

# Clinical Aspects of Antimicrobial Agents- Biofilms and Antimicrobial Resistance

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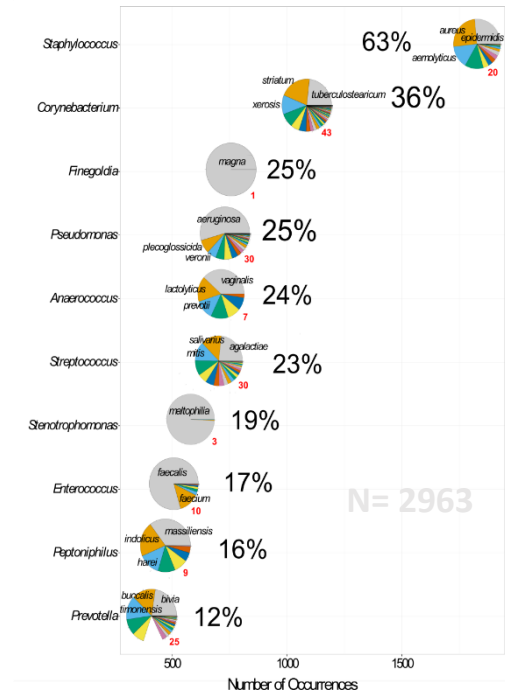
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# Key Points

- Bacteria matter...not just a broken host
- Wound care is successful
- Antimicrobial dressings are important to care
- Little evidence to show that antimicrobial wound dressings cause resistance



# Chronic Wounds are Chronic Infections caused by Biofilm

## ESCMID\* guideline for the diagnosis and treatment of biofilm infections 2014

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**Biofilms cause chronic infections...**

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# Antimicrobial Products Were Main Agents to Heal a Complex Wound



MRSA, Clostridium and Finegoldia

8 weeks of systemic antibiotics

16 weeks of Ag alternating with Iodine

Antimicrobial products were important treatments



# In these type of complicated wounds, dressings must be protected from bacteria or else they form biofilm which is harmful and impede the wound healing process

## Development of an experimental model of infected skin ulcer

Masahiro Tachi, Shinichi Hirabayashi, Yoshiyuki Yonehara, Yasutoshi Suzuki, Philip Bowler

### ABSTRACT

A model of infected skin ulceration could prove useful in assessing the clinical effectiveness of antimicrobial ointments and dressings. However, no such models have been previously established. Three types of wound were induced in rats: full-thickness wounds covered with gauze, burn wounds and wounds resulting from mechanical trauma. Wounds were inoculated with *S. aureus* or *P. aeruginosa*. Persistent infected wounds were observed only in full-thickness wounds covered with gauze. In a second experiment, colonies of *P. aeruginosa* or *S. aureus* were counted within 15 × 15 mm full-thickness wounds covered with gauze. Wounds were inoculated with  $1.0 \times 10^6$  colony-forming units (CFU) of *P. aeruginosa* or *S. aureus* and then sealed to ensure an enclosed environment. Tissue bacterial counts exceeded  $10^7$  CFU/g from the next day until day 9 after infection. Bacterial counts exceeded  $10^7$  CFU/ml in wound exudate collected between days 1 and 7. We have developed a model of wound infection in which persistence of infection can be achieved for 9 days following ulceration due to the application of gauze to the base of a full-thickness wound.

**Key words:** Animal model • Colonization • Rat • *S. aureus* • Wound infection

### INTRODUCTION

Skin ulceration is a serious clinical complication of surgical wound infections, atherosclerotic disease, venous stasis and diabetes mellitus and occurs with decubitus ulcers (1). Infection of skin ulcers may necessitate hospitalisation or even amputation, as may occur with diabetic foot disease, posing significant morbidity and expense (1). Although systemic antibiotics are the mainstay of treatment for infected wounds, debate surrounds the con-

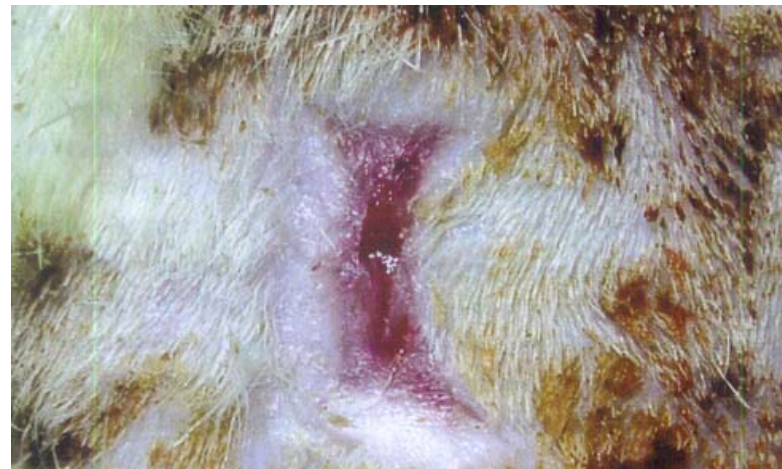
current use of topical antimicrobial ointments

or dressings (2–4). To investigate the role of antimicrobial ointments and dressings in the treatment of infected chronic ulcers, a robust animal model that closely mimics clinical infection is needed. However, no animal models have been established to date. Rats, mice and other rodents are convenient for handling; however, it is difficult to induce chronic ulcers in these animals because full-thickness wounds on their backs tend to heal naturally in most cases, even following inoculation with bacteria (5,6). To prepare infected wounds surgically, researchers have attempted dermal injury, including burns (7) and crush wounds (8,9), in combination with the introduction of foreign bodies, such as sutures (10,11), sand (12) or dextran beads (13,14). These models have been used primarily to investigate the effects of antibiotics on mortality rates, and ulceration as a result of chronic infection has not been established in these models (7,11,14,15). There is also a significant amount of research surrounding burn infections.

