Silver Dressings

1. Understand the mechanisms of action

2. Choose the appropriate times to use a silver dressing

3. What does the research tell us about its efficacy and monetary value
Antimicrobial Performance of Silver Dressings

• Silver is effective against superficial pathogens, but it may not inhibit bacteria that have penetrated a significant distance into the wound bed
SILVER ION DRESSINGS

(A) Silver ions are absorbed into the wound site, where they exert their antimicrobial activity on bacterial cells. The ions bind to bacterial cell membranes and are transported into the cell.

(B) Interfering with the membrane transport system, silver ions impede the bacterial cell's energy source and disrupt peptidoglycan within the wall, causing structural damage. Inside the cell they bind to DNA, impairing cell replication; they also bind to and inactivate intracellular enzymes.

(C) The bacterial cell is then prevented from growing or replicating, or more commonly, dies as vital components leak through a weakened cell wall no longer able to maintain osmotic pressure.
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✓ binds to the bacterial cell membrane, damaging it and interfering with various receptors

✓ interferes with bacterial electron transport, impeding the production of adenosine triphosphate, the cell's energy currency

✓ binds to bacterial DNA, impairing cell replication

✓ causes the intracellular formation of insoluble compounds with certain nucleotides, proteins, and the amino acid histidine, making them unavailable as intracellular building blocks.
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Bacterial Resistance to Antimicrobials

• Easier to develop resistance to antibiotics
  – Usually have one specific mode of attack on the cell wall

• Not so easy to develop resistance to antiseptics
  – Usually have multiple modes of attack and multiple target sites on cell walls or membranes
What is Bacterial Resistance?

- When bacteria have evolved to “outsmart” or prevent the antimicrobial agent from attacking or entering the cell

- Via mutations that result in:
  - A change in the target binding site for the antimicrobial agent
  - Development of enzyme systems that:
    - “Kick” the agent out of the cell or;
    - Inactivate the agent
Bacterial Resistance to Silver

- Incidence and prevalence of clinical resistance to silver is low despite decades of medicinal use
- Cases reported to date have been in patients treated with silver nitrate and silver sulfadiazine
- And involve primarily gram negative bacterial species including
  - E.coli, Proteus mirabilis, Klebsiella pneumoniae, Pseudomonas aeruginosa

Bacterial Resistance to Silver

• A variety of resistant species of bacteria have developed in burn patients whose wounds were treated with either silver sulfadiazine or silver nitrate.

• Canadian clinicians have cultured resistant strains of Pseudomonas from wounds that were treated with nanocrystalline silver dressings
Bacterial Resistance to Silver

• A variety of resistant species of bacteria have developed in burn patients whose wounds were treated with either silver sulfadiazine or silver nitrate.

• Canadian clinicians have cultured resistant strains of *Pseudomonas* from wounds that were treated with nanocrystalline silver dressings.
Bacterial Resistance to Silver

- Silver has a maximum of 5 mechanisms of action that occur at different concentrations.

Therefore:

- At high concentration of silver - 5 mutations would need to occur simultaneously for resistance to develop.

Resistance = $1 \times 10^{40}$ Cell Divisions

*Infection and the Chronic Wound: A Focus on Silver*

Warriner, Robert; Burrell, Robert

Advances in Skin & Wound Care. 18(8):2-12, October 2005.
Bacterial Resistance to Silver

• At low concentration – there are fewer mechanisms of action that need to be overcome simultaneously for resistance to develop

• So at lower concentrations of silver, the probability of developing resistance is about:

\[
\text{Resistance} = \frac{1}{1 \times 10^8} \text{ cell divisions.}
\]

Infection and the Chronic Wound: A Focus on Silver

Warriner, Robert; Burrell, Robert
Advances in Skin & Wound Care. 18(8):2-12, October 2005.
In other words...

High concentrations of silver have 5 mechanisms of action to kill bacteria

Lower concentrations of silver have fewer mechanisms of action

Resistance = the bacteria overcoming each mechanism of action

Therefore - the lower the concentration of silver, the easier the bacteria can form resistance
Bacterial Resistance to Silver

• The limited application of silver in clinically relevant situations is not expected to significantly impact the spread of resistance.

• However, since resistance is possible and has been seen in selected situations, a prudent approach to topical silver dressings in terms of duration of use is advised.
Protecting other Tissues
Delivering Silver Without Harming Host Cells

• High levels of silver are known to have negative effects on host cells like fibroblasts and epithelial cells¹,²


Fibroblast Protection from Low Silver Concentrations

% Fibroblast Present

- Negative Control (Serum Free)
- Brand X
- Brand Y
- Brand Z
- Positive Control
Silver and MMPs

- The proteolytic property of the MMPs is important during wound healing to remove debris and facilitate cell migration.
- Excessive accumulation and activation of MMPs can compete with cell proliferation, angiogenesis, and matrix proteins needed for cell migration.
- MMPs are also produced by bacteria in chronic wounds, and these bacterially derived MMPs may be responsible for the increasing tissue damage leading from critical colonization to infection.
Silver and MMPs

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• Excessive accumulation and activation of MMPs can compete with cell proliferation, angiogenesis, and matrix proteins needed for cell migration.

