

Shifting the clinical paradigm: Copper versus silver wound dressings – Where we are and what we are looking for

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This narrative review compares silver-based wound dressings with copper oxide–impregnated dressings (copper dressings), focusing on antimicrobial activity, impact on healing, safety, and clinical evidence.

The authors suggest that while silver remains useful for short-term infection control, copper dressings offer a dual antimicrobial and pro-healing profile, with growing clinical data to support broader use.

Silver dressings have a long history in managing infected and high-risk wounds and remain effective in reducing bioburden.

However, their performance is highly formulation- and dose-dependent, and traditional preparations (e.g. silver sulfadiazine, silver nitrate) are associated with cytotoxicity, frequent changes, and limited evidence for accelerating closure of chronic wounds.

Even newer silver formulations show mixed results in terms of long-term healing and raise ongoing concerns about toxicity to keratinocytes and fibroblasts.

Copper dressings combine broad-spectrum, contact-kill antimicrobial activity with stimulation of key healing pathways. By releasing copper ions into the wound environment, they can disrupt microbial membranes while also upregulating HIF-1 α , VEGF, and other mediators involved in angiogenesis, extracellular matrix formation, and re-epithelialization.

Preclinical work and early clinical studies—including case series and a randomized trial versus NPWT—indicate that copper dressings can help restart healing in hard-to-heal wounds and can be used safely across multiple phases of wound repair, often with longer wear times and simpler regimens.

The authors conclude that more robust, head-to-head randomized trials are needed to fully define their role relative to modern silver dressings.

“Copper oxide dressings offer a biologically appealing alternative [to silver dressings] with dual antimicrobial and regenerative effects.”

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Shifting the clinical paradigm: Copper versus silver wound dressings - Where we are and what we are looking for

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Abstract

The development of nanoparticle-based wound dressings marks a significant advancement in the management of chronic and non-healing wounds. Silver-based dressings have been used in wound management due to their strong antimicrobial properties. However, their clinical effectiveness depends on formulation, concentration, and duration of use. Recently, copper oxide dressings (CODs) have emerged as a novel alternative, offering both antimicrobial and regenerative benefits. We reviewed clinical studies, meta-analyses, and cost-effectiveness analyses on silver nanoparticle (AgNP), ionic silver, nanocrystalline silver, and copper oxide dressings across various wound types, including diabetic foot ulcers, venous leg ulcers, pressure ulcers, surgical wounds, and burns. Emphasis was placed on dressing formulations, silver or copper concentrations, clinical efficacy, safety, and cost-effectiveness. Traditional silver formulations, such as silver sulfadiazine (1%) and silver nitrate (0.5%), demonstrate antimicrobial activity but are limited by cytotoxicity and lack of long-term healing benefits. Nanocrystalline silver and ionic silver hydrofiber dressings provide sustained release, proving most effective in infection-prone and early inflammatory phases. Enhanced formulations (Aquacel® Ag + Extra™) show promise in treating biofilm-related wounds but need more robust data. By contrast, CODs have demonstrated antimicrobial efficacy alongside stimulation of angiogenesis, fibroblast proliferation, and extracellular matrix remodeling. Early clinical evidence suggests that CODs may accelerate healing in refractory wounds and offer cost advantages over negative pressure therapy, though large-scale trials remain limited. Silver dressings, particularly nanocrystalline and ionic hydrofiber formulations, remain clinically useful for infection control and short-term wound management, while older silver salts are less favorable due to toxicity and limited efficacy. CODs represent a biologically attractive alternative with dual antimicrobial and regenerative properties. Nonetheless, the current body of evidence is insufficient to declare a paradigm shift in wound healing, and CODs should presently be regarded as promising adjuncts pending validation in high-quality randomized trials.

Keywords

nanoparticles, copper nanoparticles, silver nanoparticles, silver dressings, wound dressing, wound healing, wounds

Highlights

- CODs dressings support all phases of wound healing.
- Newer formulations of silver products exhibit a better toxicity profile.
- CODs outperform silver in accelerating the healing of chronic wounds.
- CODs is a promising next-generation solution for modern wound treatment protocols.

Introduction

The emergence of nanoparticle-based dressings has significantly advanced the field of wound care. Among the metallic nanoparticles, silver nanoparticles (AgNPs) have

garnered the most clinical attention. In contrast, copper nanoparticles (CuNPs) have been recently introduced into

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clinical practice as copper oxide dressings (CODs) and are emerging as a clinically relevant option. The various formulations of silver dressings are widely recognized for their antimicrobial efficacy against a broad spectrum of pathogens, including multidrug-resistant strains, CODs have demonstrated remarkable regenerative capabilities by promoting angiogenesis, collagen synthesis, and modulating the wound microenvironment.^{1,2}

Wound healing is a complex physiological process that involves inflammation, tissue proliferation, and remodeling. Chronic wounds, such as diabetic foot ulcers (DFU) and venous leg ulcers, often become stagnant due to ongoing inflammation and infection, which further impair cellular repair pathways. While silver dressings have long been used to control bioburden and minimize infection-related delays, they do not actively contribute to tissue regeneration and may even show cytotoxicity at higher doses.^{3,4}

Silver dressings are available in multiple formulations as displayed in Table 1, which differ substantially in their chemical form, ion release kinetics, and biological activity. The most widely used are nanocrystalline silver dressings, which contain metallic silver nanoparticles (Ag^0) embedded in a carrier matrix that slowly releases Ag^+ ions into the wound environment. In contrast, many commercial products use ionic silver salts such as silver sulfadiazine (AgSD), silver chloride (AgCl), silver oxide (Ag_2O), and silver

phosphate (Ag_3PO_4). These ionic formulations often provide a more rapid but less sustained release of Ag^+ , and their toxicity and efficacy profiles differ significantly from those of nanocrystalline AgNP dressings.⁵ Because the biological effects of silver depend on both the formulation and the concentration applied, conflating all silver-based products under the label “AgNP” is a misrepresentation. Table 1 demonstrates the different silver dressing products described in this manuscript.

Copper oxide dressings (CODs) are made of woven or nonwoven polyester/cotton fabrics impregnated with micron- and nano-sized particles of copper oxide ($\text{CuO}/\text{Cu}_2\text{O}$), at a concentration of approximately 0.04% w/w, corresponding to $\sim 20\text{--}40\ \mu\text{g}/\text{cm}^2$ of copper on the fabric surface.¹⁸ Unlike colloidal copper nanoparticle suspensions tested *in vitro*, CODs represent the only commercially available copper-based wound dressing. The particles embedded in the fibers slowly release Cu^{2+} ions upon contact with wound exudate, ensuring a controlled, localized supply of bioavailable copper. In this review we will specify the exact formulation of CuNPs used in *in vitro* studies while all clinical studies so far were conducted with the use of CODs ($\sim 0.04\%$ w/w CuO , corresponding to $\sim 20\text{--}40\ \mu\text{g}/\text{cm}^2$ release).¹⁹ CODs have both antimicrobial properties and a critical role in wound healing by activating hypoxia-inducible factor 1-alpha

Table 1. Overview of characteristics of commercial silver dressings.