### Key Points

- Systemic antibiotics are mainstay of treatment for infected wounds
- Debate surrounds the current use of topical antimicrobial ointments and dressings
- Animal models are needed to scientifically evaluate these modalities
- No data re 'chronic wound' model exists

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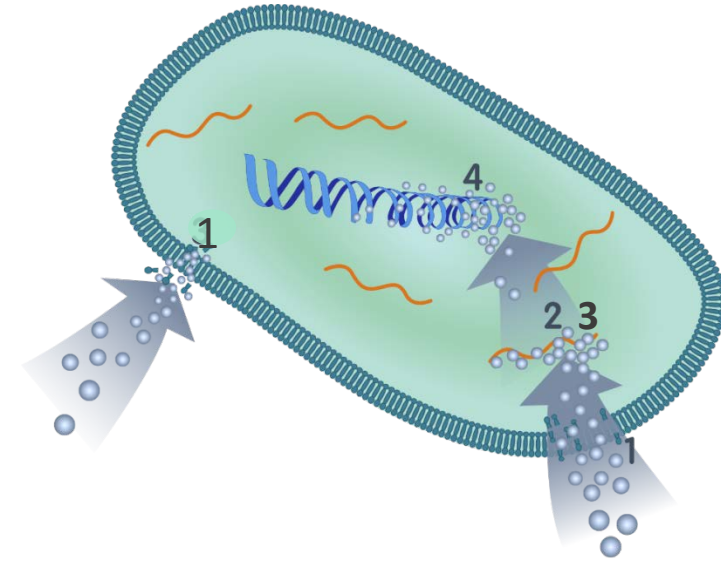


Wound microbiota and exudate form biofilm on dressings

Biofilm prevents wound healing

# Silver: a powerful antimicrobial

- **Silver has a long history as a antimicrobial agent**
- Ag<sup>+</sup> ions have broad spectrum antimicrobial activity against bacteria, fungi, and viruses<sup>1</sup> and can rapidly kill microorganisms (microbiocidal)
- Silver ions (Ag<sup>+</sup>)<sub>1</sub> bind to multiple targets on bacterial and fungal cells
- Targets are:
  1. Cell wall and membrane disruption
  2. Denature proteins and enzymes
  3. Prevent respiration
  4. Inhibit DNA synthesis
- **More targets....reduced chance of resistance development**
- Antibiotics mainly have narrow spectrum of activity (against specific types of bacteria) and usually act on 1 target in the cell
- Several formulations of silver are utilized in wound care e.g. silver sulphadiazine (SSD), silver nitrate and ionic silver dressings<sup>2</sup>



DNA=deoxyribonucleic acid.

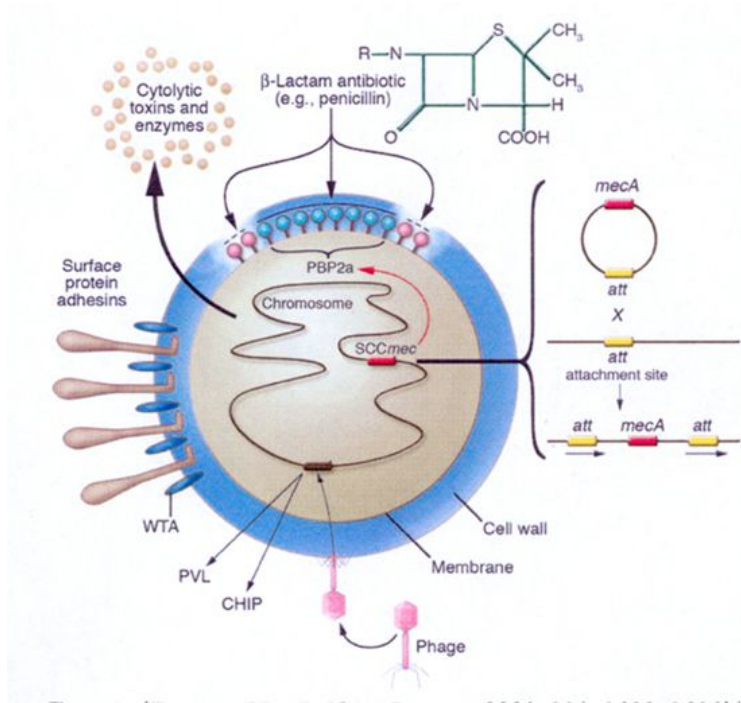
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# Resistance versus Tolerance

## Antibiotics versus Antimicrobials

### MRSA – mechanism – I



- Horizontally transferred DNA element - *SCCmec*.
- Site specific recombination.
- *mecA* gene encodes PBP2a.
- PBP2a = 78 KDa PBP - capable of cell wall synthesis.
- PBP2a has low affinity for all  $\beta$ -lactams.

**Bowler:** Despite the sporadic evidence of bacterial resistance to silver, there have been very few studies undertaken and documented to ascertain its prevalence. The risks of antibacterial resistance developing from the use of biocides may well have been overstated.

**Percival:** Results suggest that presence of silver resistance genes is rare and that genetic resistance does not necessarily translate to phenotypic resistance to silver.

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# Clinical Importance of Antimicrobial Products



## The Use of Antimicrobial Products:

- Improves outcomes
- Silver/Iodine/PHMB/etc. are Safe and Effective
- Minor risk to future patients or Public

## If the Availability of Antimicrobial Products Is Limited:

- Poor outcomes (Reservoir will remain open)
- Increased use of antibiotics