Silver: Is it standing the test of time....?

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Conflicts of Interest

• Nothing to disclose.
Brief History

• Used by Greeks and Romans for **storage containers to prevent spoilage**\(^1\).
• Ancient Mediterranean and Asiatic cultures placed **silver foil in wounds to prevent infection**\(^1\).
• 1613: The *Surgeon’s Mate* described **silver as essential medicinal product**\(^3\).
• **Early 17\(^{th}\) century:** used to treat epilepsy and cholera\(^3\).
• 1880’s: Silver nitrate drops were used in newborns to **prevent postpartum eye infections**, preventing blindness\(^1\).
• Silver foil dressings in *Physician’s Desk Reference* until 1955\(^9\).
• 1968: **1% silver sulfadiazine** started being used on **burn wound infections**\(^1\).
Today!!!
The Power of the Silver Ion
Types of Silver

• Elemental
  • Nanoparticles (Raza 2016)
    • Between 1-100nm in size
    • Various shapes: cubes, spheres, crystalloids, etc.
    • Increased surface area
  • Coatings

• Organic complexes
  • Alginaates
  • Carboxymethylcellulose
Types of Silver

- Inorganic
  - Silver Nitrate
  - Silver Acetate
  - Silver Borate
  - Silver Zinc
  - Silver Carbonate
  - Silver Chloride
  - Silver Chromate
Common Products

• Silver Sulfadiazine
  • Mixture of silver nitrate and sulfadiazine.
  • Recommended 1-2x daily dressings changes in burns.

• Acticoat
  • Nanocrystalline coated polyethylene film
  • May be left on for 3 days (Acticoat 3) or 7 days (Acticoat 7).

• Aquacel
  • Sodium carboxymethyl cellulose gel dressing (hydrofiber) with 1.2% ionic silver.
  • May be left on for 7-14 days
Common Products

• Mepilex Ag
  • Polyurethane foam with a silver sulphate.
  • Can be left on for up to 7-10 days

• Actisorb
  • Activated charcoal dressing with silver
  • Can be left on for up to 7 days

• Silvercel
  • Guluronic acid alginate, carboxymethylcellulose and silver coated nylon fibers
  • Can be left on for up to 7 days
Mechanism of Action

Silver ions from metallic silver bind to proteins in moist environments causing:

• Damaging bacterial cell wall and membranes
• Blocking respiration, electron transfer, and eliminating proton motive force.
• Preventing DNA replication and cell division.
• Deactivation and enzymes (International consensus 2012).
• Increase production of reactive oxygen species (Mijnendonckx 2013).
Mechanism of Action

• Ag Nanoparticles
  • <80nm are able to penetrate cell wall
  • <10nm can form pores causing cytoplasmic leakage

• Documented effect against planktonic (floating) and sessile (anchored) bacteria, biofilms⁹.

Image from: https://en.wikipedia.org/wiki/Biofilm
Antimicrobial Activity and Resistance

• Broad spectrum gram positive, gram negative, fungal and viral coverage including MRSA and VRE (International consensus 2012).

• Common belief that wide bacterial resistance is unlikely, due to multiple target mechanisms.
  • First documented silver resistance in 1960 involving burn wound treated with silver nitrate.
  • Other strains isolated since in clinical and environmental settings.
Bacterial Resistance

• Finley PJ. *WOUNDS* 2013. 25(4):84-88
• 130 different microorganism strains collected in tertiary care trauma and burn center.
• Corrected zone of inhibition (CZOI) determined after swab/incubation
  • Use of silver dressing and control gauze.

• No growth observed
Silver Cytotoxicity

- Argyria – irreversible gray/blue coloring of skin.
  - Caused by ingesting large amounts of silver, non-harmful.
- In vitro studies have shown toxicity of silver nanoparticles and silver nitrate to keratinocytes and fibroblasts
  - Concentrations similar to bacterial toxicity (Poon 2004)
Freshly discarded skin from diabetic (>10yrs) patients used to isolate fibroblasts and collagen.