Metal/Ion	Trademark name	Substrate/Fabric type	Valence state/Form	Silver chemistry	Loading level ($\mu\text{g}/\text{cm}^2$, mg/ cm^2 , wt%)	Reference
Metallic silver (Ag^0 /Nanocrystalline)	Acticoat™ Flex 3/7 (Smith & Nephew)	Polyethylene mesh coated with nanocrystalline silver	Metallic Ag^0 nanocrystals (slow Ag^+ release)	Silver nanocrystals	$\sim 0.69\text{--}1.64\ \text{mg}/\text{cm}^2$	1,6,7
	Silverlon® (Argentum Medical)	Knitted nylon occlusive dressing plated with metallic silver	Metallic Ag^0 (ion release when moistened)	Metallic silver plating	$\sim 2\text{--}5\ \text{mg}/\text{cm}^2$ ($\approx 546\ \text{mg}$ per $100\ \text{cm}^2$)	8,9
Silver nanoparticles (AgNPs)	SilvrSTAT® Gel (NexGen)	Hydrogel matrix	Silver nanoparticles (10–15 nm)	AgNP colloid	$\sim 32\ \text{ppm}$ (0.0032% w/w)	10,11
Silver salts/Ionic silver	Aquacel® Ag Hydrofiber® (ConvaTec)	Sodium carboxymethylcellulose hydrofiber	Ionic Ag^+	Silver ions bound to hydrofiber	$\sim 1.2\%$ w/w ($\approx 1\ \text{mg}/\text{cm}^2$)	7,12,13
	Aquacel® Ag + Extra™ (CISEB) (ConvaTec)	Hydrofiber with added anti-biofilm agents (EDTA, benzethonium chloride)	Ionic Ag^+	Enhanced ionic silver formulation	$\sim 1.2\%$ w/w	14
	Silver sulfadiazine cream (Flamazine®, generic)	Topical cream/impregnated gauze	Ionic Ag^+	Silver sulfadiazine (AgSD)	1% ($\approx 3,000\ \text{ppm}$ Ag)	15
	Silver nitrate solution	Topical solution	Ionic Ag^+	Silver nitrate (AgNO_3)	0.5% solution ($\approx 5,000\ \text{ppm}$ Ag)	16,17

(HIF-1 α), stimulating angiogenesis, and enhancing fibroblast function.^{18,20}

Despite the widespread use of both agents in clinical practice, direct comparative data evaluating their relative effectiveness, safety, and cost-efficiency remain scarce. Preclinical studies have shed light on the cellular pathways targeted by both silver and copper. At the same time, emerging clinical data suggest that CODs dressings may outperform silver dressings in promoting healing in hard-to-treat wounds, especially those unresponsive to conventional antimicrobial regimens.^{21,22} Given the growing need for cost-effective, dual-action dressings that combat infection and support regeneration, a focused comparison between silver and CODs dressings is timely and clinically relevant.

This review aims to synthesize preclinical and clinical evidence comparing silver and CODs dressings. By evaluating their antimicrobial properties, regenerative mechanisms, biocompatibility, safety profiles, and clinical outcomes. We seek to clarify the relative advantages of each and provide a foundation for evidence-based selection of nanoparticle-infused dressings in modern wound care.

Antimicrobial activity

Antimicrobial activity plays a crucial role in wound healing by preventing or controlling infection, which is one of the significant factors delaying tissue repair. Effective reduction of microbial load supports the transition from the inflammatory to the proliferative phase, promoting re-epithelialization and granulation tissue formation. Therefore, materials with inherent or enhanced antimicrobial properties are of particular interest in the development of advanced wound dressings.^{1,16}

Both silver dressings and CODs possess broad-spectrum antimicrobial properties; however, their modes of action and clinical implications differ significantly. Silver dressings are among the most thoroughly investigated antimicrobial agents used in wound management. Their effectiveness spans gram-positive and gram-negative bacteria, as well as fungi such as *Aspergillus* and *Candida*.^{1,23}

When it comes to silver-containing dressings, two main forms are usually discussed: silver nanoparticles (AgNPs) and various silver salts. In theory, metallic silver and silver cations should act through different mechanisms. In practice, however, exposure to slightly acidic wound exudate, rich in free radicals, inorganic ions, and proteins, inevitably triggers the release of silver cations from AgNPs.

Some studies have tested AgNPs coated with protective layers designed to prevent oxidation and ion release. Interestingly, even under these conditions, the nanoparticles still displayed size-dependent toxicity.²⁴ Another study demonstrated that bacteria began to undergo cell death well before silver ion concentrations rose to significant levels. The authors suggested several possible explanations: the incorporation of AgNPs into the bacterial cell wall structure,

as well as their penetration into the cytosol, where they can disrupt DNA and damage essential proteins.²⁵

However, the antimicrobial activity of AgNPs is mostly attributed to their ability to release silver cations (Ag⁺) in a sustained manner. These cations act as Lewis acids, binding to phosphate residues or sulfide bridges in bacterial membranes, which damages and ultimately ruptures the membrane. Upon entering the microbial cell, Ag⁺ initiates multiple levels of antibacterial effects. Its high affinity for sulfur disrupts disulfide bridges, altering the tertiary structure and enzymatic activity of proteins. If these proteins function as ion transporters, their inhibition can lead to cell death. Moreover, silver cations can form complexes with DNA or RNA, resulting in replication defects and denaturing key bacterial proteins.^{17,26}

A pivotal mechanism underlying the efficacy of AgNPs is the generation of reactive oxygen species (ROS). These free radicals are produced through interference with bacterial respiratory chain enzymes and depletion of intracellular glutathione.⁴ *In vitro*, antimicrobial effects were observed at 10–100 μM AgNO₃ (\approx 1–10 $\mu\text{g}/\text{mL}$ Ag⁺)^{4,17,26} and at 50–100 $\mu\text{g}/\text{mL}$ AgNPs incorporated into keratin biomaterial scaffolds.²³ Clinically, nanocrystalline AgNP dressings such as Acticoat contain 0.5–1.5 mg/cm^2 Ag⁰, while ionic silver formulations include silver sulfadiazine cream (AgSD, 1% w/w) and Aquacel Ag (1.2% ionic silver), which differ in ion release kinetics and toxicity profiles.^{1,16} Oxidative stress compromises essential biomolecules, leading to cell lysis. Additionally, AgNO₃, at 50 μM (\approx 5 $\mu\text{g}/\text{mL}$) exhibit what is known as the “zombie effect”: bacteria killed by AgNPs retain antimicrobial capacity due to their Ag⁺ content, allowing them to inhibit nearby microorganisms further.²⁷ Significantly, AgNPs also interfere with quorum sensing and biofilm formation, processes that are crucial for chronic wound colonization and resistance to conventional antibiotics. These diverse antimicrobial pathways are illustrated in Figure 1, which summarizes how AgNPs and silver ions affect bacterial cells by disrupting membrane integrity, biofilm formation, enzymatic activity, ion transport, respiration, and genetic material, ultimately leading to microbial death.

