Integration of Silver Iontophoresis Principles in a Device for Bacterial and Viral Infection Treatments, Wound-Healing, Tissue Repair and Regeneration

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The Medical Need

• Germane issues
  • “Infections”, mostly internal, are often untreatable
  • Wounds more chronic

• Reasons
  • Ineffectiveness of agents and/or methods
  • Exacerbated by superbugs
  • Agent delivery problems
  • Overall ecology of local microenvironments
  • Viruses little known
## Emerging Concepts of “Infection”

| Single pathological microbe                  | -->| Microenvironment ecology                  |
|---------------------------------------------|--|--|--------------------------------------------|
| All microbes “bad”: Presence/Absence        | -->| Symbiotic need for "good" microbes: Trillions of microbes in complex ecologies |
| Removal / Killing                           | -->| Promoting apoptosis & cellular/tissue normalization |
| Simplified gross area and organ concepts    | -->| Infinitely complex and dynamic cascading multi-category interacting events |

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**Notes:**
- Emerging concepts suggest a shift from viewing microbes as universally harmful or beneficial to understanding the complex interactions within ecological systems.
- The removal or killing of single pathological microbes is seen as promoting apoptosis and cellular normalization, rather than a simple gross area abstraction.
- A symbiotic need for "good" microbes is emphasized, recognizing the trillions of microbes in complex ecologies.
- The dynamics of infection are viewed as infinitely complex and dynamic cascading multi-category interacting events, moving beyond traditional organ-centric perspectives.
## Concepts of Treatment

| Iontophoretic ion propulsion | Multiple electromagnetic (and) signaling effects:  
- Direct internal EF/EMF effects via Ag+s  
- External EF/EMF effects |
|-----------------------------|------------------------------------------------------------------------------------------------|
| Diffusion and circulatory transport  
- Delivery to (deep) lesions problematic:  
  - circulatory problems  
  - Barriers  
    - abnormal scar tissue  
    - organ coverings | Direct transport/delivery to targeted area(s):  
- changes affected microenvironments  
- no dependence or interference with GI tract  
- painless, sterile, non-invasive  
- minimum-effective-dose control |
| Single speciality care | Multi-specialty care |
Superbugs

- Bacterial species and strains that have mutated and evolve resistance to antibiotics over decades
- Due to shotgun utilization of antibiotics
- Sped up by close housing of food animals and patients in hospitals for more infections and then more antibiotics
- (Ineffective) antibiotics may be working as placebos
- Antibiotics as growth promoting agents in animals
- Microbial distribution in microenvironments is dynamic with complex ecological relations: New adaptive organisms with 'good' and 'bad' characteristics
- Very limited indication that microbes can adapt to silver over many decades
Internal Abnormalities

- Infections of organs
  - Lung
  - Liver
  - Kidneys
  - Heart
  - Intestines
  - Nerves
  - Muscles
  - Brain
  - Ear
  - Reproductive
  - Etc.

- Abscesses
  - Abdominal cavity
  - Brain
  - Lung
  - Liver
  - Subcutaneous
  - Oral
  - Etc.

- Bones

- Sepsis
Stages of Healing

• Inflammatory (acute)
  • red
  • hot
  • swollen
  • painful

• Proliferative
  • scar tissue
  • differentiating cells/tissue
  • normalized cells/tissue

• Maturation/Remodeling
  • clastic processes
  • blastic processes
Wound Care

• Describe wound location, size and other characteristics (electrode placement)

• Identify wound etiology (non SIS things, e.g. systemic nutrition, detoxification)
  – Maximize toxin removal and nutrient provision (follow with BDORT but ancillary part of comprehensive program)

• Assay wound environment characteristics (BDORT; lab micro-assays)
  – Identify colonized pathological microbes (to plan details of dynamic individualized approach)
  – Determine antibiotic sensitivity (BDORT testing; lab culturing)

• Maintain optimal environment for wound healing locally (SIS Ag+ & EF/EMF affects)

