters, its safe and effective dose is not yet defined, adverse reactions such as skin photosensitivity and local pain occur, and high-

quality clinical evidence is lacking. In the future, technical limitations may be further overcome through novel nano-photosensitizer materials, optimized oxygen supply and irradiation parameters, and multimodal synergistic treatment combining antibiotics, along with the development of functional wound dressings, the conduct of large-sample clinical studies, and the establishment of standardized protocols—advancing the clinical translation and broader adoption of aPDT in refractory wound infections.

References

[1] Xu MT, et al. Analysis of pathogen characteristics and drug resistance in 546 cases of lower-limb ulcer infection. Chinese Journal of Clinical Pharmacy, 2026;35(5):434–439.

[2] Li G, Yang HR, Yang YB. Analysis of the distribution of pathogens and risk factors of postoperative Staphylococcus aureus infection in orthopedics. Modern Diagnosis and Treatment, 2018;29(11):1799–1800.

[3] Liang YR, et al. Comparison of drug resistance and genomes of hospital- and community-acquired methicillin-resistant Staphylococcus aureus. Chinese Journal of Infection Control, 2026;25(4):489–498.

[4] Huang HQ, et al. Research progress on the epidemiological evolution and antimicrobial resistance mechanisms of methicillin-resistant Staphylococcus aureus. Journal of Clinical Laboratory Science, 2026;44(6):438–441.

[5] Zhou SL, et al. Experimental study on berberine combined with gentamicin for the treatment of MRSA diabetic foot ulcer wound infection. Hebei Medical Journal, 2026;48(6):941–944,949.

[6] Meng GZ, et al. Meta-analysis of risk factors for methicillin-resistant Staphylococcus aureus infection in diabetic foot wounds. Clinical Misdiagnosis and Mistherapy, 2025;38(3):54–60.

[7] Gu HW, et al. Analysis of bacterial infection characteristics and factors influencing drug resistance in patients with diabetic foot ulcers. Journal of Clinical Medication, 2022;20(11):76–79.

[8] Wang HN, et al. Research progress on nanomaterials against methicillin-resistant Staphylococcus aureus biofilms. Chinese Journal of Microecology, 2026;38(3):361–367.

[9] Zhou JR, et al. Biological characteristics of the Staphylococcus aureus bacteriophage vB_SauS-P22228 and its effect on biofilm formation. Chinese Journal of Zoonoses, 2026;42(6):588–594.

[10] Hou XX, et al. Study on a polymeric antibacterial agent combined with chemo-photodynamic therapy for drug-resistant bacterial infections. In: 2020 (4th) Forum on Antibacterial Science and Technology, 2020, Guangzhou, Guangdong, China.

[11] Shi JY, et al. Research progress on photodynamic antibacterial dressings. Shanghai Textile Science & Technology, 2024;52(5):1–6.

[12] Wang JL, et al. Research progress on synergistic photodynamic therapy strategies against bacterial biofilm infections. Emerging Science and Technology Trends, 2025;4(2):160–178.

[13] Wang JG, et al. Efficacy and mechanism of antimicrobial photodynamic therapy combined with antibiotics against drug-resistant bacterial infections. Journal of Hebei University (Natural Science Edition), 2025;45(3):254–265.

[14] Qiao HL, et al. New advances in novel control strategies for methicillin-resistant Staphylococcus aureus infection. Chinese Journal of Clinical Pharmacology and Therapeutics, 2023;28(6):676–687.

[15] Yan R, et al. Preparation and performance validation of the Staphylococcus aureus–targeting nano-photosensitizer UBI/PCN-224. Research on Biomedical Engineering, 2023;42(4).

[16] Wang JX, et al. Preliminary clinical study on methylene blue–mediated photodynamic antimicrobial chemotherapy for improving infection in diabetic lower-limb ulcers. Chinese General Practice, 2021;24(15):1903–1908.

[17] Zhao JX, et al. Application and mechanism of photodynamic therapy in the treatment of diabetic foot. Journal of Hebei University (Natural Science Edition), 2023;43(2):188–196.

[18] Li WC, Shen T. Research progress on the application of photodynamic therapy in wound repair. Chinese Journal of Injury Repair and Wound Healing (Electronic Edition), 2025;20(3).

[19] Mai BJ. Research and application of photodynamic antimicrobial chemotherapy in the treatment of burn infection [dissertation]. Shaanxi Normal University; 2020.

[20] Yang Y, et al. Effect of low-dose photodynamic therapy on the function of human adipose-derived mesenchymal stem cells and its mechanism. Chinese Journal of Burns and Wounds, 2022;38(9).

[21] Xing DH. Meta-analysis of the efficacy of photodynamic therapy as an adjunct in the treatment of peri-implantitis in patients with type 2 diabetes [dissertation]. Henan University; 2024.

[22] Li W, et al. In vitro antibacterial effect of indocyanine green–mediated photodynamic therapy on Fusobacterium nucleatum biofilm. Journal of Prevention and Treatment for Stomatological Diseases, 2023;31(1):10–16.

[23] Xu YX, et al. Killing effect of microbial-targeted photodynamic therapy combined with 28-kHz ultrasound on bacteria within MRSA biofilm. Chinese Journal of Laser Medicine & Surgery, 2023;32(1):1–6.

[24] Zhen XM. Preliminary study on the antibacterial and antitumor effects and mechanisms of the novel nanomaterial Cu-CyNPs combined with potassium iodide–mediated photodynamic therapy [dissertation/PDF].

[25] Wang XG, et al. Research progress on photodynamic therapy in the treatment of microbial infections. Microbiology China, 2026;53(5):2140–2155.

[26] Kang H, et al. Application of antimicrobial photodynamic therapy in wound dressings. Shanghai Textile Science & Technology, 2025;53(3):20–24,33.

[27] Yan R, et al. Preparation and performance validation of the Staphylococcus aureus–targeting nano-photosensitizer UBI/PCN-224. Research on Biomedical Engineering, 2023;42(4):393–398.