Studies have shown that various forms of AgNPs and silver dressings disrupts bacterial communication pathways, making microbial communities more susceptible to host immune responses and antimicrobial agents.¹⁶ Furthermore, various AgNPs dressings have demonstrated rapid antimicrobial action even at low concentrations, often within minutes to a few hours of application, making them particularly suitable for wounds at high risk of infection.¹

While AgNPs’ multifaceted mode of action makes it harder for pathogens to develop resistance, specific mechanisms have nonetheless emerged. These include the expression of silver efflux pumps (e.g., SilE, SilF, SilB), the

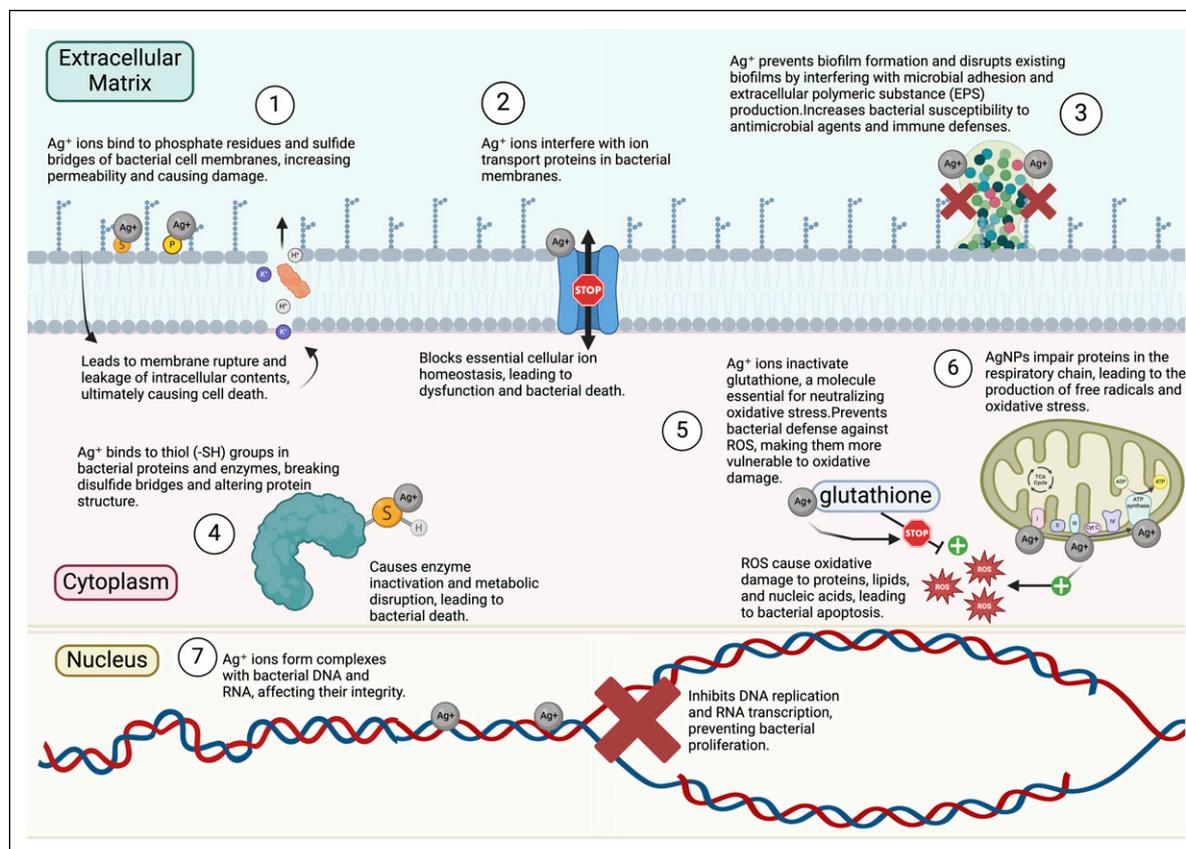


Figure 1. Schematic representation of the antimicrobial mechanisms of silver nanoparticles (AgNPs) and silver ions (Ag⁺). Both forms disrupt bacterial cell membranes, interfere with ion transport, inhibit biofilm formation and key enzymatic activities, impair oxidative stress defense systems, and suppress cellular respiration as well as DNA/RNA replication, ultimately resulting in bacterial cell death (created by the authors).

inactivation of silver ions by bacterial metallothioneins, decreased expression of porins that limit silver ion entry, and microbial-induced aggregation or reduction of silver ions into biologically inactive Ag⁰.^{28–30}

CODs also exhibit potent biocidal activity against a wide range of organisms, including fungi, viruses, and both gram-positive and gram-negative bacteria, including drug-resistant strains.^{2,31,32} Experimental studies *in vitro* using colloidal CuNP suspensions demonstrated antimicrobial effects, with growth inhibition (reported at 5–50 µg/mL),³³ and bactericidal activity (at 0.156–0.625 mg/mL).³⁴ Those results confirm similar antimicrobial effects *in vitro* but the clinical evidence is derived almost exclusively from CODs.^{18,20,21,35}

Cu²⁺ ions released from CODs decrease microbial membrane permeability, lipid peroxidation, protein interference, and nucleic acid damage.¹⁸ Cu²⁺ ions disrupt the microbial plasma membrane by exerting electrostatic forces that damage the lipopolysaccharide layer, resulting in membrane collapse.³⁶ Copper binds directly to microbial proteins or displaces essential metal ions, compromising protein structure and function. Simultaneously, redox cycling between Cu⁺ and Cu²⁺ generates hydroxyl radicals that

attack amino acids and membrane lipids, leading to oxidative degradation and membrane disintegration.^{37,38}