Five wound care products and comparable silver-free product cut into 6mm discs, placed in culture plate, incubated 3 days.
Products

• Aquacel / Aquacel Ag  Carboxymethyl cellulose, Ag⁺
• Algisite M / Acticoat Absorbent  Calcum Alginate, Nanocrystalline, Ag⁰
• Medifoam / Medifoam Ag  Polyurethane foam, Ag⁺
• Biatin / Biatin Ag  Polyurethane foam, Ag⁺
• PolyMem / PolyMem Ag  Polyurethane foam, Nanocrystalline, Ag⁰
Results

- Fibroblasts exposed to silver dressings did not exhibit normal dendritic or fusiform shape.
- Collagen levels approx. 50-60% reduced compared to non-silver products.

<table>
<thead>
<tr>
<th>Cell number % decrease from non-silver products.</th>
<th>Ag(mg/l)</th>
</tr>
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<tbody>
<tr>
<td>Aquacel / Aquacel Ag</td>
<td>67% (Ag⁺)</td>
</tr>
<tr>
<td><strong>Algisite M / Acticoat Absorbent</strong></td>
<td>69% (Nanocrystalline, Ag⁰)</td>
</tr>
<tr>
<td>Medifoam / Medifoam Ag</td>
<td>70% (Ag⁺)</td>
</tr>
<tr>
<td>Biatin / Biatin Ag</td>
<td>70% (Ag⁺)</td>
</tr>
<tr>
<td><strong>PolyMem / PlyMem Ag</strong></td>
<td>54% (Nanocrystalline, Ag⁰)</td>
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</tbody>
</table>

Highest silver content. Lowest silver content.
2007 Cochrane Study: Topical silver for treating infected wounds.

• 3 RCTs identified, comprising 847 subjects.
  • **Contreet vs hydrocellular** foam in leg ulcers (Jorgensen 2005).
  • **Silver-containing alginate vs alginate** alone in venous leg ulcers (Meaume 2005).
  • **Silver-containing foam dressing vs local best practice** in chronic wounds (Munter 2006).
2007 Cochrane Study: Topical silver for treating infected wounds.

“There is insufficient randomized controlled trial evidence available to allow conclusion....”
Randomized controlled trial and cost-effectiveness analysis of silver-donating antimicrobial dressings for venous leg ulcers (VULCAN trial)

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Correspondence to: Professor J. A. Michaels, Sheffield Vascular Institute, Northern General Hospital, Sheffield S5 7AU, UK (e-mail: j.michaels@shef.ac.uk)

• 2009 Multicenter comparison of silver dressings and non-antimicrobial non-adherent control dressings, **used under compression**.
  • Silver dressing: Aquacel Ag, Acticoat, Acticoat 7, Acticoat Absorbent, Contreet Foam, Urgotul SSD.
  • Non-antimicrobial dressings: “any non-antimicrobial dressing from any manufacturer.”

• 213 participants with venous leg ulcers present for >6mo.

• **Primary outcome** measure was complete healing at 12 weeks.
• No significant difference in number of ulcers healed at 12 weeks (59.6% in silver group vs 56.7% in control) and overall median time to healing.

• Also concluded silver dressings associated with greater incremental cost per patient.

- Failed to study the indicated use of silver dressings.
  - Used against manufacture’s instructions
  - Silver not indicated to promote wound healing, but to prevent or treat infection.
- Silver and non-antimicrobial dressings chosen from approved list with very different compositions.
- Wound care involves constant change, making it difficult for any dressing to provide a consistent effect.
Correspondence concerning 2009 VULCAN study:

• R. White commented
  • “....these dressings were **used contrary to manufacturers’ instructions** for use.”

• J. A. Michaels defended his study
  • “...none of the manufacturers is currently recommending that the use of such dressings is restricted to a patient population based on particular microbiological findings or specific high-risk groups, apart from referring to those ‘at risk of infection’ which, **without further clarification, may be applied to any patient with an open wound.”
2010 Cochrane Study: Topical silver for preventing wound infection (Review)

- 26 RCT and 2066 subjects.