• Monitor and dynamically modify treatment program (as above)
Ion (Gk) = “(to) go” i.e. *moving object*

Phoresis (Gk) = “transport, carry”

Silver Iontophoresis = electromotive transport of silver ions (Ag+s) into a living body
Ag+ effects - #1

• Broad spectrum, stand-alone microbial agent, including antibiotic resistant (MRSA, VRE, etc), gram-negative/positive bacteria

• Interruption of bacterial/viral membrane/capsid processes\(^1,2\)
  - Increases membrane permeability
  - Increases reactive oxygen species (ROS)
  - Interacts with:
    – Fe homeostasis
    – Transcription processes
    – Respiratory processes

• Enhances standard antibiotic activity

• Virus inhibiting effects, including adenovirus, HIV-1, herpes family, influenza virus, Hep B, etc

Ag+ effects - #2

Example of silver particles binding with a virus capsule:
Ag+s attach to protein-specific sites of virus

Matching protein-related spatial arrangements on surface of HIV-1 virus

Becker's Ag+ microenvironment signalling tissue regeneration 'trick'

- Iontopheretic system for stimulation of tissue healing and regeneration US Patent 5814094 A
Ag+ effects - #3-2

Microenvironment signaling for multi-type tissue healing and regeneration

[Becker et al, 1998]
Therapeutic Index

Lethal dose vs therapeutic concentration ratio of Ag+ within FDA approved antibiotics therapeutic index ranges

Iontophoresis

CLINICAL APPLICATION
1. Electro-physiological parameters

Internal infections/lesions: Skin
Electrical resistance (R): **Intact skin**

**Approximate range**

- **DRY SKIN:** $10\,\text{M}\Omega+$
- **WET SKIN:** $10$-$100\,\text{k}\Omega$

*Highly. Rapidly.*
Wound Stimulation - Summary

1) Silver ions for 'infection' - prevention and treatment

2) Real-time measurement/calculation of wound-generated electric field
   • Bioelectrically matching magnitude and polarity voltage drop generation at wound edges:
     » Real-time scaled supplementation or replacement

3) Becker's tissue regeneration method
   • Silver ions for fibroblast de-differentiation and more 'stem-like' cells for repair
   • Voltage real-time scaling to wound/electrode size

Operation regardless of 'infection' status
Finding and testing Ag+ microcurrents for microbial/microenvironment effects

- Clinical presentations
  - Symptomatic → asymptomatic

- Laboratory pathology results

- Organ/tissue/cellular/microenvironment assays
  - Bi-Digital O-Ring Test (BDORT) resonance phenomena
    [Omura Y] antimicrobial effect predictive testing
    - BDORT reference control substance mono- polyclonal antibody slides
    - Microbe antigen samples
**Stimulation Current Comparison**

<table>
<thead>
<tr>
<th>‘Medicine’</th>
<th>Drug solution iontophoresis</th>
<th>Silver-nylon (Ag+) iontophoresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation current range (amperes)</td>
<td>3-5 milliampere (approximate)</td>
<td>0.5-10 microampere (approximate)</td>
</tr>
</tbody>
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Narrow 'window' of effective delivery without applied voltage damaging skin - and so increasing skin electrical resistance.
2. Electro-physiological parameters: Wounds
Electrical resistance (R): **Wound**

→ 1\(^{\text{st}}\) - 3\(^{\text{rd}}\) degree, full thickness

**Wound bed**

- 5kΩ
- Granulation Tissue
- 50kΩ

**New epidermis**

**Periwound/wound edge**

- 20kΩ
- Granulation Tissue
- 100kΩ

Approximate range
Trans-epidermal-epithelial Potential (TEP) ~20-70 millivolts

Ohms Law: Current of Injury (COI) = \frac{\text{TEP (V)}}{R}

Current of Injury (COI): Amperes

Amperes

100µAmps

1µAmps

INJURY DEGREE

INTACT SKIN

PARTIAL / FULL THICKNESS

AMPUTATION

(approximate)
Current of Injury (COI): Voltage Supplementation

- Minimum voltage must not reduce COI
- Matching COI polarity
- Real-time scaling to COI