Notably, despite extensive use, no microbe has yet been shown to develop complete resistance to copper. While microorganisms can express genes that modestly increase copper tolerance, such as those regulating envelope permeability, efflux pumps, or copper-binding secretions, these defenses are typically overwhelmed by the simultaneous and synergistic antimicrobial actions of copper. The absence of resistance may be attributed to copper acting through multiple concurrent pathways, unlike antibiotics that often target a single site, or to limited clinical use.^{32,39}

Angiogenesis, tissue regeneration, and immune modulation

Copper is vital for wound healing, and its deficiency can delay wound closure.^{18,40} It plays a crucial role in wound healing by interacting with key stimulating factors.¹⁸ At the core of CODs action is the redox reaction between CuO and Cu₂O. This redox cycling generates ROS, such as hydrogen peroxide (H₂O₂) and hydroxyl radicals. These ROS act as

signaling molecules at low concentrations, triggering various healing pathways; at higher concentrations, they exhibit antimicrobial effects.¹⁸ The hypoxia-inducible factor 1- α (HIF-1 α) pathway is a critical pathway influenced by copper oxide. Hypoxia in the wound environment stabilizes HIF-1 α , a transcription factor that orchestrates a complex response to low oxygen levels. Cu²⁺ released from CODs stabilize HIF-1 α ⁴¹ activating the transcription of multiple genes involved in wound healing. HIF-1 α is up-regulated following wounding due to local hypoxia in the damaged skin.^{18,41} This upregulation triggers a cascade of events resulting in angiogenesis, increased metabolism, dermal cell division and migration, growth factor release, immune cell recruitment, extracellular matrix (ECM) synthesis, and epithelialization.¹⁸

In the inflammatory stage of wound healing, Cu²⁺ released from CODs stimulate platelet-derived growth factor (PDGF). Additionally, copper ions promote the recruitment of immune cells by releasing chemokines such as MCP-1 and IL-8, which attract macrophages and neutrophils to the wound site.^{18,40} These immune cells are essential for clearing debris, combating infections, and releasing growth factors that aid healing. Copper also serves as a cofactor for superoxide dismutase (SOD), protecting against oxidative stress.^{2,18,34}

During the proliferation stage, Cu²⁺ released from CODs stimulates the production of vascular endothelial growth factor (VEGF) and angiogenin. It also supports the secretion of collagen and elastin by dermal fibroblasts, as well as lysyl oxidase (LOX) activity, which is essential for ECM formation and stabilization during the proliferation and remodeling phases.^{2,18} Copper ions modulate the activity of integrins and laminins, which are crucial for endothelial cell migration and proliferation. *In vitro* studies with colloidal CuNP suspensions confirm these findings at concentrations of 5–25 $\mu\text{g/mL}$ ⁴² and 10–50 $\mu\text{g/mL}$.⁴³ Clinically, CuO dressings (~ 20 –40 $\mu\text{g/cm}^2$) influences epithelialization by activating the epidermal growth factor receptor (EGFR) pathway, leading to increased cell proliferation and migration, both of which are necessary for wound closure. Furthermore, factors such as keratinocyte growth factor (KGF) and fibroblast growth factor receptor 3 (FGFR3), which contribute to epithelial cell growth and differentiation, are upregulated by copper ions.¹⁸

During the remodeling phase, Cu²⁺ released from CODs modulates matrix metalloproteinases (MMPs) and influences ECM synthesis by regulating TGF- β 1 and TGF- β 3 activity, which are critical for collagen production and ECM remodeling. Cu²⁺ released from CODs induce superoxide dismutase (SOD), which reduces oxidative stress, supports tyrosinase, which is vital for melanin production and skin pigmentation.¹⁸ Histological, immunohistochemical, and PCR analyses have demonstrated the enhanced generation of new blood vessels, sebaceous glands, and hair follicles, along with increased expression of proangiogenic factors such as VEGF, FGFR3, TGF- β , and notably, the key wound healing stimulating factor—HIF-1 α .^{41,44}

Recently, it has been discovered that SLC31A1, a copper transporter, is reduced in diabetic foot ulcers, which partially explains the challenges associated with healing diabetic ulcers.⁴⁵ Additionally, in individuals with diabetes, and likely in other chronic conditions, HIF-1 α activity is diminished^{41,46,47} thereby enhancing the potential of CuO dressings in diabetic wounds.

In vitro studies have demonstrated that exposure to CuNPs enhances fibroblast proliferation, increases expression of matrix metalloproteinases (MMPs), and supports reorganization of the extracellular matrix at 5–25 $\mu\text{g/mL}$ ⁴² and 10–50 $\mu\text{g/mL}$.⁴³ Animal models have further validated these findings.^{31,33,48} For instance, in a porcine burn model, wounds treated with CODs exhibited significantly increased granulation tissue, improved angiogenesis, and faster re-epithelialization compared to untreated controls without notable systemic toxicity.³¹ Similarly, Cu²⁺ released from CODs³⁷ and topical CuNP suspensions (0.01%–0.1% CuNP, ≈ 100 –1000 $\mu\text{g/mL}$)³⁴ integrated into wound dressings were shown to reduce wound size and accelerate closure in rat models, accompanied by increased collagen deposition and vascular density.^{33,48} Figure 2 summarizes these diverse mechanisms by which CuO dressings facilitate tissue repair and regeneration.

While silver is primarily known for its antimicrobial properties, some studies have shown that AgNPs can reduce excessive inflammation in the wound environment. Specifically, AgNP–keratin biomaterial scaffold dressing, tested at 50–100 $\mu\text{g/mL}$ equivalent silver *in vitro* and validated in a full-thickness diabetic mouse wound model has been reported to suppress the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B).²³ In addition some clinical formulations (Acticoat, 0.5–1.5 mg/cm² Ag and AgSD cream 1%) showed inhibition of NF- κ B leads to decreased levels of tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6), potentially lowering the inflammatory burden in infected or colonized wounds.³

While some AgNPs-based products may reduce inflammation and promote indirect healing, high concentrations of silver ions are cytotoxic to keratinocytes and fibroblasts. *In vitro* studies consistently demonstrate that various forms of silver dressings (Acticoat, 0.5–1.5 mg/cm² Ag, Aquacel Ag 1.2% ionic silver) inhibit mitochondrial activity and impair cell viability at concentrations exceeding 10–50 $\mu\text{g/mL}$, depending on the cell type and particle coating.^{48,49} Furthermore, AgNPs (colloidal AgNP suspensions <20 $\mu\text{g/mL}$) has been linked to delayed wound closure in some models due to its inhibition of cell proliferation and interference with growth factor signaling pathways.⁵⁰

Toxicity, biocompatibility, and safety

AgNPs have been extensively studied for their biomedical and antimicrobial applications, with a focus on how their shape, size, and concentration significantly influence toxicity and