“authors concluded that there is not enough evidence to support the use of silver-containing dressings or creams...”
2012 International Consensus: Appropriate use of silver dressings in wounds

• Group of experts from around the world met to provide guidance for proper use of silver dressings, based on experience in clinical practice and all the available evidence.
  • Unrestricted education grant from B Braun, Conva Tec and Systagenix.
<table>
<thead>
<tr>
<th>BOX 5: When not to use silver dressings</th>
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</thead>
<tbody>
<tr>
<td>In the absence of signs of localised (overt or covert), spreading or systemic infection</td>
</tr>
<tr>
<td>Clean surgical wounds at low risk of infection, eg donor sites, closed surgical wounds</td>
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<tr>
<td>Chronic wounds healing as expected according to comorbidities and age</td>
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<tr>
<td>Small acute wounds at low risk of infection</td>
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<tr>
<td>Patients who are sensitive to silver or any of the dressing components</td>
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<tr>
<td>Wounds being treated with enzymatic debridement</td>
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<td>During pregnancy or lactation</td>
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<td>When contraindicated by the manufacturer, for example, some manufacturers recommend that their silver dressings are not used during magnetic resonance imaging (MRI), or on/near body sites undergoing radiotherapy</td>
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Dispel misconceptions

- Silver can improve healing rates when used appropriately.
- Silver dressings are unlikely to cause true argyria due to low level of silver being absorbed systemically.
- Resistance is rare and lack of response to silver is likely due to inappropriate treatment of underlying infection and/or wound etiology.
- Resistance of antibiotics is not likely to result from correct use of silver dressings.
- Silver dressings in children can be used with caution as should not exceed two weeks without good clinical reasoning.
Recommended two week ‘challenge’ to assess treatment.

Define wounds of high risk of infection as:

- Burn wounds
- Pressure ulcers near anus
- Wounds with exposed bone
- Wounds in immunocompromised patients
- Peripheral Vascular Disease
- Unstable diabetes or neoplastic disease
• Techniques to evaluate antimicrobial activity are not standardized and in vitro studies cannot be extrapolated to clinical application.

• Parson, *WOUNDS* 2005. Found no correlation between silver content or amount of silver released and antimicrobial activity in an in vitro dissolution assay, indicating that silver dissolution from a dressing is not a predictor of antimicrobial activity.

• Zou, *International wound journal* 2012. Diabetic fibroblast study showing cytotoxicity not related to silver concentration.
Objective: To determine effects of systemic antibiotics and topical antibiotics and antiseptics on the healing of venous leg ulcers.

- **Silver-based preparations** - 12 RCTs showed no between group differences.

“Current evidence does not support the routine use of silver-based products.”
<table>
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<tr>
<th>Product</th>
<th>Outcome</th>
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<td>Systemic antibiotics</td>
<td>4/5 RCTs without between group differences. No evidence to support.</td>
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<tr>
<td>Cadexomer iodine</td>
<td>4 of 7 RCTs showed benefit in healing. Some evidence to support.</td>
</tr>
<tr>
<td>Povidone-iodine</td>
<td>2 RCTs showed no between group differences, 2 RCTs deemed unreliable.</td>
</tr>
<tr>
<td>Peroxide-based preparations</td>
<td>4 RCTs showed benefit in change in size. Further research required to definitive conclusion.</td>
</tr>
<tr>
<td>Honey-based preparations</td>
<td>2 RCTs showed no between group differences. Not supported in current evidence.</td>
</tr>
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2017 - First RCT concerning effects of nanocrystalline silver on diabetic foot ulcers.
• DMII (A1C <10%), wound >1cm diameter, ABI >0.4, given oral abx if needed.

• Offloading insoles for plantar ulcers, weekly cleansing and debridement.

• N = 31; 11 nAg, 10 MH, 10 conventional

Conclusion

• **Healing at 12 weeks:** 81% nAg, 50% MH, 40% Conventional
  • Non-significant

• **Size reduction rate:** nAg(97%) potentially higher that MH(86%) and conventional (77%).

• **Bacteriology:** nAg showed greater decreasing trend
  • Non-significant

• **Antibiotics:** 12 nAg, 11 MH, 7 conventional episodes of taking oral abx.
Conclusion

• Silver dressings use different forms of silver
• Low chance for developing resistance to silver due to multiple MOA.
• In vitro testing supports antibacterial properties of silver
• Silver is not a healing agent
• Consider 2 week silver challenge
• RCTs due not support the use of silver in treatment of VLUs.
• Limited evidence to support use in DFUs.
References

References

Thank you!