150++ milliV

~70-150 milliV

INTACT SKIN

PARTIAL / FULL THICKNESS

Wound edge

Wound bed

Resistance (Ω)
ELECTRIC FIELD GENERATED ACROSS WOUND GEOMETRY

VOLTAGE SUPPLEMENTATION: INCREASING E-FIELD AND COI THROUGH WOUND
Superficial Wound COI

VOLTAGE SUPPLEMENTATION: ELECTRODE POSITIONING

Reverse polarity!

Stratum corneum
Epidermis-dermis
Hypodermis
Deeper Wound COI

SUPPLEMENTATION VOLTAGE: ELECTRODE POSITIONING

Epidermis
Dermis
Hypodermis

Reverse polarity!
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Operation regardless of 'infection' status
Bioelectric & Electronics: Basic Solutions

- Delivery along pathway of least resistance
  - Anatomical cross-sectioning with electrodes
  - Low voltage ‘gated’ sweat gland ion channels
- Microcontroller regulated self-adaptive circuitry:
  - Nanoampere accuracy constant ultra-low microcurrent
  - Real-time measurements of electrical skin/wound resistance (Ω)
  - Voltage producing & switching
  - Self-adaptive temperature calibration
  - Electrode stimulation efficiency (ESE) smart software
ELECTRODES: FDA 510(K)/EU(CE) Class I conformity Ag-nylon material
DEMONSTRATION OF CLINICAL EFFICACY:
Illustrative Case Studies
1. Acute Periodontitis

2-3 days continuous near 24 hour use

- Asymptomatic:
  - No pain
  - No swelling

- No antibiotics nor painkillers

- Coincidental gum regeneration
  *(Becker's stem cell 'trick'?)*

Apple-sized lesion
1-1. Jaw electrode placement
2. Symptomatic H. Pylori

16 days continuous near 24 hour use (prototype SIS equipment)

- C14 Urea Breath Test positive

- No antibiotics, painkillers, proton pump inhibitors

- BDORT negative

- 90% reduction of symptoms

- C14 Urea Breath Test negative
2-2. H Pylori electrode placement
3. Infected oozing antibiotic-resistant Cesarean section surgical scar

Positive Electrode placement directly on wound

- 7 days: no signs of infection or swelling (prototype SIS equipment)

- Complete healing, not requiring any further treatment

- No pain/painkillers
4. Symptomatic cervical Human Papiloma Virus (HPV) infection

- 10-12 days of continuous near 24 hour use
- Asymptomatic
- Pathology testing not obtained/unavailable
- BDORT negative
4-1. Cervical electrode placement
5. Symptomatic ear infection in 7yo child

12 hours of near continuous use

- Asymptomatic

- Recurrence after several weeks and repeat treatment; again asymptomatic.
5-1. Ear electrode placement
6. Internal chronic scar tissue reversal: Decades of *Mycobacterium tuberculosis* induced lung scarring:

Several weeks continuous treatment
6-1. Lung electrode placement

Major effect proximal to +ve electrode
6-1. CAT SCAN IMAGE:
APICAL SCARRING
6-2. CAT SCAN IMAGE COMPARISON: NO SCARRING
Medical Need Fulfilment

• Iontophoresis precedences established for surface and internal tissue targets
• Data based development
• Ag+ iontophoresis via low amperage direct current
• Delivery through variable:
  – Distance
  – Tissue type: varying electrical impedances
  – Time-frames
• Supported by case study results
SIS machines

- Dedicated and portable silver iontophoresis stimulators (SIS) and electrode system
- RCM, FCC, CE electronics conformity tested
- Bacterial & viral infections
- Wound protection & healing
- Tissue healing & regeneration
- Patent pending devices and technology.

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