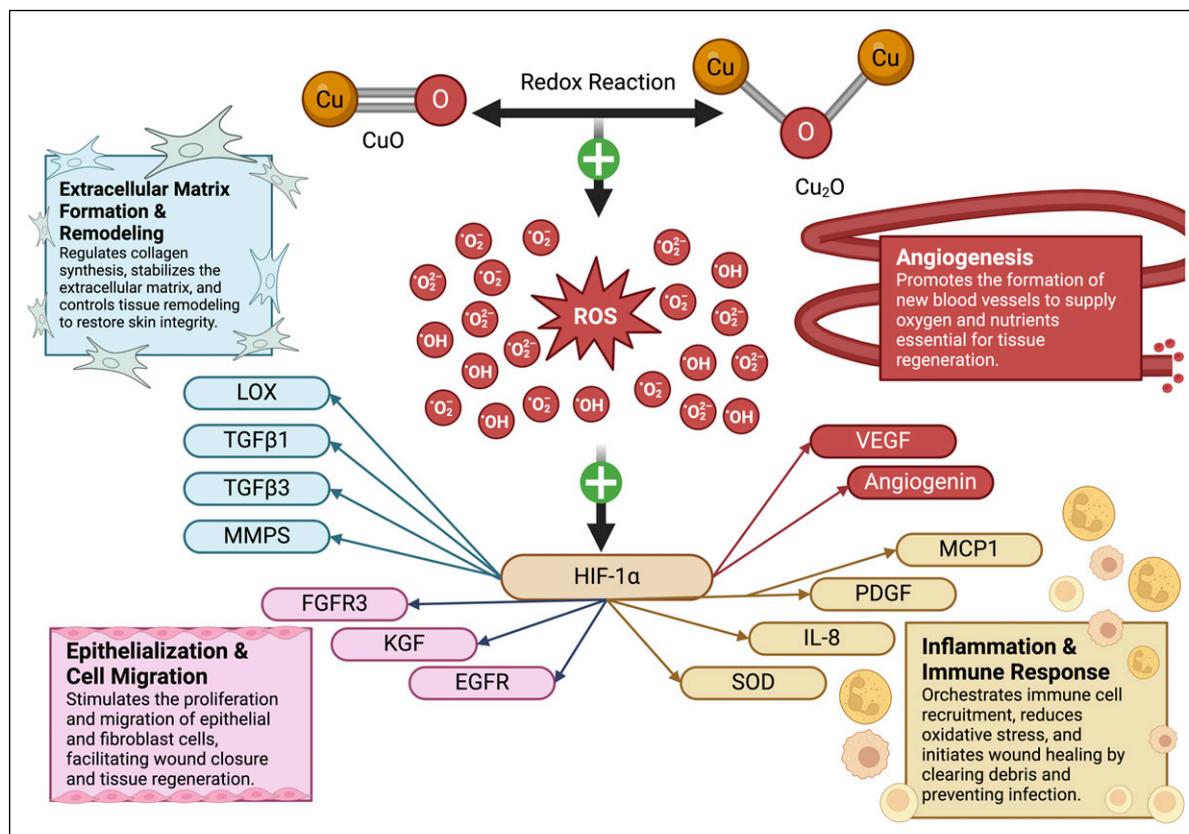


Figure 2. Selected mechanisms of copper oxide in wound healing. Figure 2 illustrates how copper oxide (CuO) and cuprous oxide (Cu_2O) facilitate wound healing through redox reactions that generate reactive oxygen species (ROS), which activate hypoxia-inducible factor 1-alpha ($\text{HIF-1}\alpha$) and drive key processes such as angiogenesis, extracellular matrix (ECM) formation and remodeling, epithelialization and cell migration, and inflammation and immune response, involving multiple molecular factors. ROS – Reactive Oxygen Species, $\text{HIF-1}\alpha$ – Hypoxia-Inducible Factor 1-Alpha, ECM – Extracellular Matrix, VEGF – Vascular Endothelial Growth Factor, LOX – Lysyl Oxidase, $\text{TGF-}\beta 1$, $\text{TGF-}\beta 3$ – Transforming Growth Factor-Beta 1 and 3, MMPs – Matrix Metalloproteinases, FGFR3 – Fibroblast Growth Factor Receptor 3, KGF – Keratinocyte Growth Factor, EGFR – Epidermal Growth Factor Receptor, MCP-1 – Monocyte Chemoattractant Protein-1, PDGF – Platelet-Derived Growth Factor, IL-8 – Interleukin-8.

therapeutic efficacy. Research indicates that smaller nanoparticles generally exhibit higher toxicity due to their larger surface area-to-volume ratio, enhancing cellular interaction and ROS generation. Nanoparticles ranging from 10 to 50 nm are the most investigated, with those smaller than 20 nm demonstrating significant toxic effects on various cells, including dermal fibroblasts (HDFa), murine fibroblasts (NIH/3T3), and keratinocytes.^{23,51–54} Another factor influencing toxicity is shape; spherical nanoparticles are the most studied due to their ease of synthesis and stability. Other morphologies, such as triangular and rod-shaped nanoparticles, reveal varying toxicity levels; triangular particles often display enhanced antimicrobial activity due to their larger surface area.^{23,51} Toxicity is dose-dependent, with elevated concentrations leading to significant cytotoxic and genotoxic effects. For example, concentrations of AgNPs exceeding 20 ppm ($\approx 20 \mu\text{g/mL}$) can cause hemolysis and reduce cell viability.^{23,52,55}

The cytotoxicity of AgNPs in mammalian cells limits their safe concentration range. Research highlights the

importance of surface modifications, such as capping with biocompatible materials, to mitigate these effects. After systemic exposure, AgNPs can accumulate in various organs, including the liver, spleen, lungs, and kidneys. Studies on applications have shown localized effects without significant systemic penetration; however, some skin models indicated deep dermal penetration.^{54,55}

In vivo, examinations demonstrated that AgNP-loaded hydrogels and dressings enhance wound healing by reducing bacterial load and modulating the inflammatory response. Histological analyses revealed improved re-epithelialization and collagen deposition in treated wounds.^{23,54}

In vivo, silver's adverse effects are more difficult to isolate due to variability in formulations and clinical context. However, delayed epithelialization has been reported in some animal studies using AgNPs-containing products, and silver overload (argyria) remains a theoretical concern in long-term or high-dose use, particularly over large wound areas.^{56,57} In clinical practice, patient-reported adverse

events associated with AgNPs dressings are typically limited to mild irritation or discoloration. However, these are more frequent with older formulations, such as silver sulfadiazine.