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Bacteriology, Inflammation, and Healing: A Study of Nanocrystalline Silver Dressings in Chronic Venous Leg Ulcers
Sibbald, R. Gary; Contreras-Ruiz, Jose; Coutts, Patricia; Fierheller, Marjorie; Rothman, Arthur; Woo, Kevin
Silver and MMPs

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- **MMPs are also produced by bacteria** in chronic wounds, and these bacterially derived MMPs may be responsible for the increasing tissue damage leading from critical colonization to infection.
• So one protocol for the use of silver dressings might be to reduce the MMP count during the proliferatory phase of healing (to counter MMPs produced by bacteria in a subacute infection)
Silver Availability
Differences in Various Types of Silver Preparations

All silver-based dressings contain the same active ingredient, the silver cation, but use different methods for creating and incorporating a reservoir for the release of the silver cation.
Silver Availability

• Hydrogel dressings allow diffusion of an agent to the wound surface in ways that differ from those of gauze or hydrocolloid dressings.

• This is one reason why data generated for one type of dressing cannot be extrapolated to another type, even if they both contain the same active agent (such as silver).
Silver Availability

The total amount of silver in a dressing &

The crystalline structure of the silver

- Contributes to how much and how quickly silver is dispersed from the dressing onto the wound surface.
- If a given amount of silver is divided among a large number of smaller crystals, its chemically active surface area will be greater than when the same amount is divided among fewer, larger crystals.
Silver and Biofilms

- Silver binds to proteins and ...
- Biofilm bacteria are surrounded with a non-proteinaceous material
- This offers them a level of protection against silver antimicrobials.

Literature both ways!
Antibacterial Performance of Silver Dressings
Antimicrobial Performance of Silver Dressings

• Nanocrystalline silver dressings were applied to nonhealing wounds without the classic clinical signs of infection. This resulted in decreased wound-surface bacterial loading that was associated with clinical improvement and accelerated healing.

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Sibbald, R. Gary; Contreras-Ruiz, Jose; Coutts, Patricia; Fierheller, Marjorie; Rothman, Arthur; Woo, Kevin
Antimicrobial Performance of Silver Dressings

- Exudate levels decreased, and surface bacterial swab results improved, but the deep quantitative bacterial biopsy results did not change.

Bacteriology, Inflammation, and Healing: A Study of Nanocrystalline Silver Dressings in Chronic Venous Leg Ulcers
Sibbald, R. Gary; Contreras-Ruiz, Jose; Coutts, Patricia; Fierheller, Marjorie; Rothman, Arthur; Woo, Kevin
MMPs are also produced by bacteria in chronic wounds, and these bacterially derived MMPs may be responsible for the increasing tissue damage leading from critical colonization to infection.

Antimicrobial Performance of Silver Dressings

• By reducing the number of bacteria and the associated inflammatory response, nanocrystalline silver dressing may facilitate wound healing.

Commercial Silver Dressings
Micro-contouring, bacteria killing*1,2
Don’t miss this remarkable new data.*
*As demonstrated in vitro

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<th>Proprietary Name</th>
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Cell Growth

Evidence Based Medicine
The Cochrane Collaboration
Cochrane Reviews

A tool to insure the application of Evidence Based Wound Care Protocols

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"Silver based wound dressings and topical agents for treating diabetic foot ulcers"

This is a Cochrane review abstract and plain language summary, prepared and maintained by The Cochrane Collaboration, currently published in The Cochrane Database of Systematic Reviews 2010 Issue 9, Copyright © 2010 The Cochrane Collaboration.

The authors of this Cochrane review wanted to find evidence on whether silver based dressings reduced infection and encouraged wound healing.

They searched the medical literature for randomized and controlled clinical trials but found no studies which were eligible for inclusion in the review.

We therefore do not know if silver containing dressings and topical agents containing silver are beneficial to diabetic foot ulcer healing.

Selection criteria

Randomised controlled trials and non-randomised controlled clinical trials were considered for inclusion. Studies were included if they met the requirements for randomisation, allocation and concealment where appropriate, and compared the intervention with a placebo or a sham dressing, an alternative non silver based dressing or no dressing, and reported outcomes that represent healing rate or infection.

Authors' conclusions

Despite the widespread use of dressings and topical agents containing silver for the treatment of diabetic foot ulcers:

**no randomized trials or controlled clinical trials exist that evaluate their clinical effectiveness**

Trials are needed to determine clinical and cost-effectiveness and long term outcomes including adverse events.

“What I am saying is that we should be practicing evidenced based medicine and not costing our patients or the health care system dollars that none of us can afford to spend on a therapy without solid science behind it.

So, next time a sales rep comes to speak to you about their latest and greatest silver product, ask for scientific proof that it contributes to wound healing, not some pretty “before and after” pictures.

Unfortunately, I doubt you will get much. These products are all approved by the FDA as 510k medical devices. Therefore, there is little clinical science necessary to get them approved.

www.WarrenJoseph.com
Evidence Based Wound Care

1. Medline search
2. www.Cochran.org
Thank you!! Thank you!! Thank you!!