The toxicity and biocompatibility of CuNPs have been assessed through both *in vitro* and *in vivo* studies. *In vitro*, the toxicity of CuNPs was examined using various cell lines (human keratinocytes - HaCaT, monkey kidney cells - Vero, and A375 human melanoma cells). CuNPs exhibit size-dependent toxicity, with smaller particles (<50 nm) being more reactive and potentially toxic due to an increased surface area and ion release.^{31,48} CuNPs at high concentrations (e.g., >12.5 µg/mL for Vero cells) reduced cell viability, indicating dose-dependent toxicity.³³ Moreover, higher concentrations (≥50 µg/mL) induced ROS generation, DNA damage, and cell death.^{33,48} Antimicrobial examinations showed that CuNPs exhibited selective antibacterial effects, particularly against *Escherichia coli* and *Pseudomonas aeruginosa*, at minimum inhibitory concentrations (MICs) ranging from 0.156 to 0.625 mg/mL (156–625 µg/mL).³³

CODs, in contrast, demonstrate a more favorable safety profile. Unlike AgNPs, which are entirely exogenous and not involved in normal human physiology, copper is an integral element in cellular processes, thereby reducing the risk of unintended cellular damage.

Although copper is also redox-active and capable of generating reactive oxygen species (ROS), it is an essential trace element regulated by natural homeostatic mechanisms in the human body. These include metallothioneins and ATP7A/ATP7B copper transporters, which bind and sequester excess copper to prevent toxicity.^{2,32} The main organs for accumulating CuNPs are the liver, kidneys, spleen, and, to a lesser extent, the brain.^{33,48,58} Wound healing examinations in rats showed that CuNP-based treatments (topical suspensions at 0.01%–0.1% CuNPs, ≈100–1000 µg/mL)³⁷ accelerated healing without significant toxic effects. In burn wounds in mice, CuNP creams (5–50 µg/mL) reduced inflammation and promoted regeneration with negligible changes in copper levels in systemic circulation.³¹

Clinical aspects

CODs and silver dressings are attracting considerable interest as antimicrobial agents for wound treatment due to their broad spectrum of activity and unique biological properties. Recent studies have highlighted their potential to improve treatment outcomes for various types of wounds, including acute, chronic, and infected wounds. In the following subsections, we have selected and described the use of CODs and various forms of silver dressings in the treatment of wounds of various etiologies.

Diabetic foot ulcers

AgNPs-based dressings are commonly used to manage diabetic foot ulcers because of their broad-spectrum

antimicrobial properties. A randomized controlled trial comparing SilvrSTAT® hydrogel (24 ppm of AgNPs, 0.0024% w/w) to conventional paraffin gauze dressings in patients with diabetic foot ulcers indicated that the SilvrSTAT® group experienced significantly faster healing. By week four, the SilvrSTAT® group achieved a 75% reduction in ulcer area compared to 52% in the control group.¹⁰ Conversely, another randomized controlled trial using Acticoat™ Flex 3 dressings (~1.2 mg/cm² of Ag⁰) found no statistically significant difference in ulcer healing rates between AgNP dressings and standard wound care. Healing occurred in 75% of patients in the Acticoat group versus 69% in the control group over a 12-week period.⁶ The authors concluded that while Acticoat dressings may aid in infection control, their impact on long-term healing outcomes may be limited, particularly beyond the early inflammatory phase. A meta-analysis focusing on hard-to-heal diabetic ulcers revealed that although SilvrSTAT® hydrogels outperformed traditional silver dressings, still, AgNPs dressings showed limited evidence of sustained healing advantages over conventional dressings.¹¹ Additionally, some studies have raised concerns about the cytotoxicity of silver to fibroblasts and keratinocytes, which may hinder later phases of healing.¹⁰

In contrast, CODs dressings have demonstrated efficacy not only in controlling microbial growth but also in promoting wound healing in diabetic foot ulcers through their pro-regenerative effects. A prospective study assessed CODs in 20 patients whose wounds had not responded to AgNPs dressings (various forms). After transitioning to CODs, patients exhibited wound closure at a rate approximately 2.4 times faster than during AgNPs dressings treatment, with granulation and epithelialization evident within a few days of application.²¹ Additionally, a non-inferiority randomized controlled trial compared CODs to negative pressure wound therapy (NPWT) in diabetic wounds. This study included 46 patients and found that CODs achieved comparable wound size reduction and granulation tissue development while offering a 90% reduction in treatment costs and greater ease of use.⁵⁹ These findings highlight the potential of CODs as a first-line, cost-effective option for DFU management, particularly when used throughout all stages of wound healing.

Pressure ulcers

AgNPs-containing dressings have been widely used in the management of pressure ulcers due to their antimicrobial properties. However, clinical evidence regarding their efficacy yields mixed outcomes. A randomized clinical trial involving 70 patients with spinal cord injuries compared the effectiveness of Silver sulfadiazine (AgSD)-containing dressing to hydrocolloid dressings in treating pressure ulcers. The study found that the AgSD group experienced a significantly higher healing rate, with 85.7% of ulcers

showing improvement compared to 57.1% in the hydrocolloid group.¹⁵ In contrast, a study evaluating the efficacy of Aquacel® Ag Hydrofiber (~1.2% w/w silver ≈1 mg/cm²) in treating bedsores reported that while Aquacel® contributed to wound healing, the results were not significantly superior to those of standard treatments. The study emphasized the need for further research to establish definitive conclusions regarding the benefits of silver dressings in pressure ulcer management.¹²

CODs have been shown to facilitate wound healing in pressure ulcers, including cases that do not respond to conventional treatments such as silver dressings and negative pressure therapy. In a series of clinical cases, Melamed and Borkow detailed patients with stage 2 to 4 pressure ulcers treated with CODs. In these instances, wounds that had been stagnant for weeks or months showed significant improvements, including visible granulation and epithelialization. Wound area reductions ranged from 37% to 87% over a 25-days treatment period, with patients displaying decreased exudate, improved pain management, and no adverse reactions.²² A clinical case series documented the usage of CODs in patients with chronic wounds, including pressure ulcers, that were unresponsive to conventional treatments. The application of CODs resulted in significant enhancements in wound healing, characterized by increased granulation tissue formation and epithelialization. Notably, these benefits occurred in wounds previously treated with silver dressings, indicating the potential of CODs in refractory cases.²¹

Venous leg ulcers

AgNPs-containing dressings have been extensively utilized in the management of VLU due to their antimicrobial properties. However, clinical evidence regarding their efficacy presents mixed outcomes.

The VULCAN trial, a multicenter randomized controlled study involving 213 patients, compared Acticoat™ Flex 3 (nanocrystalline silver, ~1.2 mg/cm²) and Aquacel® Ag Hydrofiber®Ag (~1.2% w/w silver ≈1 mg/cm²) dressings with non-silver low-adherence dressings under compression therapy. The study found no significant difference in healing rates in 12 weeks between the silver dressings group (59.6%) and the control group (56.7%). Additionally, the cost-effectiveness analysis indicated a high incremental cost-effectiveness ratio for silver dressings, suggesting limited economic benefit.⁷ In contrast, a meta-analysis focusing on the short-term use of Acticoat™ Flex 3 (nanocrystalline silver, ~1.2 mg/cm²) and Aquacel® Ag Hydrofiber®Ag (~1.2% w/w silver ≈1 mg/cm²) in hard-to-heal VLUs demonstrated a statistically significant improvement in healing rates. Patients treated with silver dressings for 4 weeks exhibited a higher proportion of healed ulcers (7.6%) compared to those with non-AgNPs dressings (3.4%). Moreover, the average time to wound

healing was reduced by approximately 3 weeks in the silver dressings group (13.8 weeks) compared to the control group (16.7 weeks), resulting in an estimated cost savings of £141.57 per patient.¹³ Further supporting evidence comes from a recent randomized controlled trial evaluating the Aquacel® Ag + Extra™, made of carboxymethylcellulose gelling fiber dressing containing ionic silver, EDTA, and benzethonium chloride (CISEB) versus dialkylcarbamoyl chloride-coated dressing (DACC) in hard-to-heal VLUs. The study reported that the CISEB dressing group achieved a greater reduction in ulcer area and improved healing outcomes compared to the control group, without additional safety concerns.¹⁴

CODs have emerged as a promising alternative in VLU management, offering both antimicrobial and pro-healing properties. A clinical case series documented the use of CODs in patients with chronic wounds, including VLUs, that were unresponsive to conventional treatments. The application of CODs resulted in significant improvements in wound healing, characterized by enhanced granulation tissue formation and epithelialization. Notably, these benefits were observed in wounds previously treated with AgNPs dressings, indicating the potential of CODs in refractory cases.²¹

Furthermore, a recent study highlighted the idea of a “Continuum of Care” using CODs, demonstrating their effectiveness across different stages of wound healing in challenging wounds, including VLUs. The study noted accelerated healing rates and a decreased need for dressing changes, emphasizing the practical benefits of CODs in clinical environments.²²

Surgical wounds

AgNPs-based dressings have been widely used in surgical wound care due to their antimicrobial properties. A prospective multicenter observational study involving 218 patients undergoing general surgical procedures compared the incidence of incisional surgical site infections (SSIs) between those treated with Aquacel® Ag Surgical (~1.2% w/w silver ≈1 mg/cm²) dressings and those with conventional dressings. The study found a significantly lower SSI rate in the AgNPs group (9.2%) compared to the control group (19.3%).⁶⁰ In orthopedic surgery, a trial evaluated the efficacy of Aquacel® Ag Surgical (~1.2% w/w silver ≈1 mg/cm²) in preventing SSIs following total knee arthroplasty. The study reported a decrease in SSI rates from 6.7% in the control group to 1.1% in the Aquacel® dressing group, indicating a significant protective effect.⁶¹ However, not all studies have shown substantial benefits. A randomized trial assessing the impact Silverlon® (~2–5 mg/cm² Ag⁰) dressings on SSIs in patients undergoing elective colorectal surgery found no significant difference in infection rates between the Silverlon® dressing group and the control group.⁹

A clinical case series documented the use of CODs in patients with chronic wounds, including surgical wounds, that were unresponsive to conventional treatments. The application of CODs led to significant improvements in wound healing, characterized by enhanced granulation tissue formation and epithelialization.²¹ Further supporting evidence comes from a study evaluating the impact of CODs on surgical site infections. The study demonstrated a significant reduction in SSI rates following cesarean sections with the use of CODs, highlighting their potential in surgical wound care.⁶² Clinical case series have shown that CODs are beneficial in managing challenging surgical wounds. In patients with ischemic post-operative wounds that failed to respond to antibiotics and traditional dressings, including AgNPs dressings, the application of CODs resulted in marked wound improvement. These effects included decreased local edema, improved granulation, revascularization of ischemic margins, and eventual full epithelialization without the need for skin grafts or NPWT.²² These findings suggest that CODs not only reduce microbial load but also promote wound remodeling, potentially serving as a primary dressing for post-operative recovery, especially in complex or chronic wounds.

Burn wounds

AgNPs dressings are commonly used in burn care due to their strong antimicrobial properties and availability in various formulations, including silver sulfadiazine, silver nitrate, and nanocrystalline silver dressings. Clinical guidelines recommend silver dressings for managing burn wounds with high bioburden or established infections, especially during the inflammatory phase. However, the role of silver dressings in the later stages of healing remains a topic of debate. A review of clinical practice indicated that while silver dressings reduce the risk of infection and promote optimal conditions for early wound healing, they do not prevent pathological scarring or consistently speed up epithelialization.⁵

A comprehensive review of commercial silver dressings concluded that they are effective in reducing microbial load in burn wounds and support healing through bioburden control. However, variability in dressing formulations, silver concentrations, and clinical protocols makes it difficult to define universal guidelines for their use. While infection rates and wound exudate are often reduced, the data on long-term healing outcomes remain inconsistent.⁶³

Another important consideration is the use of silver dressings in pediatric patients. A systematic scoping review analyzing the safety of silver dressings in infants concluded that, although they are widely used, silver may pose risks due to systemic absorption, especially in large area burns. The authors emphasized the need for cautious use in neonates and recommended limiting the duration of treatment

and monitoring for toxicity. Nevertheless, no significant adverse events were reported across the studies reviewed, indicating a generally acceptable safety profile under appropriate conditions.⁶⁴

CODs have emerged as an innovative alternative that combines antimicrobial action with pro-regenerative effects. A recent clinical case series demonstrated that CODs significantly accelerate burn wound closure, reduce inflammation, and enhance angiogenesis and re-epithelialization. In cases of partial-thickness burns, complete or near-complete closure was observed within 12 to 14 days, without the need for surgical intervention. No local or systemic adverse effects were noted. The treatment resulted in complete healing after previous regimens, such as silver dressings and NPWT, had failed. Wound closure was associated with visible improvements in granulation tissue formation and a decrease in fibrin and necrotic burden.³⁵ These cases indicated faster healing trajectories and a reduced need for grafting or NPWT, suggesting that CODs may serve as a viable single step dressing from injury to full closure.²²

Cost-effectiveness and longevity of use

Cost-effectiveness is a crucial factor in selecting wound care products, particularly for managing chronic wounds. These contribute significantly to healthcare expenditures due to prolonged treatment duration, hospital admissions, and frequent dressing changes. While nanoparticle-based dressings may initially be more expensive than standard non-active materials, their potential to reduce healing time, prevent infection, and lower overall resource utilization makes them an attractive option in appropriate clinical contexts.

Silver dressings have demonstrated the ability to reduce the overall cost of wound treatment. A 2014 study estimated the cost of treating venous ulcers with Silverlon® dressings at approximately \$2,188, compared to \$2422 for patients not using silver dressings during the first 4 weeks of treatment.⁸ The overall cost of therapy with silver dressings varies primarily by wound type and treatment duration. Most silver dressings are recommended to use for up to 3 days, with the entire therapy duration often being shorter compared to standard treatment. This leads to fewer dressing changes throughout whole treatment.^{1,65}

CODs, in contrast, are indicated for use up to 7 days, depending on wound exudate levels. High-exudate wounds may require more frequent changes. A single manufacturer produces modern CODs, providing a cost-effective solution with an estimated monthly expense ranging from \$576 to \$1,376, based on dressing size and change frequency.⁶⁶ Although clinical use of CODs is increasing, no comprehensive cost-analysis study has been published to date, highlighting the need for further research into their economic impact.

Table 2. Head-to-Head comparison of AgNPs and CuNPs dressings.

Aspect of comparison	Silver dressings (AgNPs/Ag ⁺)	Copper dressings (CODs)	References
Antimicrobial mechanism	Broad-spectrum, rapid kill via Ag ⁺ release; membrane disruption, ROS, DNA/protein damage; biofilm inhibition; 'zombie effect'.	Broad-spectrum, Cu ²⁺ disrupts membranes, proteins, nucleic acids; redox cycling (Cu ⁺ /Cu ²⁺) generates ROS; effective vs fungi/viruses too.	17,31
Resistance potential	Resistance reported via efflux pumps, reduced porins, and metallothioneins	No complete resistance observed; multi-pathway attack	28,39
Pro-regenerative effect	Limited; higher Ag ⁺ doses cytotoxic to keratinocytes/fibroblasts; may delay epithelialization; minimal angiogenic effect.	Strong; activates HIF-1 α , VEGF, angiogenin; enhances fibroblast proliferation, collagen/elastin synthesis, LOX activity; stimulates epithelialization and ECM remodeling.	18,50
Inflammation modulation	Can reduce NF- κ B signaling, lowering TNF- α , IL-1 β , IL-6.	Stimulates PDGF, MCP-1, IL-8, macrophage/neutrophil recruitment; enhances antioxidant SOD response.	18,23
Toxicity and biocompatibility	Cytotoxic at >10–50 μ g/mL; systemic absorption possible (argyria); risks in pediatrics with large burns; delayed epithelialization in some models.	Safer profile; copper is essential trace element with physiological regulation (metallothioneins, ATP7A/B transporters); CODs show no systemic toxicity in clinical studies.	2,51
Duration of use	Typically \leq 3 days (depends on exudate load and cytotoxicity risk).	Effective up to 7 days (depending on exudate), supporting 'continuum of care'.	1,66
Full healing cycle suitability	Best in early/infected stages; less suitable long-term due to cytotoxicity.	Supports all phases - inflammation, proliferation, remodeling; used successfully after silver failure.	22
Clinical efficacy in chronic wounds	Effective in acute and chronic wounds, but limited regeneration	Effective in recalcitrant wounds, even where silver failed	10,21

Importantly, CODs may provide longevity of use advantages. While silver dressings are generally limited to early stages of healing due to their cytotoxic potential, they are typically not suited for continuous use across all healing phases.^{1,65} This often necessitates transitioning between different types of dress, adding cost and logistical complexity. Conversely, CODs have demonstrated effectiveness throughout all wound healing phases.⁶⁶ This supports the "Continuum of Care" model, in which single dressing is suitable for the entire healing process, offering both clinical and logistical advantages over silver dressings.²²

Head-to-head comparison

In Table 2, we present a direct comparison across key clinical and biological parameters to provide a structured evaluation of silver and CODs dressings. This table highlights the differences in antimicrobial action, regenerative potential, safety, and duration of use.

Future perspectives

Further research should focus on direct, large-scale, randomized controlled trials comparing CODs and silver dressings across specific wound etiologies, particularly in

diabetic foot ulcers and pressure ulcers, where conventional treatments often fail. Advanced omics technologies, such as transcriptomics and proteomics, could elucidate the specific molecular cascades triggered by CuNPs versus AgNPs in human wound beds. Additionally, wearable sensors integrated into CODs could be explored to monitor real-time biomarkers, such as exudate pH or inflammatory cytokines, thereby optimizing dressing change intervals and personalizing wound care. Finally, cost-utility modeling in real-world hospital settings should be conducted to assess the long-term economic impact of replacing multi-dressing protocols with CODs regimens.

Conclusions

Silver dressings continue to be essential in wound management, but their clinical effectiveness relies greatly on the formulation employed. Traditional preparations, such as silver sulfadiazine cream (1%) and silver nitrate solution (0.5%), offer prompt antimicrobial activity; however, they are linked with cytotoxicity, require frequent dressing changes, and have a limited effect on long-term healing. Nanocrystalline silver dressings (e.g., ActicoatTM) and ionic silver hydrofiber dressings (e.g., Aquacel[®] Ag) have demonstrated more favorable release kinetics, offering sustained antimicrobial effects with lower toxicity, and are

most useful in the early inflammatory and infection-prone phases of wound healing. Newer enhanced formulations, such as Aquacel® Ag + Extra™, which combine ionic silver with biofilm-disrupting agents, show promise in improving outcomes in hard-to-heal wounds, although high-quality data remain limited.

On the other hand, CODs represent an emerging class of wound dressings that combine antimicrobial efficacy with regenerative potential, including stimulation of angiogenesis, fibroblast proliferation, and extracellular matrix remodeling. Clinical series and early prospective studies suggest that CODs may accelerate closure in wounds unresponsive to silver or negative pressure therapy, while offering a favorable safety and cost profile. However, the clinical evidence base for CODs is still small, and large randomized controlled trials are needed to confirm their role in standard wound care.

Taken together, silver dressings, especially nanocrystalline and ionic hydrofiber formulations, remain valuable tools for infection control in acute and high-burden wounds. Copper oxide dressings offer a biologically appealing alternative with dual antimicrobial and regenerative effects, but currently, the available data are insufficient to determine that they represent a paradigm shift in wound healing. CODs should therefore be regarded as promising adjuncts, with their definitive role in clinical practice awaiting further high-quality evidence.

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